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COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

PSYCHOTROPIC DRUGS

SUMMARY AND ANALYSIS

SELECT COMMITTEE ON SMALL BUSINESS
UNITED STATES SENATE

PREPARED BY THE
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A SUMMARY ANALYSIS AND DISCUSSION OF ISSUES HIGHLIGHTED DURING THE 1969, 1971, 1975, AND 1977 HEARINGS ON PSYCHOTROPIC DRUGS, WITH A REVIEW OF CURRENT FINDINGS AND SUBSEQUENT GOVERNMENT ACTIONS RELATING TO THESE DRUGS

SEPTEMBER 20, 1979

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LETTER OF SUBMITTAL

THE LIBRARY OF CONGRESS,
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Washington, D.C., March 20, 1979.

Hon. GAYLORD NELSON,
Chairman, Select Committee on Small Business,
U.S. Senate, Washington, D.C.

DEAR MR. CHAIRMAN: I am pleased to submit this analysis and review of the psychotropic drug hearings that were conducted before the Subcommittee on Monopoly and Anticompetitive Activities in 1969, 1971, 1975, and 1977. This summary report, prepared at your request, is particularly timely in light of a Food and Drug Administration panel's recent review of over-the-counter nighttime sleep-aid and stimulant products.

The hearings summary was prepared by Ms. Stephanie Forbes, a private consultant, under a Congressional Research Service contract (CRS 78–62–9). It was reviewed and edited by Ms. Vikki Zegel, Analyst in Life Sciences, of the CRS Science Policy Research Division. The report provides an analytical review of testimony presented during the 1969, 1971, 1975, and 1977 hearings, as well as an update of what has been learned since those hearings with regard to the risks and benefits of the so-called "mood drugs". The effects of advertising and promotion on the use of sedatives, tranquilizers, stimulants, sleep aids, and other psychotropic drugs, as well as recent Federal Government actions relating to these products, are also highlighted.

May I express my appreciation for this opportunity, on the part of the Congressional Research Service, to cooperate with your subcommittee in the preparation of this timely and most useful report.

Sincerely,

GILBERT GUDE, *Director.*

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Psychotropic Drugs

I. Introduction

A. PURPOSE

This report reviews the major issues raised during the Subcommittee's 1969, 1971, 1975, and 1977 hearings on psychotropic drugs;[1] it examines these and related issues in the light of current information on these substances; and it discusses Federal Government actions related to the marketing and labeling of psychotropic agents.

B. BACKGROUND

During 1969 and again in 1971, 1975, and 1977, the Subcommittee on Monopoly of the Senate Select Committee on Small Business heard testimony on the advertising, use, effectiveness, and safety of prescription and over-the-counter psychotropic drugs. This testimony, which forms part of the Subcommittee's " * * * continuing study of the effect of promotion and advertising on competition, small business, and the health and welfare of the public,"[2] was taken from expert witnesses in science, medicine, and government. In his opening statement printed in the record of the 1969 hearings, Subcommittee Chairman Senator Gaylord Nelson summarized a major aim of these hearings:

> Over the past few years, if we can believe only a small part of what has been written, Americans have been insulating themselves from the pressures of modern life by using tranquilizing drugs in rapidly increasing numbers.
>
> Our problem is that we don't really know very much about the tranquilizing drugs or what they are doing to us as individuals and to our society as a whole. These hearings will be seeking answers to what many thoughtful people believe to be vitally important questions. To my knowledge, no one has gathered the best information available in one place on psychotropic drugs. We hope to begin that compilation today.[3]

Psychotropic drugs have their main effect on behavior, thought processes, and mood, hence the term "mood drugs."[4] Prescription

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[1] U.S. Congress. Senate. Select Committee on Small Business. Subcommittee on Monopoly. Competitive Problems in the Drug Industry. Hearings, 91st Congress, 1st Session on the Present Status of Competition in the Pharmaceutical Industry: Psychotropic Drugs (pt. 13). Hearings held July 16, 29, and 30; October 27, 1969. Advertising of Proprietary Medicines. Hearings, 92nd, 94th, and 95th Congresses, 1st sessions on the Effect of Promotion and Advertising of Over-The-Counter Drugs on Competition, Small Business, and th Health and Welfare of the Public: Mood Drugs (Sedatives, Tranquilizers, and Stimulants) (Pt. 2) and Over-the-Counter Tranquilizers, Sedatives, Sleep-Aids, and Stimulants (Pt. 5). Hearings held July 21, 22, and 23, September 22, 1971; October 29 and 30, 1975; June 14 and 21, 1977. Washingtcn, U.S. Govt. Print. Off., 1969 (pages 5273–5477), 1971 (pages 425–938), 1977 (pages 1673–1935). Hereinafter referred to as The Psychotropic Drugs Hearings.

[2] Ibid., p. 425.

[3] The Psychotropic Drugs Hearings, p. 5273.

[4] Ibid., p. 5284.

psychotropics are generally divided into six classes: the major tranquilizers, the minor traquilizers, antidepressants, stimulants, sedatives, and hypnotics. Over-the-counter [5] mood drugs fall into three groups: Daytime sedatives, sleep-aids, and stimulants.

The 1969 hearings concentrated on the prescription psychotropic drugs. A major focus of those hearings was "* * * to ascertain whether psychotropic drugs are being overprescribed and overused in the United States." [6] Witnesses at those hearings generally agreed that psychotropic drugs are being overprescribed and overused.[7] They noted, however, that the extent of the problem is difficult to determine because of the lack of objective data in this area and because of interpretive problems which arise when these data are subjected to analysis.[8] Several witnesses added that there is a trend in our society to overprescribe and overuse all kinds of drugs.[9]

Witnesses also considered the causes and consequences of psychotropic drug overprescription and overuse. Chief among the possible causes named was advertising which, according to several witnesses, has created a climate of need for these drugs, extending their indications beyond the treatment of true mental illness to therapy for the everyday stresses and strains of normal living. Witnesses also named the lack of adequate pharmacological training in medical schools and the pressures brought to bear by patients on their doctors as possible reasons for the overprescription of these and other drugs.

The major problem named in association with psychotropic drug overuse was drug abuse with all of its attendant effects on the individual and society. Some witnesses also expressed a concern that the overprescription and overuse of psychotropic drugs could mask real physical and psychological problems, thus interfering with diagnosis and treatment.

Later hearings focused on the OTC mood drugs—the daytime sedatives, sleep-aids, and stimulants. While a fair number of different chemicals comprise the various classes of prescription psychotropics, the OTC mood drugs are composed of only a few active ingredients. All OTC stimulants, regardless of the brand, contain from 100 to 200 milligrams of caffeine—about the amount of caffeine found in a cup of brewed coffee. Depending upon the product, OTC stimulant preparations may or may not also contain dextrose, an odd vitamin or two, and even a bronchodilator. All OTC sleep-aids and sedatives contain the antihistamine methapyrilene, either as the hydrochloride or the fumarate. They may also contain another antihistamine (pyrilamine maleate), the amnesiac drug scopolamine, and an analgesic. Bromides, which were often included in OTC sedatives and sleep-aids at the time of the hearings, are no longer used in these preparations.

In particular, the 1971, 1975, and 1977 hearings examined the effects of advertising on the use of OTC mood drugs. In his 1971 opening statement, Senator Nelson commented that

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[5] The term "over-the-counter" will hereinafter appear as OTC, its common designation.
[6] The Psychotropic Drugs Hearings, p. 5285.
[7] Ibid., pp. 5286, 5299, 5304, 5307, 5308, 5312, 5317, 5326, 5475.
[8] Ibid., pp. 5282, 5283, 5286, 5295, 5297.
[9] Ibid., pp. 5326, 5475.

* * * the purpose of current advertising of nonprescription medicines goes well beyond the recommendation of a product for a recognized medical need, and instead, encourages the consumer to take a pill for anything which worries, disturbs, or annoys him. [10]

Witnesses at these hearings also discussed the safety and efficacy of OTC mood drugs and the role of the Federal Government in controlling the advertising and marketing of these preparations.

Much of the testimony on both prescription and OTC psychotropic drugs was subjective and anecdotal. Witnesses emphasized that they were reporting what they believed to be true about these drugs but that they had little, if any, objective information with which to support their ideas. This subjective testimony emphasized the moral consequences of psychotropic drug use, the effects of these drugs on the psychological growth and mental health of the individual and society, and the problems of both medical and nonmedical drug abuse.

Relatively little attention was given to the physical risks associated with psychotropic drug use, a paucity of data again being the problem. Among the adverse effects mentioned were tardive dyskinesia, agranulocytosis, thrombocytopenic purpura, glacoma, and bromism. The recognized side effects associated with the use of various prescription psychotropics were described early in the 1969 hearings. Later, witnesses explained that the side effects of OTC mood drugs are not well established. A major problem is that people who take these preparations seldom consult a physician or report the untoward effects experienced during self-medication.

While there is little data on the side effects of OTC psychotropic drugs, there is perhaps less on their efficacy. None of the witnesses knew of any studies proving that OTC sedatives and sleep-aids really relieve simple nervous tension or induce relaxation and sleep as is claimed in advertising. Witnesses were divided on whether or not these products should remain on the market. They all agreed, however, that something had to be done about the false and misleading advertising claims being made for OTC mood drugs.

The problems associated with psychotropic drug use remain in effect today. Popular articles continue to be written about the overprescription and overuse of mood-altering drugs, the relationships between psychotropic drug use and general drug abuse, and the influence of advertising and promotion on psychotropic drug prescription and use. Several scientists discussed these problems at hearings held in September 1978 by the House Select Committee on Narcotics Abuse and Control. Much of this material is still, however, subjective. There is still a paucity of reliable survey data on psychotropic drug prescription and use patterns.

While research for and development of new psychotropic drugs continue, there have been no new research reports on the health hazards associated with the use of currently available psychotropics. A long-recognized effect, tardive dyskinesia, has been the subject of some research effort to understand and control the problem.

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[10] Ibid., p. 425.

C. FEDERAL ACTIONS

A major action taken by the Federal Government since the hearings adjourned is the publication in the Federal Register of a tentative final monograph on OTC mood drugs.[11] This monograph is the result of a 1975 report to the Food and Drug Administration (FDA) by the agency's Advisory Review Panel on OTC Daytime and Nighttime Sedatives and Stimulant Products. With the publication of the tentative final monograph, the FDA has allowed further time for public comments on the panel's findings and FDA's proposals. FDA expects to publish the final monograph sometime in 1979.

The OTC monograph proposes restrictions that would end the sale of daytime sedatives altogether[11a] and prohibit the inclusion of scopolamine and bromides in nighttime sleep-aids. The monograph also proposes to end the use of methapyrilene, and antihistamine now found in all OTC sedatives. Scientists suspect that methapyrilene may possess carcinogenic (cancer-causing) or co-carcinogenic activity, a possibility which was first brought to public attention by Dr. William Lijinsky at the 1977 psychotropic drug hearings.[11b]

One other Federal Government action worth noting is the passage of S. 2399 on October 7, 1978.[11c] This bill amends the Controlled Substances Act, the Controlled Substances Import and Export Act, the Federal Food, Drug, and Cosmetic Act, and the Public Health Service Act to meet obligations under the Convention on Psychotropic Substances. The Convention, held by the World Health Organization in 1971, provided the groundwork for evaluating old and new psychoactive drugs and for controlling their manufacture, distribution, importation, and exportation internationally.[12]

D. POLICY ISSUES

The hearings raised a number of policy issues chief among which was the question of drug safety and efficacy. Senator Nelson was particularly interested in the efficacy of OTC mood drugs and asked repeatedly why these products were on the market at all when, as many witnesses had affirmed, no scientific proof of their effectiveness existed. The Senator's criticisms of what he saw as FDA's failure to enforce the 1962 Kefauver Amendment on efficacy led to another important question: Where does the burden of proof belong? It is FDA's responsibility to prove a drug is ineffective and that it should, therefore, be taken off the market? Or is it the drug company's responsibility to prove that its product is effective and that it should remain on the market?

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[11] Over-the-Counter Nighttime Sleep-Aid and Stimulant Products. Tentative Final Orders. Federal Register, v. 43, no. 114, June 13, 1978 : 25544–256 02. [Hereinafter referred to as The OTC Monograph. See also Appendix E.]

[11a] The FDA announced its decision in June: "Based on evidence presently available, there are no ingredients that can be generally recognized as safe and effective for use as OTC daytime sedatives." Effective December 24, 1979, any OTC drug product that is labeled, represented or promoted as an OTC daytime sedative will be regarded as a new drug and must have an approved new drug application. Drugs for Human Use; Over-the-Counter (OTC) Daytime Sedatives. Final Order. Federal Register, v. 44, no. 122, June 22, 1979: 36378–36380.

[11b] In a May 1, 1979, "Talk Paper" (T79–21), the FDA said it had received an interim report from the National Cancer Institute indicating that methapyrilene is a potent carcinogen in animals and a potential carcinogen in humans. On June 8, The Proprietary Association, which represents manufacturers of nonprescription medicines, announced that its member companies were voluntarily recalling to the retail level all ingested products containing methapyrilene. It said most companies planned to replace them promptly with reformulated products.

[11c] Public Law 95–633, signed November 10, 1978.

[12] Controlling Psychotropic Substances. WHO's Responsibilities Under the New Convention. WHO Chronicle, January, 1978: 3–8.

Government witnesses also brought out an apparent problem in the interpretation of the efficacy statute. The pharmaceutical companies have been arguing that any drugs which were on the market before 1962 enjoy "grandfather" status and do not have to prove their effectiveness. The FDA does not agree with this interpretation and has, so far, been able to convince the courts that its position is legally correct.

Other issues discussed during the hearings and examined in this report include the lack of adequate physician education in pharmacology; the responsibility of the consumer, the prescribing physician, and the medical community for the problem of psychotropic drug overuse; governmental regulation of drug use; and the need for more research and researchers to study psychotropic drugs, their risks and benefits. This report will also consider the issue of consumer information. Is safe and effective self-medication possible in light of the information now available to the average consumer? What kinds of information does the consumer need to make reasoned choices about OTC mood drugs? What is the best way to deliver this information? Answers to these questions are particularly important in light of the growing belief that the individual is responsibile for his or her own health care.

II. Health Hazards of Psychotropic Drugs

A. INTRODUCTION

The psychotropic drugs were developed for the treatment of mental illness and it is in this context that they have had a profound effect. Several witnesses testified during the hearing that not only were the drugs useful in psychiatric practice but also that psychiatry could not have achieved its present success rate without them. Dr. Fritz A. Freyhan, Director of Research, Department of Psychiatry at St. Vincent's Hospital in New York, commented:

> * * * I must say at the outset that psychiatry could not have progressed to its present standards of therapeutic achievement without the discovery of not only new drugs, but unique methods of drug treatment for the benefit of a great multitude of patients with minor and major psychiatric disorders. After 15 years of drug treatment in psychiatry, one cannot seriously question that the merits and accomplishments greatly outweigh the combined disadvantages of toxicity and misuse.[13]

Dr. Daniel X. Freedman, Professor and Chairman of the Department of Psychiatry, University of Chicago, noted, in the same vein:

> The advent of the major tranquilizers—the anti-psychotic drugs—while not miraculous—brought a consequential step in the degree to which disabling mental disorders can be modified, and had a significant impact on the extent to which effective and humane delivery of health services—called community mental health—might be organized * * *. They also have a definite effect on preventing relapse which is of equal medical and social importance.[14]

Dr. Richard C. Pillard of Boston University School of Medicine began his testimony by praising the scientific discipline responsible for developing psychotropic drugs and applying them to the practice of psychiatry.

> The field of psychopharmacology is only 15 years old but has already made an impressive contribution to the recovery of mentally ill people. This would, of course, never have been possible without the variety of high quality psychotropic drugs which are available * * *[15]

Witnesses also testified that, thanks to psychotropic drugs, the number of mentally ill patients who must be hospitalized has decreased drastically. Dr. Stanley F. Yolles, then director of the National Institute of Mental, Health, testified in 1969,

> drugs shortened the patient's hospital stay, and they have allowed treatment and rehabilitation in the community of an increasing number of the mentally ill without serious disruption of family relationships and work.[16]

Dr. Yolles added that the number of hospitalized mental patients decreased by 30 percent between 1956 and 1969 thanks to psychotropic drugs. The late anthropologist Margaret Mead commented:

> It is true that psychotropic drugs made inaccessible people accessible, they have made awards filled with screaming disturbed people peaceful so that the patients who went weren't more disturbed, they made it posssible for us to begin discharging large numbers of patients from mental hospitals, and they made it possible for us to keep millions of others out.[17]

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[13] The Psychotropic Drugs Hearings, p. 5326.
[14] Ibid., p. 5440.
[15] Ibid., p. 5403.
[16] Ibid., p. 5275.
[17] Ibid., p. 5462.

According to Dr. Mead, "Instead of condemning hundreds of thousands of people to a life which permitted no recovery, these drugs have been exceedingly useful in permitting their treatment." [18]

The development of psychotropic drugs, like many lines of research, has had implications beyond the expected clinical benefits. Dr. Freedman commented on this fact during his testimony:

> A major consequence of all these drugs has been the astonishing advance in data on the chemical systems which regulate brain functions. With the support of the National Institutes with their programs in psychopharmacology and behavioral sciences, there have been genuinely new thrusts in psychiatry. Behavior cannot be explained solely by chemistry, but we are far readier to know what part hormones and chemicals may play in disordered behavior and when in a given disorder changes in brain chemistry may be important. Such data takes years to develop but can provide elegant control over the body's molecular systems and the possibility for a rational design of new molecular approaches, as well as understanding disease mechanisms. Such basic pharmacological research has been advanced in our field. Research has also been initiated into the causes of mental disorders and into more precise means of identifying different subpopulation of patients for whom such drugs might be specific.[19]

The psychotropic drugs have relieved much personal suffering, returned many formerly hospitalized patients to their families and jobs, and have furthered our basic understanding of brain biochemistry. The use of these drugs can, however, have negative consequences. Like any drug therapy, psychotropic drug use entails risk as well as benefits. Dr. Natalie Shainess of the William Alanson White Institute of Psychiatry commented on some of these consequences in her 1971 testimony.

> The development of the so-called "mind drugs" or psychotropic drugs has been a mixed blessing, permitting more successful management (not treatment) of mental disturbance, and at the same time furthering "escape," and promoting the growth of a nation of "zombies." And by "zombies," I mean individuals with little emotional response, not responding to some inner executive direction, but moving without feeling and without thought in a state which psychotropic drugs induce.[20]

Dr. Shainess' testimony hit upon two of the major objections to psychotropic drugs: the do not cure but only manage mental patients, and they carry within them the threat of what many people see as a "Brave New World" brought terrifyingly to life.

In his 1969 testimony, Dr. Yolles described the nature and use of psychotropic drugs noting, as did Dr. Shainess, that these chemicals do not cure mental parients.

> Psychotropic agents act by unknown mechanisms to reduce the level of symptomatology of patients but do not, to our knowledge, directly affect the causative agent attack the microbes which cause infectious diseases.[21]

Dr. Richard I. Feinbloom of Harvard Medical School touched on the same problem when he commented that "drugs may make the symptoms go away but leave the causes untouched." [22] The use of psychotropic drugs, then, carries an inherent danger; they are so convenient and so effective in managing patients that they can be used in place of

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[18] Ibid., p. 5460.
[19] Ibid., p. 5441.
[20] Ibid., p. 543.
[21] Ibid., p. 5283.
[22] Ibid., p. 521.

therapy designed to find and correct the underlying problem. Dr. Shainess expressed a concern that:

> * * * there is something terribly disheartening taking place. In place of careful thought about human beings, and the effects of various interactions and various situations the drug solution has become increasingly prevalent." [23]

She added that there is evidence of "drug dependence and simplistic thinking among psychiatrists." [24]

While all of the witnesses agreed that psychotropic drugs are overused, most of them were unwilling to discard the drugs altogether. A notable exception was Dr. Robert Seidenberg of Upstate Medical Center, State University of New York. Dr. Seidenberg testified,

> * * * I feel that drugs have no place at all in psychiatry. I think the addition of drugs in psychiatric treatment has set the discipline back on its heels when it was starting to get into areas of human understanding, of psychology, and sociology dealing with a variety of forces that impinge upon a person. This understanding evolves slowly; this takes many years, many decades to understand, and when drugs came along as a 'magical' way of dealing with it (a way of really not dealing with it), it led to a nonsolution of problems.[25]

Dr. Seidenberg objected in particular to the use of tranquilizers, probably the most widely prescribed of the psychotropic drugs.

> Tranquilizing people into submission, medical social engineering, this to me is all regressive, and I think it is a dark chapter in the history of psychiatry.[26]

Unlike prescription psychotropics, OTC mood drugs were not developed and are not used for treating true mental illness. Millions of people use these preparation, without ever seeing a physician, to relieve minor anxiety or tension, to induce sleep, or to provide mild stimulation. The history of OTC mood drug use is far older than that of prescription psychotropic drug use. Most of the active ingredients in OTC preparations have been around for some time; many were in use before the 1938 safety statute was passed. Yet even less is known about these chemicals than about the prescription psychotropics. And the issues involved in their use are perhaps more complicated. Certainly the hearings witnesses were more divided in their opinions on what these drugs are good for and what should be done about them than they were in their opinions on prescription psychotropics.

Some witnesses felt that OTC drugs and the whole concept of self-medication are important alternatives to physician care.[27] Without safe and effective OTC compounds, it was reasoned, people might return to home remedies of dubious value and possible harm. In his written statement prepared for the 1975 hearings, Dr. Louis Lasagna of the University of Rochester Medical Center commented on the value of self-medication with OTC sleep-aids and on the people who use these products.

> These mild or occasional insomniacs are just the sort of people who should not be spending their money for doctors' fees, or sitting in busy medical waiting rooms, since such behavior will result not only in expense for the patient, and a wasting of the precious time of already overworked doctors, but a prescription for more potent, more dangerous, and possibly addicting hypnotics.

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[23] Ibid., p. 550.
[24] Ibid., p. 550.
[25] Ibid., pp. 550–551.
[26] Ibid., p. 551.
[27] Ibid., p. 434.

There is, therefore, an important need for OTC drugs, including very mild ones, as a medically and economically sound alternative to prescription drugs for people who insist on medicinal aid for sleep disorders.[28]

Dr. Lasagna concluded his statement by writing, "With proper control of advertising, I see no reason why these drugs should be banned or even discouraged." [29]

Some witnesses felt that OTC mood drugs and self-medication in general are dangerous. The use of such drugs, according to these witnesses, might interfere with proper medical diagnosis and treatment.[30] Dr. David J. Greenblatt of Massachusetts General Hospital in Boston testified that the OTC psychotropics should be subject to prescription regulation, a procedure which would insure that patients were receiving proper medical care.[31] It was argued, however, that such wholesale regulation of OTC mood drugs is not reasonable. OTC stimulants, for example, contain mostly caffeine—about the equivalent of a cup of coffee. It makes little sense to offer these preparation as prescription drugs when caffeine-containing doods are freely available to everyone.[32]

Psychotropic drugs, both prescription and OTC products, are made up of chemicals with wide range of physiological effects quite apart from their mood-altering effects. The following sections of this chapter will discuss these effects—the common, recognized side effects and the important health hazards associated with the use of psychotropic drugs.

B. COMMON SIDE EFFECTS

Like all foreign chemicals, psychotropic drugs can cause side effects in many people who take them. The common side effects of the prescription psychotropic drugs are well-recognized by medical authorities and have not changed since Dr. Jerome Levine of the National Institute of Mental Health described them to the subcommittee in 1969.

The first class of prescription psychotropic drugs is composed of the major tranquilizers. These drugs, also called anti-psychotic agents, are useful in the treatment of severe psychiatric disturbances, such as schizophrenia. The most common side effects of the major tranquilizers include drowsiness, extrapyramidal symptoms such as are seen in Parkinson's disease, and orthostatic hypotension (lowered blood pressure).

The minor tranquilizers make up the second class of prescription psychotropics. These are the "anti-anxiety" agents which work like barbiturates to alleviate anxiety, but they do not cause drowsiness. The most common problem with these compounds is that with prolonged use and/or high dosage, they can produce physiological dependence and true addiction.

Side effects for the third class of drugs, the antidepressants, are generally mild. Dry mouth, blurred vision, and orthostatic hypotension all commonly result from antidepressant use.

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[28] Ibid., p. 1708.
[29] Ibid., p. 1709.
[30] Ibid., p. 1685.
[31] Ibid., 1676.
[32] Ibid., p. 1700.

Drugs of the stimulant class, composed mostly of amphetamines, can cause psychotic paranoia when taken in large quantities. These drugs can also produce psychological dependence and minor physiological dependence.

Long- and intermediate-acting barbiturates are the major chemicals in the sedative class. Drowsiness is the most common side effect caused by these drugs. They can also produce psychological and physiological dependence.

The hypnotics, used for treating sleep disturbances, include two substances: short-acting barbiturate and nonbarbiturate hypnotics. Both subclasses can produce marked intoxication and can depress respiration, a potentially fatal side effect. Both subclasses also produce psychological and physiological dependence. Hypnotic drug withdrawal is extremely severe and can be fatal.

Scientists know less about the side effects caused by OTC mood drugs than they do about those related to prescription psychotropic drug use. Dr. Anthony Kales of Penn State University explained part of the problem in his 1975 testimony.

> It is very difficult to assess quantitatively the side effects of these drugs as compared to prescription drugs. With prescription drugs, the patient not only describes to the physician the severe side effects of a drug but is also likely to indicate the side effects which are less troublesome. In addition the physician is trained to inquire into and assess the effects of the drugs he or she is prescribing. In the case of the nonprescription drugs, only the most severe effects of the drugs are likely to be reported, for example, if the patient overdoses or in some way his or her medical condition is seriously jeopardized. Otherwise, the individual is unlikely to relate less severe side effects to anyone or possibly even be unaware that certain effects are due to the drug.[33]

In talking about the common side effects of OTC mood drugs, one is essentially talking about the side effects of a very few chemicals—scopolamine, methapyrilene, and caffeine—singly or incom bination. Bromine, no longer found in OTC mood drugs, and salicylamide, found infrequently, cause problems of a more uncommon nature.

Scopolamine is a chemical with anticholinergic effects. This means that it blocks the passage of nervous impulses through the parasympathetic part of the nervous system. The results of this anticholinergic activity include blurred vision, increased pressure in the eye, and increased urinary retention. Scopolamine also has the potential for producing mental confusion, excitement, and delirium when it is taken in relatively high doses over a fairly long period of time.[34]

The common side effects of methapyrilene and, for that matter, the other antihistamines sometimes used in OTC mood drugs, include drowsiness and sedation.[35] Antihistamines can also cause restlessness or nervousness in some people. Dry mouth, blurred vision, dizziness, ringing in the ears, and gastrointestinal irritation are some of the more frequent side effects of most antihistamines, including methapyrilene.[36] Antihistamines can also produce facial dyskinesia,[36a] probably as a result of their anticholinergic potential.[37]

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[33] Ibid., p. 1687.
[34] Ibid., pp. 504, 1674, 1676, 1678, 1687.
[35] Ibid., pp. 1676, 1679.
[36] Ibid., p. 440.
[36a] Lacking control of facial muscles.
[37] The Psychotropic Drugs Hearings, pp. 1883, 1884.

Methapyrilene combined with alcohol causes the same sort of addictive central nervous system depression seen when barbiturates are combinations of alcohol.[38] Dr. David J. Greenblatt testified that combinations of scopolamine and methapyrilene, common in OTC sedatives, can cause excitement, hallucinations, delirium, psychosis, and dangerous elevations of body temperature and blood pressure when large quantities are ingested. According to Dr. Greenblatt, cases of intentional overdosage of these readily available drugs are being seen in emergency rooms with increasing frequency.[39]

Even common, garden-variety caffeine has undesirable side effects in some individuals. In sensitive people caffeine can cause nervousness and restlessness.[40]

Several witnesses emphasized that different people respond to these drugs in different ways. What sedates one person may stimulate another. Furthermore, there is no way to determine in advance who will experience some of the more disturbing side effects which can be caused by OTC mood drugs.[41]

C. TARDIVE DYSKINESIA

Tardive dyskinesia, also called "fly-catcher tongue," and a similar condition called akathisia are linked to the chronic use of the phenothiazines and butyrophenones, antipsychotic drugs belonging to the major tranquilizer class. The condition, which usually occurs in the elderly, resembles Huntington's chorea. Its symptoms include slow, rhythmic and involuntary movements of the face and limbs; cheek-puffing; lip-smacking or lip-pursing; undulation of the tongue or repeated tongue thrusts in a "flycatcher" movement; occasional stiffening of the neck and arms; difficulty in swallowing or speaking in severe cases; rotation of the ankles or toes; or wrist and finger movements.

Unlike other psychotropic drug-related conditions which generally fade and completely disappear after the drug is removed, tardive dyskinesia usually develops some months or even years after a patient has been taken off the medication. Tardive dyskinesia has been known to develop, however, in patients who have been taking phenothiazines for no longer than three weeks. By the time tardive dyskinesia is diagnosed in most patients, it is a permanently established condition. Tardive dyskinesia can, however, be reversed if found early enough and if corrective steps are taken as soon as the condition develops.

1. *Psychotropic drugs hearings.*—Dr. Jerome Levine brought up the problem of tardive dyskinesia for the first time during the 1969 hearings.[42] The subject was raised again by Senator McIntyre in the 1971 session.[43] The condition was then only newly recognized by the National Institute of Mental Health even though cases had been reported in the psychiatric journals for years. Senator McIntyre asked if most physicians were aware of the existence of tardive dyskinesia and its association with the use of antipsychotic drugs. Dr. Richard I.

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[38] Ibid, p. 1680.
[39] Ibid., pp. 1675, 1676, 1678.
[40] Ibid., pp. 433, 752.
[41] Ibid., pp. 440, 443, 752, 1674, 1757.
[42] Ibid., p. 5300.
[43] Ibid., p. 533.

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Feinbloom responded that while he could not speak reliably on this specific problem, his impression was ". . . that the general level of understanding about pharmacology, the side effects and contraindications of drugs by physicians in general is not very high." [44] Tardive dyskinesia was not mentioned again at any time during the remainder of the hearings.

2. *1977–78.*—Tardive dyskinesia is still a poorly understood disorder. Research is being conducted to find ways to treat the condition. One such project, involving Dr. Stanley Fahn of Columbia University in New York, is successfully treating tardive dyskinesia with a combination of the drugs reserpine and alpha-methyltyrosine, an experimental compound. While these drugs have proven effective so far in controlling the symptoms of tardive dyskinesia, they have to be used very carefully. Since too high a dosage can induce parkinsonism, the amounts of both drugs must be titrated exactly, a very time-consuming procedure. A fringe benefit of this drug combination is its effect on the original psychosis; it may help control the disorder for which the psychotropic drugs were originally prescribed.[45]

Since about 1973, pharmaceutical manufacturers have included warnings about tardive dyskinesia in the package inserts of all neuroleptics.[46] Despite these warnings and concern over the toxicity of neuroleptics, practitioners appear to have changed their prescribing habits very little since the hearings. The reason may be found in a statement made by the 1973 FDA-American College of Neuropsychopharmacology Task Force and quoted in a recent journal article:

> Because of the lack of adequate substitutes for the neuroleptic drugs in the treatment of psychosis, tardive dyskinesia has been accepted as an undesirable but occasionally unavoidable price to be paid for the benefits of prolonged neuroleptic therapy.[47]

It is estimated that at least 50,000 people will be paying that "occasional unavoidable price" in the next year.[48]

D. CANCER

1. *Psychotropic drugs hearings.*—Dr. William Lijinsky, Director of the Chemical Carcinogenesis Laboratory, Frederick Cancer Research Center in Frederick, Maryland, discussed the possibility of cancer related to methapyrilene in his 1977 testimony before the subcommittee.[49] Methapyrilene, as mentioned earlier, is an antihistamine and a common ingredient of OTC daytime sedatives and nighttime sleep-aids.

Dr. Lijinsky explained that methapyrilene, like many similar antihistamines, is a tertiary amine. As such, methapyrilene can react with nitrite to form dimethylnitrosamine, one of the most potent carcinogens (cancer-causing agents) known. Dr. Lijinsky added that the amount of dimethylnitrosamine produced decreases as the concentration of methapyrilene decreases, but as long as there is some methapyrilene present with nitrites in a mildly acid solution, some dimethylnitrosamine will be formed.

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[44] Ibid., p. 533.
[45] Drug Combination Combats Dyskinesia. Medical World News, October 16, 1978: 16.
[46] A neuroleptic is a neuropharmacologic agent with antipsychotic action affecting principally psychomotor activity.
[47] Horowitz, Joy. The Hidden Cost of Mind Medicines. Human Behavior, May, 1978: 55.
[48] Ibid., p. 54.
[49] The Psychotropic Drugs Hearings, pp. 1727–1731.

During his testimony, Dr. Lijinsky described an experiment he conducted with methapyrilene, nitrite, and laboratory rats.

To demonstrate that the reaction of methapyrilene with nitrite takes place equally well in an animal's stomach as in a flask, a feeding test of the compound in rats was undertaken. Methapyrilene and sodium nitrite were fed to rats dissolved in drinking water for one and a half years. The concentrations were 0.1 percent of methapyrilene and 0.2 percent of sodium nitrite.

At the end of this time, the rats were allowed to die naturally. Nine of thirty rats in the experiment died with liver tumors, whereas there was only 1 rat with a liver tumor in a group of 56 given 0.2 percent sodium nitrite solution for their lifetime.

This high incidence, 30 percent, of liver tumors indicates a potent carcinogenic effect of a combination of methapyrilene and nitrite, and suggests that these two substances together represent a source of dimethylnitrosamine to anyone ingesting them. Since everyone is exposed to nitrites, either that present in cured meats, or in saliva, taking of methapyrilene always poses the possibility of formation of dimethylnitrosamine.[50]

This particular experiment was flawed, as Dr. Lijinsky himself admitted, because it did not look at the effects of feeding methapyrilene alone. So it is possible that methapyrilene by itself could have caused the observed liver tumors. At any rate, there is a strong suggestion the methapyrilene promotes liver cancer in rats.

Dr. Lijinsky expressed a belief that methapyrilene should be banned and that some compound of similar biological activity but unreactive with nitrites be used instead. Another possible solution, according to Dr. Lijinsky, would be to compound methapyrilene with a nitrosation inhibitor such as ascorbic acid.[51]

2. *1977–78.*—The Food and Drug Administration has reviewed Dr. Lijinsky's study on methapyrilene and has concluded that, at least with respect to its use in OTC mood drugs, methapyrilene should be classified as a Category II ingredient—not generally recognized as safe and effective—and taken off the market. The National Cancer Institute in concert with the Frederick Research Center is currently testing methapyrilene for carcinogenic potential. The situation, as it now stands, was summarized in FDA's tentative final orders on OTC mood drugs.

FDA has requested and received assurance from the National Cancer Institute (NCI) that high priority will be given to methapyrilene testing in short term carcinogenicity screening tests developed at the Frederick Research Center; NCI has initiated a carcinogenesis bioassay on methapyrilene at the Frederick Research Center.

In the event that data from these other studies produce evidence that methapyrilene poses a health hazard as a carcinogen, the agency will take appropriate action to remove this active ingredient from the market, whatever its use, i.e., sleep-aid, antihistamine.[52]

E. OTHER HEALTH HAZARDS

A number of health problems, not so common as the recognized side effects discussed earlier in this chapter, associated with the use of psychotropic drugs were mentioned during the hearings. That these problems can arise, albeit rarely, with the use of some psychotropics is an undisputed fact. Therefore these side effects in themselves are not particularly interesting from the standpoint of current research. Indeed, there is no new information on these drug-related problems in the recent literature. These problems are of interest, however, to

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[50] Ibid., p. 1728.
[51] Ibid., pp. 1728–1729.
[52] The OTC Monograph, p. 25544. [See also Appendix E.]

the practitioner whose job it is to monitor the effects of any drug he has prescribed for his patients. They are also important, as they apply to OTC mood drugs, for consumer information.

1. *Agranulocytosis.*—During the 1969 hearings Dr. Jerome Levine named agranulocytosis as a dangerous side effect associated with the use of the phenothiazines, drugs belonging to the major tranquilizer class of psychotropics. In particular the phenothiazine called chlorpromazine has been shown to cause agranulocytosis.[53] Patients with this condition suffer from a severe decrease in the number of their agranuocytes, a type of white blood cell in which the cytoplasm is free of granules. These cells, composed mostly of lymphocytes, are extremely important for the body's ability to fight off infection.

2. *Thombocytopenic purpura.*—Salicylamide, an analgesic compound, is a common ingredient of OTC mood drugs. In large doses salicylamide may cause thrombocytopenic purpura. This disease is characterized by a decrease in the number of blood platelets (important in the blood-clotting mechanism), by hemolytic anemia, bizarre behavioral manifestations, excess urea in the blood, fever, and thromboses (blood clots) in terminal arterioles and capillaries.[54]

Dr. Charles C. Edwards, then Commissioner of Food and Drugs, testified in 1971 that the risk of developing thrombocytopenic purpura from taking the recommended doses of OTC sedatives containing salicylamide is not significant. He added, however, that "* * * there is a risk in regard to this particular drug if used in large enough amounts. Obviously it can be used in large enough amounts if you take enough of this particular drug." [55] This problem—consumers taking more than the recommended dosage of OTC mood drugs and thus increasing their chances of developing serious drug reactions—was mentioned several times throughout the hearings.[56] Witnesses speculated that consumers overdose on these drugs because of the relative ineffectiveness of these preparations when taken in the recommended amounts.[57]

The use of salicylamide, with its potential for causing thrombocytopenic purpura, in OTC mood drugs makes even less sense when one realizes that its efficacy in these preparations is questionable. According to Dr. Edwards, "The rationale for using salicylamide as part of a sleep medication has yet to be established." [58]

In its tentative final order on OTC sedatives and sleep-aids, the Food and Drug Administration has included salicylamides among the Category II active ingredients—agents not generally recognized as safe and effective.[59] After the order is finalized, this compound will be removed from OTC mood drugs.

3. *Glaucoma.*—Witnesses at the 1969 and 1975 hearings touched on the risk of developing glaucoma—a disease of the eye marked by increased intraocular pressure, damage to the optic disc, and gradual loss of vision—associated with use of certain psychotropic drugs. In an arti-

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[53] The Psychotropic Drugs Hearings, p. 5299–5300.
[54] Dorland's Illustrated Medical Dictionary. 25th Edition. W.B. Saunders Company, 1947: 1290.
[55] The Psychotropic Drugs Hearings, p. 439.
[56] Ibid., pp. 1676, 1687, 1691, 1703.
[57] Ibid., pp. 1691, 1703.
[58] Ibid., p. 441.
[59] The OTC Monograph, p. 25566. [See also Appendix E.]

cle from the Medical Tribune, printed in the 1969 hearings record, Dr. Fritz A. Freyhan of St. Vincent's Hospital in New York wrote:

> A recent congress of ophthalmologists was reported to have brought to light an increasing incidence of glaucoma and other serious eye disorders due to antidepressants with anticholinergic effects. The ophthalmologists were critical of the seemingly injudicious use of antidepressants by general practitioners, internists, and psychiatrists, since many patients had repeated episodes of glaucoma prior to the prescription of these drugs and because, in some instances, there had been repeated prescriptions despite the recurrence of serious ocular symptoms.[60]

The antidepressants with their anticholinergic effects can lead to glaucoma, as can scopolamine and methapyrilene, both of which possess anticholinergic activity. Dr. Anthony Kales of Penn State University commented in 1975, "As has been noted by the manufacturers themselves, the recommended doses for these drugs [OTC sedatives and sleep-aids] may precipitate acute glaucoma, especially in elderly patients who have a narrow corneal-iris angle." [61] Here is a serious condition which can be caused by an OTC compound not when it is abused, but when it is taken strictly according to package directions.

The Food and Drug Administration has named both scopolamine and methapyrilene as Category II ingredients for OTC mood drugs. Their use in these products will be banned when the FDA tentative final order is finalized.[62]

4. *Bromism.*—Bromides, usually in the form of the bromide salts—ammonium bromide, potassium bromide, and sodium bromide—have been common ingredients of OTC sleep-aids and sedatives. Bromides produce a sedative effect by displacing chloride in the body; the effect is one of central nervous system depression.[63]

Hearings withnesses warned that bromides are dangerous because they can accumulate in the body.[64] It takes the kidneys about 12 days to remove only half of an ingested dose of bromide. Research findings have suggested that the daily ingestion of the maximum recommended OTC dose of bromides can produce intoxication in about eight days in an average adult.[65]

The symptoms of bromide intoxication, also called bromism, include an acne-like rash, confusion, irritability, tremor, appetite and weight loss, ataxia, stupor, and coma. The American Pharmaceutical Association, in its "Handbook of Nonprescription Drugs," reiterated a finding of the FDA Advisory Review Panel on OTC Daytime and Nighttime Sedatives and Stimulant Products:

> Bromide compounds are unsuitable as sleep-aids or sedatives because single doses produce no effect and continuous use poses a high risk of toxicity.[66]

The FDA has taken the panel's advice and placed bromides in its Category II for OTC drugs. Consumers will not have to wait for the agency's final order before they are no longer exposed to the potential danger of bromide poisoning, however, since bromides are no longer used in OTC sedatives and sleep-aids.

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[60] The Psychotropic Drugs Hearings, p. 5328.
[61] Ibid., p. 1687.
[62] The OTC Monograph, p. 25566. [See also Appendix E.]
[63] Goodman, Louis S. and Alfred Gilman, Eds. The Pharmacological Basis of Therapeutics. Fifth Edition. MacMillan Publishing Company, Inc., 1975: 126.
[64] The Psychotropic Drugs Hearings, pp. 441, 442, 750, 1755.
[65] Handbook of Nonprescription Drugs. Fifth Edition. American Pharmaceutical Association, 1977: 186.
[66] Ibid., p. 186.

III. Health Benefits of Psychotropic Drugs

Quite apart from the problem of adverse health effects caused by psychotropic drugs is the question of how much good these drugs actually do. Most practitioners, as well as the Food and Drug Administration are willing to accept a fair amount of toxicity from a drug which is unequivocally beneficial. Many psychiatrists, for example, believe that the benefits derived from using the major antipsychotic drugs outweigh the risk that the patients will develop tardive dyskinesia.

The question of health benefits from psychotropic drugs can be viewed in two ways. First, it can be seen, in a narrow sense, as a question of efficacy. Do these drugs really have the effects they are supposed to have, according to advertising claims? Do they impart relief from anxiety and tension? Do they induce sleep? Do they provide mild stimulation?

The question can also be interpreted, perhaps more critically, as one of value. Given that the drugs do exert their purported pharmacologic effects, are these effects of value to the consumer? Are sedation, tranquilization, stimulation, and mood elevation of benefit to the ineffects, are these effects of value to the consumer? Are sedation, tranindividual's health? Is a mild degree of insomnia really harmful? Should a person experience or be chemically insulated from the ordinary stresses and strains of modern living?

This chapter will deal for the most part with the OTC sedatives and sleep-aids, the health benefits of which are the most highly disputed of all the psychotropic drugs. Most prescription psychotropics and OTC stimulants—i.e. caffeine—have been shown to be relatively effective. This does not mean, of course, that all people will derive benefits from these compounds. Individual differences make drug responses and drug research a confusing, unpredictable affair.

A. PSYCHOTROPIC DRUGS HEARINGS

Throughout the hearings a great deal of emphasis was placed on the efficacy of psychotropic drugs. In 1969 Dr. Daniel X. Freedman's testimony touched on the National Academy of Sciences National Research Council evaluation of the efficacy of prescription psychotropics, sponsored by the Food and Drug Administration.[67] In 1977 Dr. Karl Rickels discussed the efficacy evaluations made by the FDA Advisory Review Panel on OTC Daytime and Nighttime Sedatives and Stimulant Products.[68] Both groups found drugs on the market for which there were no controlled clinical studies offering proof of efficacy as required by the 1962 Kefauver Amendment.

Most of the testimony on efficacy focused on OTC sedatives and sleep-aids. The underlying theme of all these discussions was one of data insufficiency. There are simply not enough data to prove that

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[67] The Psychotropic Drugs Hearings, pp. 5446–5449, 5452.
[68] Ibid., pp. 1736–1746.

OTC sedatives and sleep-aids are either effective or ineffective in promoting relaxation and sleep.[69]

A few studies, both published and unpublished, were mentioned during the hearings as possible evidence of the inefficacy of these preparations. The first of these studies was conducted by Dr. Karl Rickels and discussed in his 1975 testimony. Dr. Rickels and his colleagues evaluated the action of Compoz, chosen because of advertising claims that it is the largest selling nonprescription sedative for temporary relief of simple nervous tension and because it is typical of preparations containing methapyrilene and/or scopolamine.[70] Results from the Rickels study suggested that Compoz is no more effective either aspirin or an inert placebo in reducing simple nervous tension.[71]

Dr. Anthony Kales reported that he and co-workers found that Sominex, an OTC sleep-aid, had no favorable effect on the sleep of insomniacs.[72] Similar studies with other commercial preparations of methapyrilene alone have concluded that OTC sleep-aids and sedatives are ineffective.[73]

In 1971 Dr. Charles C. Edwards testified that while methapyrilene probably does not hasten the onset or improve the quality of sleep, there is some evidence showing that it does suppress REM sleep—the phase of sleep characterized by rapid eye movements and during which dreams are believed to occur. Dr. Edwards added,

> When a drug suppresses this phase of sleep, withdrawal of the drug can lead to an increase in REM sleep in subsequent nights, accompanied by unpleasant dreams and nightmares. This can in turn lead a person to resume the drug in the belief he needs it for a restful sleep. In some individuals a psychological dependency can thereby be created.[74]

According to Dr. Rickels' 1977 testimony, there is some evidence that OTC sleep-aids may possess mild sleep-inducing properties. Both the Frost study and the Sprouse study, Dr. Rickels testified, showed some evidence of efficacy for OTC preparations.[75]

All of these studies suffer from real methodological problems. In the first place, some of the studies evaluated only methapyrilene while others looked at combination products. This makes it very difficult to compare results from different studies or to make conclusive statements about all OTC sleep-aids and sedatives. In addition, it is very hard to find research subjects with the mild degrees of anxiety, tension, or insomnia for which these products are advertised.[76]

Sleep itself is a very elusive, very difficult factor to quantify. Sleep patterns can vary from night to night. Furthermore, subjects in a sleep experiment might be distrubed by the laboratory setting and thus experience sleep difficulties. Electrodes attached to sleep subjects for monitoring brain waves could interfere with sleep. All of these technical problems make it exceedingly difficult to extrapolate from the sleep laboratory to the home environment.[77]

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[69] Ibid., pp. 447, 478, 505, 780, 1681, 1707, 1743.
[70] Ibid., p. 502.
[71] Ibid., pp. 503, 790.
[72] Ibid., p. 1682.
[73] Ibid., pp. 1675, 1701, 1707.
[74] Ibid., p. 44.
[75] Ibid., p. 1742.
[76] Ibid., p. 1685.
[77] Ibid., pp. 1701, 1707.

In his 1975 written statement, Dr. Louis Lasagna commented that one of these studies not only failed to demonstrate the superiority of methapyrilene over a placebo but also failed to demonstrate the superiority of 100 milligrams of Seconal (secobarbital sodium), "a drug of unquestioned efficacy * * * for many people." [78] Obviously, research on sleep aids is no simple, straight-forward matter.

If these OTC sedatives and sleep-aids are really ineffective from a pharmacological point of view, why do so many people use them? One explanation witnesses suggested is that these preparations are effective as placebos. The products work not because of any pharmacologic action in the body but simply because the person taking them believes that they will induce relaxation or sleep.[79] This "placebo effect" further complicates the task of evaluating the efficacy of OTC sleep-aids and sedatives and it raises another important question: Is the derivation of a placebo effect a valid reason for taking a chemical? At least two of the witnesses, Drs. Edwards and Lasagna, testified that it is a valid reason in certain situations.[80] According to Dr. Lasagna, the mild insomniac who insists on taking sleep medicatiou would be better off using an OTC preparation—even though it may be effective only as a placebo–than to use a potentially addicting prescription hypnotic with its proven pharmacologic efficacy.[81]

It should perhaps be noted here that not even prescription sleep-aids are unquestionably effective all of the time. According to Dr. Anthony Kales, many of the prescription hypnotics are effective only "* * * for 1 or 2 nights, or perhaps at the most a week of consecutive use, and yet most of these drugs are used by insomniacs and prescribed by physicians for much longer periods of time * * *" [82]

The Food and Drug Administration, according to Dr. Rickels' 1977 testimony, decided to deal with the lack of research data on the efficacy of OTC sedative and sleep-aids by placing some of their active ingredients in Category III—insufficient data to permit final classification. Ingredients in this category will be allowed to remain on the market for three years during which time drug companies are expected to develop proof of efficacy. If that proof is not forthcoming, then the ingredients will be removed from OTC mood drugs.

Senator Nelson objected to FDA's plan on the grounds that the Kefauver-Harris Amendments required substantial proof of efficacy for a drug to remain on the market.[83] A simple lack of proof that the durgs are ineffective is not sufficient justification, according to the Senator, for the presence of these products in the marketplace. Senator Nelsno did not understand why FDA was allowing the drug companies more time to produce efficacy data, data which had shown no signs of appearing, rather than just removing all of these products from the market until efficacy studies are provided.[84]

In addition to testimony on simple efficacy, the subcommittee also heard discussions on the value of these drugs to the health of the individual. While most witnesses felt that the prescription psychotropic drugs have contributed a great deal to the health of the mentally ill

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[78] Ibid., p. 1707.
[79] Ibid., pp. 5317, 428, 433, 1683, 1701, 1708.
[80] Ibid., pp. 433, 1708.
[81] Ibid., p. 1708.
[82] Ibid., p.1684
[83] Ibid., p. 1674.
[84] Ibid., p. 1737.

and to the practice of psychiatry, they were somewhat less sanguine on the value of OTC mood drugs, be they pharmacologically effective or not. Dr. Ernest Hartmann, Director of the Sleep and Dream Laboratory of Boston State Hospital, made a salient point when he quoted from the OTC panel report:

> The determination of whether a benefit is produced by a drug must precede testing for effectiveness. The panel recognizes that even the most convincing demonstration of effectiveness in producing a change is worthless of the change is detrimental or there is no benefit to the consumer.[85]

Some witnesses claimed that the relief from simple anxiety, tension, or occasional sleeplessness imparted by these drugs, either by actual pharmacological action or placebo effect, alleviated unnecessary suffering and enabled many people to cope more successfully with their daily lives.[86] Other witnesses objected to any treatment for mild anxiety which, they believed, is an important and necessary part of human existence.[87]

Occasional sleeplessness, for which OTC sleep-aids are advertised, was a real bone of contention for many witnesses. Dr. Robert Seidenberg pointed out in 1971 that ". . . sleeplessness, except in rare and extraordinary instances, is not harmful to mind or body." [88] Dr. Anthony Kales echoed that sentiment in 1975 when he testified that ". . . transient sleeplessness is a normal phenomenon and that transient or partial sleep loss is not extremely deleterious." [89] Dr. Kales argued that sleeplessness is far better treated with counseling, regular exercise, and even warm milk than with sleeping pills.[90]

The FDA Advisory Review Panel on OTC Sedatives and Sleep-Aids was unequivocal in its judgment of the health benefits of these products. The panel made the following statement which became part of its recorded minutes:

> Attempting to "treat" . . . "simple tension" may be similar to attempting to treat anger, annoyance, or for that matter sadnsss, calmness, placidity. We are here in an area of normal or relatively normal variation in mood, and we do not believe this is an appropriate area for pharmacological intervention.[91]

It should be remembered that witnesses had no controlled, prospective clinical studies of the long-term effects of OTC mood drugs on which to base their testimony. Most of the statements made were subjective and do not allow final conclusions to be made about the health benefits of OTC mood drugs.

B. 1977–78

There are still no well-controlled studies proving either that OTC sleep-aids and sedatives are effective or that they are of value to the health of the consumer. FDA's tentative final order on these products has placed daytime sedatives in Category II—not generally recognized as safe and effective. These products will be banned when the orders become final.

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[85] Ibid., p. 1750.
[86] Ibid., pp. 5467, 433, 434, 1708.
[87] Ibid., pp. 5440, 551, 1688.
[88] Ibid., p. 539.
[89] Ibid., p. 1686.
[90] Ibid., p. 1686.
[91] U.S. Department of Health Education, and Welfare. Minutes of FDA Advisory Panel on OTC Sleeping Aids, Sedatives, and Stimulants. Washington, U.S. Government Printing office, 1975.

Despite Senator Nelson's objection, several antihistamines were placed in Category III, which allows the pharmaceutical manufacturers three years from the time the orders are finalized to produce efficacy data. Three of the antihistamines placed in this category are not now available in any OTC preparations. Marketing of these compounds as OTC sleep-aids, recommended by the FDA Advisory Panel, awaits approved new drug applications.[92]

The FDA tentative orders have also placed methapyrilene in Category II because of its suspected role in causing cancer. Therefore, its sleep-inducing abilities are no longer a matter for controversy.

The NAS/NRC study on the efficiency of prescription psychotropics did not, apparently, solve all of the problems. On September 19, 1978, T. Donald Rucker, Ph.D., of the Ohio State University College of Pharmacy, presented testimony before the House Select Committee on Narcotics Abuse and Control in which he listed several psychotropics of questionable value which are still being used in hospitals today. Of these drugs Dr. Rucker commented, "* * * their therapeutic utility is so marginal that the justification for marketing in the first place seems obscure." [93]

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[92] The OTC Monograph, p. 25579 [See also Appendix E.]

[93] Rucker, T. Donald. Prescribing Patterns of Psychoactive Drugs. Statement before the House Select Committee on Narcotics Abuse and Control, September 19, 1978: 6.

IV. Society and Psychotropic Drugs

The effects of psychotropic drugs are not limited to the individual. These mood-altering agents carry with them the potential for affecting society. It is this potential which generates the greatest concern among many people who fear that we, as a society, are approaching a "Brave New World."

A. PSYCHOTROPIC DRUGS HEARINGS

Testimony concerning the effects of psychotropic drug use on society were, for the most part, subjective. Moral judgments on drug use were common. Statements were quite diverse and ran the gamut from, "* * * the American public is literally enmeshed in an orgy of self-medication," [94] to, "I see no data indicating widespread use of the scope that should cause undue alarm." [95] One witness expressed a fear that we are racing pell-mell toward a sensate society in which goal-directed activity is subordinated to pleasure.[96] Another witness commented that most societies use drugs recreationally and that self-medication, properly structured, could conceivably be a useful social practice.[97]

Several witnesses saw the growing use of psychotropic drugs not as a symptom of an emerging hedonism but as an expression of a desire, in our already highly goal-oriented society, to do even better. Dr. Jerome Levine testified in 1969 that

> * * * the drugs are used, by and large, to help people perform better and to cope with life more effectively rather than using them as agents to dull them and to help them escape from their problems.[98]

During that same session, Dr. Bernard Barber of Columbia University expressed a belief that

> * * * most Americans are using the minor tranquilizers to ease some of the stresses of their achievement-oriented activities and to permit them to engage more successfully in those activities.[99]

Both witnesses admitted that these statements represented their impressions of a situation about which there are really no objective data. Dr. Levine added that it is up to society to decide if the enhancement of normal performance is a legitimate use for drugs.[99a] Such a decision could be of central importance to the direction society will take in the future.

Dr. Stanley Yolles commented in 1969, "It is one thing to reverse situations in an illness, but the ability to change what has been considered normal in order to improve the norm is something else again." [1] He asked, as society must ask,

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[94] The Psychotropic Drugs Hearings, p. 507.
[95] Ibid., p. 5439.
[96] Ibid., p. 508.
[97] Ibid., p. 5439.
[98] Ibid., p. 5302.
[99] Ibid., p. 5305.
[99a] Ibid., p. 5303.
[1] Ibid., p. 5276.

> Should athletes take drugs which will enhance their prowess on the track? Should truck drivers take stimulants so that they can drive for longer periods? Should fatigued executives take drugs which will allow them to enjoy the theater at night or be the life of the party at the end of an exhausting day? [2]

In her 1969 testimony the late anthropologist Dr. Margaret Mead attempted to explain why psychotropic drug use is such a volatile issue about which emotions sometimes run high and opinions differ in the extreme. According to Dr. Mead, what we are seeing is a conflict between our traditional religious and moral ethic and our distinctly American emphasis upon finding external solutions to all problems. She commented,

> There is a general emphasis in this country upon finding external solutions to all problems; if you don't like where you are living move somewhere else; if you haven't got any land make it; if you have the wrong shaped nose get it fixed; if you have too big a nose and too small a chin take a piece of your nose and put it on your chin and don't complain that you are going to have to sing in the choir or be a spinster all your life. Right straight through our history we have adopted a policy that invention, technology, ingenuity, resources ought to be available to deal with anything that we want to have dealt with.
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> * * * * * * *
>
> The practical desire to fix things comes into conflict with a belief that some measure of pain is part of man's lot in the world. If you carry that far enough you use no analgesics of any sort in childbirth because pain is what man was born to and woman was condemned to and she should continue to bear the pain.
>
> If you carry the Protestant Puritan ethic far enough people take the attitude that everyone should develop enough character so that they never need anything to support them, except vitamins, and it is even doubtful if they should have too many of them because maybe if you depended on vitamins your character wouldn't develop properly.[3]

Discussions of the social consequences of drug use led inevitably throughout the hearings to discussions of drug abuse, considered to be one cost of using psychotropic drugs to enhance performance. Drug abuse, according to Dr. Stanley Yolles, is not a simple unitary phenomenon.

Dr. Yolles commented,

> Drug use and abuse is a health, legal, social, economic, and moral problem These are extremely complex phenomena in which the major interacting factors are the characteristics of the drug used, the characteristics of the person using the drug, and the characteristics of the society within which the drug is used.[4]

One factor in drug abuse might be our society's belief in the chemical solution to problems. Americans expect more from drugs now than they ever did in the past.[5] The use of drugs to treat drug addiction, such as the methadone program for heroin addicts, is one example of what Dr. Mitchell S. Rosenthal, Director of Phoenix Programs in New York, called " . . . the dangerous public illusion that drugs are a fast, cheap, and magical answer to human and social problems."[6]

Dr. Donald B. Louria, of the New Jersey College of Medicine and Dentistry, whose rather heated testimony compared modern American society to Rome in its last stages of decline, cited excessive self-medication with OTC preparations as another factor in drug abuse.

> Let no one delude himself into thinking there is no nexus between excessive self-medication and use of illegal drugs. Good epidemiological studies show that parents who use inordinate amounts of medicants breed children who have a far greater likelihood of using illicit drugs.[7]

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[2] Ibid., p. 5276.
[3] Ibid., pp. 5458–5459.
[4] Ibid., p. 5279.
[5] Ibid., p. 5313.
[6] Ibid., p. 459.
[7] Ibid., p. 509.

Dr. Anthony Kales testified, "I believe that for youngsters it is a very small step to extend this concept of immediate self-medication of nonprescription drugs to immediate mood alteration with drugs of abuse.[8]

Should drugs be used for recreation and pleasure? Is it legitimate to use drugs to enhance performance? Does our society's attitude toward psychotropic drug use and toward self-medication with OTC preparations create a climate in which drug abuse can flourish? In addition to these questions, witnesses also discussed the effects psychotropic drug use might have on social interaction—the way in which different members of society respond to each other. Dr. Mitchell S. Rosenthal considered this question in his 1971 testomony:

> Another interesting and potentially more important amputation occurs at the level of social interaction and concerns the group and its responsiveness to its own members, Drugs may well amputate or weaken a group's ability to respond to particular psychological reactions among its members, such as anxiety, grief, rage, or other extreme forms of behavior * * *
>
> Psychoactive drugs may diminish the basic human function of concerned, empathic interaction for any group into which they are introduced—families, classrooms, work groups, hospital wards.
>
> The eventual cost in human group relatedness of the widespread decision to substitute a drug medium for an interpersonal one is higher than society should pay. It will contribute still further to the dehumanization process of contemporary society.[9]

B. 1977–78

The effects of psychotropic drugs on society, the overreliance on mood-altering chemicals, the fear of an emerging "Brave New World" are still being discussed today. In January of last year The Washington Post carried an article proclaiming the imminent possibility of

> * * * drugs to expand the childhood sense of curiosity and learning and cut short the turbulence of adolescence; drugs to reduce the psychological need for sleep; drugs to provide a safe, short-acting degree of intoxication; drugs to regulate sexual response; drugs to prolong or shorten memory; drugs to provoke or relieve guilt; drugs to deepen our awareness of beauty and our sense of awe.[10]

The clear possibility, if not probability, of such drugs makes it more important that society find answers to the questions raised during the hearings.

The problem of psychotropic drug abuse, recognized as a growing concern during the hearings, is an international, not a local, problem. In 1971 the World Health Organization held a convention to set up guidelines for controlling psychotropic drugs worldwide. Just before adjournment last year, the 95th Congress, recognizing the United States' responsibility to the world community, enacted S. 2399, a bill to amend the Controlled Substances Act, the Controlled Substances Import and Export Act, the Federal Food Drug, and Cosmetic Act, and the Public Health Service Act to meet obligations under the convention [Public Law 95–633].

It is important to remember that the questions which have been raised during discussions of society and psychotropics cannot be answered with the weight and conviction of scientific fact since the necessary research base does not exist. Dr. Mitchell S. Rosenthal testified in 1971,

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[8] Ibid., p. 1687.
[9] Ibid., pp. 457–458.
[10] Psychic Presto! Getting Ready for The Pick Your Mood Society. The Washington Post, January 10, 1978: B1.

It is especially clear that priority must be assigned to studying the social and psychological implications of extensive psychotropic drug use in addition to their physical effects. A core issue is what are the long-range effects of a chemical solution to social and human problems.[11]

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[11] The Psychotropic Drugs Hearings, pp. 453–454.

V. Advertising and Psychotropic Drugs

A. PSYCHOTROPIC DRUGS HEARINGS

Advertising for psychotropic drugs was a key topic of discussion throughout the hearings. Witnesses made a distinction between advertising for prescription psychotropic drugs and for OTC mood drugs. The former is aimed at the prescribing physician and is carried in medical journals and "throwaway" news sheets, and is provided through direct mailing and company detail men. The latter is directed at the consuming public and appears on television and radio and in popular magazines.

Both forms of advertising were named by several witnesses as major factors contributing to the overuse of psychotropic drugs.[12] Advertising exerts its influence, according to Dr. Charles C. Edwards in his 1971 testimony, by "* * * creating a climate of need in which the consumer feels that reaching for a pill, tablet, or capsule is a panacea for all of his ills."[13] Advertising for prescription psychotropics has extended the indications for their use. These drugs were originally and legitimately approved for the treatment of true mental illness. But the symptoms of psychiatric disorders—symptoms such as anxiety, tension, frustration—can appear in anyone and arise as a normal part of daily living. Advertisers have taken these symptoms out of context and applied them to the day-to-day situations with which everyone is confronted. Drug ads, according to Dr. Mitchell S. Rosenthal, imply that the normal problems of life are medical-psychiatric conditions requiring chemical intervention. "Such advertisements," testified Dr. Rosenthal, "present a grossly oversimplified conception of human behavior and of behavior change."[14] Dr. Rosenthal added,

In its attempt to increase the market for its products, the pharmaceutical industry is redefining and relabeling as medical problems calling for drug intervention a wide range of human behaviors which, in the past, have been viewed as falling within the bounds of the normal trials and tribulations of human existence.[15]

Dr. Rosenthal's sentiments were echoed by several other witnesses. Dr. David C. Lewis of Harvard Medical School commented,

The part of that [advertising] effort that I find most disturbing is the kind of advertising whose main intent, I feel, is to convince physicians that psychoactive drugs may be indicated for the normal functioning of large numbers of our population. In essence, it attempts to widen our concept of what we call disease.[16]

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[12] The Psychotropic Drugs Hearings, pp. 426, 466, 468, 543, 544, 742, 769, 1674, 1675.
[13] Ibid., p. 426.
[14] Ibid., p. 452.
[15] Ibid., p. 452.
[16] Ibid., p. 468.

In an earlier session of the hearings, Dr. Richard C. Pillard, of Boston University School of Medicine, quoted from a report to the trustees of the American Psychiatric Association:

> Many of the advertisements for psychotropic drugs in the medical and psychiatric literature expand the indications for these drugs beyond their use in mental illness to include their use as palliatives to ordinary problems of living.[17]

Dr. Robert Seidenberg testified in 1971,

> A 10-year survey showed that many of the advertisements in the above publications vigorously "push" the use of these drugs to psychiatrists as well as to other physicians as the 'treatment of choice' before psychotherapy or possible social action, often for life situations and problems beyond the traditional medical and psychiatric concepts of illness or diseases; through picture and text, the psychiatrist as well as other physicians are being advised to prescribe "mind drugs" for an ever-expanding variety of conditions, old and newly conceived, in addition to their use as "needed" adjunts to relieve the "anxiety" accompanying practically every medical illness and surgical procedure.
>
> We see pictures and captions of women distressed by washing dishes or giving a child a bath, of athletes who must be quickly returned to the game, or men who are irritated by environment noise, et cetera—conditions hardly psychiatric diseases.[18]

By extending the indications for psychotropic drugs to the normal problems of life, advertisements have created a need for the drugs. Dr. Levine summed up the situation when he commented that "* * * once daily living is defined as disease, how logical it is for us to treat that disease."[19]

Not only has advertising for prescription psychotropic drugs extended the indications for these drugs from the treatment of true mental illness to the stresses of daily living, but it has also, according to several witnesses, actually created new mental illnesses—conditions such as "behavioral drift" and "environmental depression."[20] Drug advertising also proposes that psychotropic drugs be used as a solution to what Dr. Richard I. Feinbloom sees as essentially political problems. In his testimony, Dr. Feinbloom quoted from a Ritalin advertisement ment which recommended that the drug be used for depression "* * * engendered by such problems as the constant assault of noise on the eardrums, frustrations from situations out of control, ecologic pollution, and social unrest."[21]

In addition to the drug advertisements in medical journals and "trowaway" news sheets, the prescribing physician is the target of drug detail men, promotional mailing, and free drug samples. Medical journals depend upon drug advertising for a large chunk of their revenues, scientific meetings are sponsored by drug companies, even the graduating medical student is remembered with a free black bag and set of instruments. Dr. David C. Lewis estimated that drug companies spend about $4,000 per physician per year on promotional efforts.[22]

Similar tactics are used in the advertising for OTC mood drugs. In this case, however, the effects of such advertising may be more serious since the consumer has no medical expertise on which to rely. In 1971 Dr. Charles C. Edwards testified,

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[17] Ibid., p. 5409.
[18] Ibid., p. 536.
[19] Ibid., p. 471.
[20] Ibid., pp. 427, 536, 744, 810, 5373.
[21] Ibid., p. 519.
[22] Ibid., p. 472.

There is no meaningful way for the consumer to weigh the need for such a drug. In the case of prescription drugs, there is a body of professional opinion, the physician, who can make the decision whether are not such a drug should be used.[23]

According to Dr. Edwards, there is no medical necessity for these preparations and a market for these products has been created by advertising.[24] These advertisements have accomplished this feat, in the main, first by convincing people that they are sick and then by advising them not to suffer any pain or discomfort, however mild, for more than a few seconds.[25] Dr. Lewis illustrated the first ploy with a Sominex commercial which implies that you are abnormal if it takes you longer than 15 minutes to fall asleep. The advertisement fails to note, as Dr. Lewis pointed out, that normal sleep patterns can vary a great deal from night to night.[26] Most people have seen ads which proclaim a drug's speed as its major virtue.

According to Dr. Kales' testimony in 1975, OTC drug advertisements also create a need for their product by creating fear.

A major concern of mine is that the current advertising for nighttime sedatives contributes greatly to the public developing an acute fear of sleeplessness which is in itself a major factor underlying the problem of insomnia. Advertisements for these drugs suggest that there is a need to treat temporary or transient and partial sleeplessness and in so doing there is an implication that such transient and limited sleep loss is very deleterious.

In terms of the daytime tranquilizers, advertisements for these drugs help to create a fearfulness of anxiety and in some respects this type of fear may be even more harmful than the fear of sleeplessness. Certain levels of anxiety are part and parcel of our everyday lives and serve a useful purpose in providing us with warning signals. Yet these advertisements give the impression that mild levels of anxiety are to be avoided and actively treated.[27]

During the 1971 session, staff economist Benjamin Gordon read two statements from the Code of Advertising Practices of the Proprietary Association:

Depiction of consumers continually relying on medicaines as sibplistic solutions to emotional or mood problems should be avoided.

Advertising for proprietary medicines should avoid representations by word or picturization which, in reasonable construction, are commonly associated with the "drug culture," or which imply a casual attitude toward the use of drugs.[28]

Witnesses present at the time agreed that these provisions of the code are violated commonly.[29]

While witnesses were of one mind on the problems of advertising, they could not agree on how those problems should be handled. Some witnesses felt that all prescription drug ads should be banned from medical journals.[30] Others believed that the journals would fold without the revenues provided by drug advertising and that, at any rate, drug ads do provide some useful information on new drugs.[31] Many witnesses felt that OTC drug advertisements should be banned from television or at least be made subject to approval by some central agency of the government.[32] Education, both for the prescribing phy-

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[23] Ibid., p. 432.
[24] Ibid., pp. 427, 432.
[25] Ibid., pp. 450, 476, 777, 798.
[26] Ibid., p. 477.
[27] Ibid., p. 1686.
[28] Ibid., pp. 552–553.
[29] Ibid., p. 553.
[30] Ibid., pp. 5320, 5321, 5411, 5412, 5414, 5418, 527, 528.
[31] Ibid., pp. 5339, 5432, 499.
[32] Ibid., pp. 541, 543, 602, 620, 1687, 1688, 1690.

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sician and the consumer, to combat the effects of drug advertising, was also suggested.[33]

Dr. Edwards testified in 1971 that the FDA had begun to deal with the problem of misleading advertising by requiring FDA clearance on all promotional material for any new product which was about to be introduced.[34] This applies only to prescription psychotropic drugs, however, since the FTC and not the FDA has jurisdiction over advertising for OTC products. The FTC, according to Ms. Joan Bernstein, is waiting for a final FDA monograph on mood drugs before implementing general rules on advertising for these preparations.[35]

B. 1977–78

The advertising problems discussed during the hearings still exis[t] today. Advertising still plays an important role in a physician's choice of prescription drug.[36] And, since FDA's final monograph on OTC mood drugs has yet to appear, FTC has yet to make its final decisions on proposed rules to control misleading advertising for these products.

On September 19, 1978, Dr. John Pekkanen testified before the House Select Committee on Narcotics Abuse and Control that the drug industry spends about $5,000 a year on each and every one of the approximately 200,000 practicing physicians in this country. Some 20,000 drug detail men are employed in representing the drug company and its products directly to the practitioner.[37] The impact of advertising on drug prescription and use is a significant matter.

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[33] Ibid., pp. 5317, 5318, 5324, 5330, 5341, 5347, 5349, 5412, 5414, 5418, 522.
[34] Ibid., p. 430.
[35] Ibid., pp. 1712, 1713.
[36] Smith, Mickey C. Appeals Used in Advertisements for Psychotropic Drugs: An Exploratory Study. American Journal of Public Health, February, 1977: 171–173.
[37] Pekkanen, John. Statement Before the U.S. House of Representatives Select Committee on Narcotics Abuse and Control, September 19, 1978: 2.

VI. The Federal Government and Psychotropic Drugs

During the hearings the subcommittee heard testimony from witnesses representing the Food and Drug Administration, the Federal Trade Commission, and the Federal Communications Commission. It was the subcommittee's intention, in particular, to ascertain what the Government agencies, which were established to protect the public, planned to do about the marketing and advertising of OTC mood drugs in light of the testimony on the established hazards and dubious benefits of these products.[38]

A. THE FEDERAL COMMUNICATIONS COMMISSION

1. *Psychotropic drugs hearings.*—In his opening statement to the September 22, 1971 session, Senator Gaylord Nelson listed the following questions the subcommittee wished FCC witnesses to discuss:

(1) What can the Commission tell us about the quality of advertising of analgesics and mood altering drugs which are presented to the public through FCC licensed facilities?

(2) Does the Commission feel that this advertising contributes to intelligent self-medication of the public?

(3) Is the use of publicly owned, scarce frequencies for this type of advertising, as the law reads, "in the public interest, convenience, and necessity?"

(4) What has the FCC done and what can it do to protect the public against harmful advertising? [39]

FCC Chairman Dean Burch responded to the Senator's questions, in essence, by shifting the emphasis to the Federal Trade Commission. According to Chairman Burch,

This Commission, the FCC, has neither the facilities nor the expertise to evaluate claims going to a drug's effectiveness or its superiority over other products. That authority, and the means to exercise it, have been given to the FTC—which looks to the Food and Drug Administration for scientific backup—with respect to all products sold in interstate commerce. Moreover, and of equal importance, the FTC's authority in the matter is plenary. It reaches to all modes of advertising—print, broadcasting, even labeling and packaging.[40]

Chairman Burch also explained that FCC's authority is over broadcast licensees, not advertisers.

You know, we have no jurisdiction over advertisers. We do not order advertisers to do or not do anything. The only jurisdiction we have is over licensees. We can't force an advertiser to run an ad that cleans up something * * * I do not think we have any injunctive power to go out to Proctor and Gamble and say you are going to spend $1 million on a new ad.[41]

While Chairman Burch agreed that drug abuse is an important national health problem, he stressed that

* * * the determination of any correlation, direct or indirect, between drug abuse and the advertising of over-the-counter pain relievers, sleeping aids, stimulants, and tranquilizers is wholly outside of the Commission's expertise—as well as that of the typical broadcast licensee.[42]

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[38] The Psychotropic Drugs Hearings, pp. 559, 1675, 1770.
[39] Ibid., p. 559.
[40] Ibid., p. 562.
[41] Ibid., pp. 606–607.
[42] Ibid., p. 588.

He also noted that drug advertising is a substantial source of broadcast revenue, revenue which is important for a healthy broadcast industry.[43]

It was Chairman Burch's final opinion and recommendation that "* * * the determination to ban the advertising of any class of drug products should and must be left to Congress—and that they should draw on the best available expert advice."[44] The precedent for congressional action was established, according to Mr. Burch, when Congress banned the advertising of cigarettes over the electronic media.

With the exception of FCC Commissioner Nicholas Johnson, the other FCC witnesses present agreed with opinions expressed by Chairman Burch. Commissioner Houser summarized this position in his testimony:

> * * * the Federal Communications Commission has neither the manpower, the special expertise, nor the overall regulatory responsibility necessary to shoulder the primary role in drug advertising review, regulation and enforcement.[45]

Interestingly—and perhaps contradictorily—enough, he added the statement,

> I am also pleased with the Chairman's pledge to you today that our agency will do all that is within its capacity to contribute to the solution of a problem which appears to be escalating.[46]

The one dissenting witness, Commissioner Johnson, testified that, contrary to the chairman's statement, the Commission has adequate procedures to handle the advertising problem. All that is necessary, Mr. Johnson felt, is the will to act:

> I think the procedures are there. I think it is a simple matter of the will to act, and when this Commission wants to move immediately, we can.[47]

When asked by staff economist Benjamin Gordon why the FCC has not established standards for evaluating drug advertising, Commissioner Johnson replied,

> * * * I think it is fair to say, historically these are simply areas in which the FCC has not desired to involve itself. We are gradually changing in some areas involving public access and right of response to commericals and so forth, largely because of the court of appeals forcing us to in reversing our decisions. And I think there may be some changes here as well. But, historically the FCC has not really concerned itself with either programming or advertising, and especially not advertising.[48]

He added that he knows of no instance in which a broadcaster has lost his license "* * * because his advertising has had an adverse impact upon the community."[49]

Mr. Johnson also disagreed with Chairman Burch in his evaluation of the Commission's ability to deal with questions requiring scientific expertise:

> In the cigarette area, we had no difficulty reading the Surgeon General's report and responding to it is our rulemaking, although presumably that would have required some scientific expertise.
>
> Even in the area of the drug problem, we had no difficulty whatsoever in concluding that rock music was contributing to the drug problem in America and issuing a rulemaking, and I would note on fairly short notice, dealing with what

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[43] Ibid., pp. 590–591.
[44] Ibid., p. 589.
[45] Ibid., p. 720.
[46] Ibid., p. 720.
[47] Ibid., p. 600.
[48] Ibid., p. 600.
[49] Ibid., p. 599.

I presume are equally difficult issues, as those involved here. We issued a notice in fairly short order providing that broadcasters have a special responsiblity to review, and presumably to remove from the air, song lyrics that have to do with the drug problem. Presumably that involves some scientific expert in the field finding a correlation between rock music and drug abuse. I am not aware of the scientific studies that back up the Commission's judgment, but we were prepared to make it in that particular area.[50]

Commissioner Johnson expressed a belief that "The FCC has a responsibility for making a judgment that these ads are serving the public interest, convenience, and necessity." He added, "And I would suggest that they are serving none of those, and that we would be falling within our rights in simply banning this advertising."[51]

Commissioner Johnson made several recommendations, chief among which was the suggestion that Congress establish one single agency with jurisdiction over the entire field of advertising. That responsibility is now divided among three agencies—the FDA, FTC, and FCC—none of which is equipped to deal with all of the advertising involved in the drug problem.[52]

2. *1977–78.*—Since the hearings were adjourned, there have been no changes in FCC policy relevant to the advertising of OTC mood drugs over the electronic media.

B. THE FEDERAL TRADE COMMISSION

The FTC has authority over all advertising for over-the-counter preparations. The agency has been actively engaged in identifying and prohibiting false and misleading advertising for OTC products on a case-by-case for some time. This process is, however, extremely. time-consuming; some cases have required years for their resolution. Obviously, some more efficient way must be found to handle this advertising.

1. *Psychotropic Drugs Hearings.*—In 1975 Joan Z. Bernstein, Acting Director of FTC's Bureau of Consumer Preotection, explained the agency's plans for handling OTC drug advertising. According to Ms. Bernstein,

> * * * it is presently the Commission's general policy to avoid taking formal action in most cases concerning over-the-counter drug advertising until a monograph for the appropriate drug category has been established by the Food and Drug Administration under its current over-the-counter drug review program.[53]

She added,

> * * * where advertising puts into an issue the absooute efficacy or safety of a particular product, matters specifically encompassed by the FDA monograph program, there are compelling reasons for the Commission to await the outcome of an FDA review of the relevant drug category. FDA has the greater resources and expertise in this area. It has developed a comprehensive program for systematically evaluating every ingredient which appears in over-the-counter drug product. The experts serving on the FDA panels are eminent medical scientists. It would be extremely costly, if not impossible, to duplicate the massive program FDA has undertaken. Clearly, such action by FTC would be wasteful of tax dollars.[54]

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[50] Ibid., p. 601.
[51] Ibid., pp. 602–603.
[52] Ibid., pp. 502–610.
[53] Ibid., p. 1712.
[54] Ibid., p. 1712.

Once the final monograph appears, the Commission plans to proceed by substantive rulemaking under the Magnuson-Moss Amendments to the Federal Trade Commission Act to prohibit false and misleading advertising for OTC drugs. This procedure should, Ms. Bernstein testified, be more efficient than case-by-case litigation. Ms. Bernstein made it clear that this plan does not preclude any FTC action on OTC drug advertising before the final monograph appears. "In some cases," she commented, "it may not be appropriate to await an FDA determination before the Commission taxes action.[55]

During a 1977 session of the hearings, Wallace S. Snyder, Acting Assistant Director of FTC's Division of National Advertising, discussed two rulemaking proceedings for OTC advertising in which the Commission is involved. The first of these, known as the FTC claims rule,

> * * * Would prohibit advertisers, in describing the therapeutic benefits of their OTC products, from using language which has not been approved for labelling once the FDA has published its final monograph and order for a particular category of drugs.[56]

The claims rule, according to Mr. Snyder,

> * * * would make the labelling restrictions effective immediately upon the publication of each individual monograph and order by FDA, so as to eliminate any lag between the effective date for regulation of an OTC ingredient and the regulation of advertising for the same ingredient.[57]

The second rule, referred to as the antacid warning rule, addresses the question of

> * * * whether label warnings as a general rule should be disclosed in advertising, or at least whether certain of the warnings required by FDA in the case of antiacids are of sufficient import or application among consumers to warrant disclosure in advertising. In addition, the rulemaking would consider the form and frequency with which any such warnings should be disclosed in advertising.[58]

Mr. Snyder expressed a hope that the antacid warning rule might serve as a guideline for similar rules for other OTC drugs. Mr. Snyder testified, as did Mr. Bernstein, that this rulemaking approach should be more efficient than the case-by-case litigation now in use. This approach should also, according to Mr. Snyder, prove to be more flexible and more equitable, and it should allow greater participation of industry, consumers, and public interest advocates in the decision-making process.[59]

2. *1977–78.*—The FTC is still waiting for the FDA's final monograph and order on OTC mood drugs before acting on the advertising for those products.

C. THE FOOD AND DRUG ADMINISTRATION

While the Food and Drug Administration has jurisdiction over the advertising for prescription drugs, it has no authority over OTC drug advertising. The FDA does have the authority, however, to remove OTC drugs from the marketplace if they do not meet the requirements of safety and efficacy as established by the Kefauver-Harris Amendments. The FDA is now engaged in a program to evaluate safety and efficacy for all OTC drugs by class, reasoning that such an approach is more logical and efficient than a product-by-product evaluation.

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[55] Ibid., p. 1712.
[56] Ibid., p. 1791.
[57] Ibid., p. 1792.
[58] Ibid., p. 1792.
[59] Ibid., pp. 1792–1793.

1. *Psychotropic drugs hearings.*—In 1977 Dr. Karl Rickels, former chairman of the FDA Advisory Review Panel on OTC Daytime and Nighttime Sedatives and Stimulant Products, testified on the penal's and its recommendations to the Food and Drug Administration. The panel's report was released and published in the Federal Register on December 8, 1975. Dr. Donald Kennedy, FDA Commissioner, also testified on the OTC mood drug monograph in 1977, explaining, at that time, that a final monograph was expected to be published by the end of the summer. As of this writing, the final monograph and order has yet to apear.

Of all the mood drug ingredients the panel reviewed, only caffeine was placed in Category I—generally recognized as safe and effective. Bromides, scopolamine, and a host of miscellaneous ingredients—things like vitamin B and passion flower extract—were placed in the not generally recognized as safe and effective category. The antihistamines were placed in Category III, a special classification which allows an ingredient to remain on the market for three years while the manufacturer develops proof of efficacy.

The creation of Category III was a particular problem for several of the panel members and for Senator Nelson, none of whom understood why the drug companies should be given three more years on top of the 15 years they had already enjoyed since the passage of the Kefauver-Harris amendments. Panel member Dr. Frances S. Norris testified,

> I have always had reservations about the legality, or at least the justificability, of the FDA's establishment of category III because it contradicts the existence of category I and category II. A drug either is or is not considered safe and effective.[60]

Regardless of FDA's reason for establishing Category III, Senator Nelson did not believe the classification criteria met the requirements of the law.[61]

2. *1977–78.*—FDA published the tentative final order on OTC drugs in the Federal Register on June 13, 1978. The agency made two important changes from the panel's original report. First, the FDA placed all daytime sedatives in Cateogy II since the hazards sssociated with drowsiness—a common side effect—during daytime working hours far outweighs the disputed benefits of these products. Second, the antihistamine methapyrilene was moved to Category II based on preliminary findings that the compound may promote liver cancer. FDA's final order is expected to be published sometime in 1979.

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[60] Ibid., p. 1741.
[61] Ibid., pp. 1741, 1742.

VII. Public Policy and Psychotropic Drugs

Hearings witnesses discussed a number of issues important for public policy. These issues, including consumer information, physician education, governmental regulation of drug use, research and manpower needs, and the question of who is ulitmately responsible for drug overuse and abuse, are still important, unresolved issues today.

A. CONSUMER INFORMATION AND EDUCATION

Dr. William H. Forrest, Jr., of Stanford Medical School, focused his testimomy on the problems of consumer information and their possible solutions According to Dr. Forrest,

> The consumer needs accurate and understandable information about the active ingredients in each product he may want to buy over the counter. Today the consumer is seldom given this information—not on the package he sees on the shelf, and certainly not in the advertising on radio, television, or in print.[62]

Dr. Forrest stressed the fact that consumers, who have almost a greater need for information than physicians because they have no medical training or experience on which to draw, get far less information on OTC products than physicians do on prescription drugs.

> The Food and Drug Administration's present regulations make it possible for a doctor to get essential information about the ingredients in such drugs, and about their benefits and side effects. But when it comes to nonprescription or over-the-counter medications, the situation is very different even, though the basic goal of benefitting the patient is the same. Usually a nonphysician—consumer, relative, or friend—will decide whether a certain medicine is to be used. This person has a greater need for information than a physician, because his or her knowledge is less. But the packages and advertising are woefully lacking in pertinent facts.[63]

Dr. Forrest and other witnesses did not think that OTC mood drugs should be taken off the market.[64] Rather, the consumer should be given the facts about these products and in a form which enables him to make an intelligent choice.[65] Consumers are, more and more, accepting the responsibility for that choice and asserting their right to make the final decision given fair and accurate promotional material.[66]

Dr. Forrest recommended that all OTC drug labels provide the following information: (1) A list of every active ingredient; (2) the amount of every ingredient in a tablet, capsule, or liquid dose; (3) ingredient amounts in milligrams so that different products can be compared; (4) a brief explanation of why each ingredient has been included; and (5) contra-indications. All of this information, testified Dr. Forrest, should be placed on the outside of the package in clear, legible type, and should be included in any advertisement for the product. Dr. Forrest also recommended that the authority to control OTC drug advertising be transferred from the FTC to the FDA,

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[62] The Psychotropic Drugs Hearings, p. 1393.
[63] Ibid., pp. 1693–1694.
[64] Ibid., pp. 433, 434, 1700.
[65] Ibid., p. 1698.
[66] Ibid., pp. 1700, 1702.

the agency with the technical expertise to evaluate safety and efficacy of nonprescription products.

At the end of Dr. Forrest's testimony, Dr. Anthony Kales raised an interesting question with respect to consumer information, rights, and responsibilities. Dr. Kales wondered if the consumer can really make a reasoned decision unless nondrug options are spelled out along with the detailed drug information. He commented,

> I just wanted to add in relation to what Dr. Forrest said, because I guess the major theme that comes through in what he related, (is) that the consumer has a choice, that he makes a decision after he has all of the information, but my feeling is that you really would want to make a choice when you have a fair balance, when you look at a product, even if it had all of the information that he described, you look at a television ad, which had all of the information you described, you would be getting only one side of the information.
>
> The other side, from my standpoint, is that the consumer also has a choice not to take this medication, and to do other kinds of things, and these other kinds of things are not described in the ads, or in the label, so that I think, yes, in a way, the consumer can make the final choice, but he has to have both sides of the story, and the advertisements obviously give one side of the story.[67]

B. PHYSICIAN EDUCATION

The overprescription of psychotropic drugs was cited as a serious problem in itself and as a contributing factor to the drug abuse scene by several witnesses. A major reason for the problem, witnesses agreed, was the lack of adequate physician education in basic pharmacology and in psychopharmacology. Most medical students take only about 6 semester hours of pharmacology. Later, as practicing physicians, they rely too heavily on drug ads and detail men for their information about the drugs they prescribe. Witnesses testified that pharmacology needs to receive greater emphasis in medical schools and that some program should be developed to provide physicians with a steady flow of continually updated drug information.[68] The key to solving much of the overprescription problem, witnesses felt, is better physician education.[69]

Part of the problem in physician education is a phenomenon which has been called the "knowledge-performance gap." How do you translate the knowledge gleaned from new research into improved clinical practice? Dr. Fritz A Freyhan of St. Vincent's Hospital in New York commented,

> What seems to me discouraging, if not alarming, is the widening of a gap between advances in experimental and basic pharmacological research on the one hand, and the actual quality of clinical treatment on the other hand. One should not, as often seems to be the case, take it for granted that medical research and resulting clinical application could be regarded as two sides of the same coin.[70]

Dr. Daniel X. Freedman was similarly concerned about the problem of information dispersal.[71] Should the solution to this problem come

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[67] Ibid., p. 1704.
[68] Ibid., pp. 5317–5318.
[69] Ibid., pp. 5341, 5343, 5347, 5349, 5431.
[70] Ibid., p. 5329.
[71] Ibid., p. 5450.

from the Federal Government, industry, the medical community, or a combination of all three? No one has yet found an answer that takes into account limitations of money and time and that permits the physician to engage in the creative practice of medicine.

The problem of physician education has not changed since the hearings. Dr. John Pekkanen stated on September 19, 1978 that "* * * despite what the public rightfully expects of doctors, most of them in fact have not had adequate education or training in the use of psychoactive drugs." [72]

C. RESPONSIBILITY

Who is ultimately responsibile for psychotropic drug overuse or the overuse, for that matter, of any drug? The answer is not simple and witnesses agreed that responsibility must be shared by the drug industry, the prescribing physician, the medical community as a whole, and the consumer.

False or misleading advertising encourages physicians to prescribe unnecessarily and creates a climate of need among OTC drug users. The physician, too busy to counsel an unhappy patient or too ill-informed on psychopharmacology, writes a drug prescription. The consumer, fully convinced of the magic of drugs, pressures the physician to prescribe, or seeks relief in self-medication. The medical community, having grown dependent upon revenues from the drug industry, tolerates misleading advertisements in medical journals and drug promotion at scientific meetings.

Dr. Fritz Freyhan testified in 1969, "It should be the responsibility of editors of medical journals and, in the last analysis, of every practicing physician, to develop greater resistance to seductive promotion of these agents." [73] Dr. Freyhan might have added that the same responsibility lies with the consuming public if it truly wishes to exert its right of personal mastery in health care.

D. GOVERNMENTAL REGULATION OF DRUG USE

One solution to the psychotropic drug problem offered by witnesses was tighter governmental controls of the marketing and advertising for these products. Two major objections to the solution was raised. The first, voiced by Sociologist Bernard Barber and echoed by anthropologist Margaret Mead throughout her testimony, was that a "police-punitive policy" would inevitable result in predictable and disastrous consequences to society. Professor Barber testified,

> As strongly as I can, I wish to urge that we continue to pursue the present social-medical policy that we have toward psychotropic drug abuse and that we avoid turning to the police-punitive policy which has been so ineffective, perhaps I might even say so disastrous, with regard to other "dangerous drugs" such as marihuana and heroin.
>
> * * * * * * *
>
> A police-punitive policy has little beneficial effort on the disturbed social and psychological functioning of the abusers. And worse, it is a policy that leads to a whole set of harmful secondary consequences for society. Without helping the abusers, we heap on ourselves a new set of troubles.
>
> We get racketeering; we get police brutality and corruption; we often get prostitution and petty crime to acquire money to pay the racketeers their exor-

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[72] Pekkanen, John. Statement before the U.S. House of Representatives Select Committee on Narcotics Abuse and Control. September 19, 1978: 3.

[73] The Psychotropic Drugs Hearings, p. 5338.

bitant prices for the banned drugs; and we get disrespect for the law and for a society which obviously enforces ineffective and unnecessarily harsh laws.[74]

Other witnesses objected to tight governmental control because it would interfere with creative research and the innovative, flexible practice of medicine Dr. Daniel X. Freedman testified in 1969,

But you cannot program—you cannot make rules without reason—reasoning is more important than rule. I don't want to be the doctor telling people how they must use psychotropic drugs. I will tell them why I think they must use it in this way. And I would like to join an argument and a good scientific debate and see what we can learn. That is what good medical practice is all about.

But it means that there is a limit on the extent to which you can program what has to be done. Science works by improved consent among peers—not by fiat.[75]

Later in his testimony Dr. Freedman explained that the government and public must understand that legal regulations and control cannot guarantee the quality and integrity of health care. He added,

If the appropriate practice of medicine requires flexibility, then we cannot program regulations to the nth degree; many new and useful drugs could be lost by scientifically useless regulations.[76]

E. RESEARCH AND MANPOWER NEEDS

A final issue worth noting is the problem of insufficient psychotropic drug research and researchers. This issue, while it received little direct attention during the hearings, could be considered a central factor in the whole psychotropic drug question. Indeed, if this problem did not exist, if there were adequate research—both basic and clinical—on these drugs, then the necessity for these hearings might never have arisen. All the other problems related to psychotropic drugs—problems such as drug overuse, abuse, health hazards, marketing approval, and advertising—might not exist if the research base from which to answer those problems existed.

Dr. Stanley Yolles, the very first witness in this series of hearings, decried the lack of good research and objective data on psychotropic drugs and called for the development of new knowledge, the establishment of manpower training programs, and the creation of a system by which the fruits of such research might be fed into the treatment system.[77] His sentiments were shared by other witnesses who, while they were concerned with the psychotropic drug abuse problem, felt that science must and should continue its research on these chemicals.[78]

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[74] Ibid., p. 5306
[75] Ibid., p. 5448.
[76] Ibid., p. 5452.
[77] Ibid., p. 5279.
[78] Ibid., pp. 5298, 5325, 5329.

APPENDIXES

Appendix A—Witness List

(Alphabetical list of witnesses, by volume, who presented statements during the Psychotropic Drugs Hearings)

Competitive Problems in the Drug Industry (Volume 13)

Statement of—

Balter, Dr. Mitchell, Chief, Special Studies Section, Psychopharmacology Research Branch, National Institute of Mental Health; accompanied Dr. Stanley F. Yolles, Director.

Barber, Bernard, professor and chairman, Department of Sociology; Barnard College, Columbia University, Braeside Lane, Dobbs Ferry, N.Y.

Brill, Dr. Henry, director, Pilgrim State Hospital, Box 22, West Brentwood, Long Island, New York, N.Y.

Freedman, Dr. Daniel X., professor and chairman, Department of Psychiatry, University of Chicago, 950 East 59th Street, Chicago, Ill.

Freyhan, Dr. Fritz A., director of research, Department of Psychiatry, St. Vincent's Hospital, 153 West 11th Street, New York, N.Y.

Levine, Dr. Jerome, Chief, Psychopharmacology Research Branch, National Institute of Mental Health, Department of Health, Education, and Welfare, 5454 Wisconsin Avenue, Chevy Chase, Md.; accompanied Dr. Stanley F. Yolles, Director.

Mead, Dr. Margaret, curator emeritus of ethnology, the American Museum of Natural History and adjunct professor of anthropology, Columbia University.

Pillard, Dr. Richard C., assistant professor of psychiatry, Boston University School of Medicine, 80 East Concord Street, Boston, Mass.

Yolles, Dr. Stanley F., Director, National Institute of Mental Health, Department of Health, Education, and Welfare, 5454 Wisconsin Avenue, Chevy Chase, Md.; accompanied by Dr. Jerome Levine, Chief, Psychopharmacology Research Branch, National Institute of Mental Health; and Dr. Mitchell Balter, Chief, Special Studies Section, Psychopharmacology Research Branch.

Advertising of Proprietary Medicines (Volume 2)

Statement of—

Bartley, Robert T., Commissioner, Federal Communications Commission: accompanied Dean Burch, Chairman, FCC.

Burch, Dean, Chairman, Federal Communications Commission; accompanied by Commissioner Robert E. Lee; Commissioner Nicholas Johnson; Commissioner Robert T. Bartley; Commissioner H. Rex Lee; Commissioner Robert Wells; and Commissioner Thomas J. Houser.

Caine, Eric, third-year medical student, Harvard Medical School; accompanied David C. Lewis, M.D., assistant professor of medicine, Harvard Medical School and director of the Medical Outpatient Department, Beth Israel Hospital, Boston, Mass.

Edwards, Charies C., M.D., Commissioner of Food and Drugs, Public Health Service, Department of Health, Education, and Welfare: accompanied by Henry E. Simmons, M.D., Director, Bureau of Drugs, FDA; and William W. Goodrich, General Counsel, FDA.

Feinbloom, Richard I., M.D., acting director, Family Health Care Program, Harvard Medical School.

Goodrich, William W., General Counsel, Food and Drug Administration; accompanied Charles C. Edwards, M.D., Commissioner FDA.
Houser, Thomas J., Commissioner, Federal Communications Commission.
Johnson, Nicholas, Commissioner, Federal Communications Commission.
Lee, H. Rex, Commissioner, Federal Communications Commission: accompanied Dean Burch, Chairman, FCC.
Lee, Robert E., Commissioner, Federal Communications Commission; accompanied Dean Burch, Chairman, FCC.
Lewis, David C., M.D., assistant professor of medicine, Harvard Medical School and director of the Medical Outpatient Department, Beth Israel Hospital, Boston, Mass.; accompanied by Eric Caine, third-year medical student, Harvard Medical School.
Louria, Donald B., M.D., professor and chairman, Department of Public Health and Preventive Medicine, New Jersey College of Medicine and Dentistry, Newark, N.J.
McIntyre, Hon. Thomas J., U.S. Senator, State of New Hampshire (written statement).
Rickels, Karl, M.D., professor of psychiatry, University of Pennsylvania. and director of psychopharmacology research unit, Philadelphia General Hospital, Philadelphia, Pa.; accompanied by Peter Hesbacher.
Rosenthal, Mitchell S., M.D., director of Phoenix programs, New York, N. Y.
Seidenberg, Robert, M.D., practicing psychiatrist and psychoanalyst, clinical professor of psychiatry of Upstate Medical Center, State University of New York.
Shainess, Natalie, M.D., William Alanson White Institute of Psychiatry, Psychoanalysis and Psychology.
Simmons, Henry E., M.D., Director, Bureau of Drugs, Food and Drug Administration; accompanied Charles C. Edwards, M.D., Commissioner, FDA.
Wells, Robert, Commissioner, Federal Communications Commission; accompanied by Dean Burch, Chairman, FCC.

Advertising of Proprietary Medicines (Volume 5)

Testimony of—
Bernstein, Joan Z., Acting Director, Bureau of Consumer Protection, Federal Trade Commission, accompanied by David O. Bickart. Deputy Assistant Director for National Advertising, FTC; Joel Brewer and Cynthia Ingersoil, Consumer Protection Bureau, FTC.
Forrest, William H., Jr., M.D., professor of anesthesia, department of anesthesiology, Stanford Medical School, Stanford, Calif.
Greenblatt. David J., M.D., clinical pharmacology unit, Massachusetts General Hospital, Boston, Mass.
Hartmann, Ernest, M.D., director, sleep and dream laboratory, Boston State Hospital, Boston, Mass.
Kales, Anthony, M.D., professor and chairman, department of psychiatry, Penn State University, Hershey Medical Center, Hershey, Pa.
Kalman, Sumner, M.D., department of pharmacology, Stanford University Medical School, Stanford, Calif.
Kennedy, Donald, Ph. D., Commissioner, Food and Drug Administration, Rockville, Md., accompanied by Richard Merrill, Chief Counsel, FDA; and Dr. William Gilbertson, Director, OTC Review Project, FDA.
Lasagna, Dr. Louis, professor of pharmacology and toxicology and of medicine, University of Rockester Medical Center, Rochester, N.Y.
Lijinsky, William, Ph. D., director, chemical carcinogenesis laboratory, Frederick Cancer Research Center, Frederick, Md.
Mark, Lester C., M.D., College of Physicians and Surgeons, Columbia University, New York, N.Y.
Norris, Frances S., M.D., medical director, division of licensing, Maryland Department of Health, Baltimore, Md.
Rickels, Karl, M.D., department of psychiatry, University of Pennsylvania, Philadelphia, Pa.
Snyder, Wallace S., Acting Assistant Director, Division of National Advertising, Federal Trade Commission, Washington, D.C.

APPENDIX B

SELECTED TOPICAL INDEX OF PSYCHOTROPIC DRUGS HEARINGS

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APPENDIX C

Currently Available Prescription Psychotropic Drugs*
By Trade Name

Tranquilizers

Benzodiazepine
- Ativan
- Serax
- Verstran

Butyrophenones and Combinations
- Haldol Tablets, Concentrate, Injection
- Inapsine Injection
- Innovar Injection

Chlordiazepoxide
- Libritabs
- Menrium

Chlordiazepoxide Hydrochloride
- A-poxide
- Librium Capsules
- Librium Injectable

Diazepam
- Valium Injectable
- Valium Tablets

Hydroxyzines
- Atarax Tablets
- Vistaril Capsules and Oral Suspension
- Vistaril Intramuscular Solution

Lithium Carbomate
- Eskalith
- Lithane Tablets
- Lithium Carbomate Capsules and Tablets
- Lithonate
- Lithotabs

Meprobamate and Combinations
- Deprol
- Equanil
- Meprosan
- Milpath
- Milprem
- Miltown
- Miltown 600
- Miltrate
- PMB 200 and PMB 400
- Pathibamate

Molindone Hydrochloride
- Lidone Capsules

* Physician's Desk Reference. 32nd Edition. Litton Industries, Inc., 1978.

Appendix C (cont.)

Tranquilizers (cont.)

Oxazepam
- Serax

Phenothiazines and Combinations
- Compazine
- Etrafon
- Mellaril
- Permitil Chronotab Tablets
- Pro-Banthine with Dartal
- Prolixin Decanoate
- Prolixin Enanthate
- Prolixin
- Quide
- Serentil Ampuls
- Serentil Concentrate
- Serentil Tablets
- Stelazine
- Thorazine
- Tindal
- Triavil
- Trilafon
- Vesprin

Rauwolfia Serpentina
- Raudixin

Reserpine
- Rau-Sed
- Sandril
- Serpasil Parenteral Solution
- Serpasil Tablets

Thioxanthenes
- Navane Capsules and Concentrate
- Navane Intramuscular
- Taractan

Other
- Azene
- Daxolin
- Kutrase
- Loxitane
- Moban Tablets
- Sinequan
- Trancopal
- Tranxene

Antidepressants

Adapin
Aventyl
Deprol
Elavil

Appendix C (cont.)

Antidepressants (cont.)

Endep
Etrafon
Imavate
Janimine
Marpian
Nardil
Norpramin
Pamelor
Parnate
Pertofrane
Presamine Tablets
Sinequan
Tofranil Ampuls
Tofranil Tablets
Tofranil-PM
Triavil
Vivactil

Stimulants (used today as anorectics)

Amphetamines
Benzedrine Sulfate
Biphetamine
Delcobese
Desoxyn
Dexamyl
Dexedrine
Didrex
Eskatrol
Fetamin
Obetrol
Obotan Forte Tablets
Obotan Tablets

Non-Amphetamines
Adipex-P Tablets
Anorexin
Fastin Capsules
Ionamin
Pondimin
Preludin
Pre-Sate
Sanorex
Statobex
Tenuate
Tepanil
Voranil

Sedatives

Barbiturates
Alurate
Amytal
Belap
Bentyl
Buticaps

Sedatives (cont.)

Butisol
Cantil
Carbrital
Dialog
Donphen
Emesert
Eskabarb
Gustase-Plus
Levsin/Phenobarbital
Levsinex/Phenobarbital
Matropinal
Mebaral
Nembutal
Pamine
Plexonal
Repan
Seconal
Sedapap
Solfoton
Tuinal

Non-Barbiturates

Aquachoral Supprettes
Beta-Chlor
Dalmane
Equanil
Levoprome
Noctac
Noludar
Parest
Phenergan
Quaalude
Sopor
Tranxene

Hypnotics

Aquachlor Supprettes
Carbrital Kapseals
Dalmane
Doriden
Matropinal
Nembutal
Noctec
Noludar
Placidyl
Quaalude
Triclos Tablets and Liquid
Valmid Pulvules

APPENDIX D

Currently Available Over-the-Counter Mood Drugs*

* Handbook of Nonprescription Drugs. Fifth Edition. American Pharmaceutical Association, January, 1977: 189, 193.

Products 14 SLEEP AID/SEDATIVE

Product (manufacturer)	Scopolamine	Antihistamine	Analgesic
Compoz Tablets (Jeffrey Martin)	—	methapyrilene hydrochloride, 15 mg pyrilamine maleate, 10 mg	—
Dormin Capsules (Dormin)	—	methapyrilene hydrochloride, 25 mg	—
Nervine Capsule-Shaped Tablets (Miles)	—	methapyrilene hydrochloride, 25 mg	—
Nervine Effervescent Tablets (Miles)	—	methapyrilene fumarate, equivalent to 25 mg of hydrochloride	—
Nervine Liquid (Miles)	—	methapyrilene fumarate, equivalent to 25 mg of hydrochloride/5 ml	—
Nite Rest Capsules (Amer. Pharm.)	aminoxide hydrobromide, 0.25 mg	methapyrilene hydrochloride, 50 mg	—
Nytol Capsules and Tablets (Block)	—	methapyrilene hydrochloride, 50 mg/capsule 25 mg/tablet	salicylamide, 380 mg/capsule 200 mg/tablet
Quiet World Tablets (Whitehall)	hydrobromide, 0.083 mg	methapyrilene hydrochloride, 16.67 mg	aspirin, 227.5 mg acetaminophen, 162.5 mg
Relax-U-Caps (Columbia Medical)	—	methapyrilene hydrochloride, 25 mg	—
Sedacaps (Vitarine)	—	methapyrilene hydrochloride, 25 mg	—
Seedate Capsules (Amer. Pharm.)	aminoxide hydrobromide, 0.125 mg	methapyrilene hydrochloride, 25 mg	—
Sleep-Eze Tablets (Whitehall)	hydrobromide, 0.125 mg	methapyrilene hydrochloride, 25 mg	—
Sleepinal Capsules (Thompson)	—	methapyrilene hydrochloride, 50 mg	—
Sominex Tablets and Capsules (J. B. Williams)	aminoxide hydrobromide, 0.25 mg/tablet 0.5 mg/capsule	methapyrilene hydrochloride, 25 mg/tablet 50 mg/capsule	salicylamide, 200 mg/tablet and capsule
Somnicaps (Amer. Pharm.)	—	methapyrilene hydrochloride, 25 mg	—
Tranquil Capsules (North American)	—	methapyrilene fumarate, 25 mg	sodium salicylate, 25 mg acetaminophen, 25 mg
Tranquim Capsules (Thompson)	—	methapyrilene hydrochloride, 50 mg	—

Products **15** STIMULANT

Product (manufacturer)	Caffeine	Other
Amostat Tablets (North American)	100 mg	—
Caffedrine Capsules (Thompson)	250 mg	—
Double-E Alertness Capsules (Keystone)	180 mg	thiamine hydrochloride, 5 mg
Nodoz Tablets (Bristol-Myers)	100 mg	—
Prolamine Capsules (Thompson)	140 mg	phenylpropanolamine hydrochloride, 35 mg
Quick-Pep Tablets (Thompson)	150 mg	niacin, 10 mg thiamine mononitrate, 3 mg
Tirend Tablets (Norcliff-Thayer)	100 mg	—
Verb T.D. Capsules (Amer. Pharm.)	200 mg	—
Vivarin Tablets (J. B. Williams)	200 mg	dextrose, 150 mg
Wakoz (Jeffrey Martin)	200 mg	—

TUESDAY, JUNE 13, 1978
PART II

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

■

OVER-THE-COUNTER NIGHTTIME SLEEP-AID AND STIMULANT PRODUCTS

Tentative Final Orders

[4110-03]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 338, 340]

[Docket No. 75N-0244]

OVER-THE-COUNTER NIGHTTIME SLEEP-AID AND STIMULANT PRODUCTS

Tentative Final Orders

AGENCY: Food and Drug Administration.

ACTION: Tentative final orders.

SUMMARY: These tentative orders establish conditions under which over-the-counter (OTC) nighttime sleep-aid and stimulant products are generally recognized as safe and effective and not misbranded and conditions under which daytime sedatives are not generally recognized as safe and effective and are misbranded. These orders are based on the recommendations and findings of the OTC Sedative, Sleep-Aid, and Tranquilizer Panel and a proposal by the Commissioner of Food and Drugs, in accordance with procedures for the agency's ongoing review of OTC drug products.

DATES: Written objections and/or requests for an oral hearing before the Commissioner regarding these tentative orders should be filed on or before August 14, 1978.

ADDRESSES: Send objections and/or requests for an oral hearing to: Hearing Clerk (HFC-20, Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301-443-4960).

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of December 8, 1975 (40 FR 57292), the Commissioner of Food and Drugs, pursuant to § 330.10(a)(6) (21 CFR 330.10(a)(6)), issued a proposal to establish monographs for over-the-counter (OTC nighttime sleep-aid, daytime sedative, and stimulant drug products, together with a summary of the report containing the conclusions and recommendations of the OTC Sedative, Sleep-Aid and Tranquilizer Panel (Panel), the Advisory Review Panel responsible for evaluating data on drugs in these categories. Interested persons were invited to submit comments on the proposal by March 8, 1976. Within 30 days after the final day for submission of comments, reply comments could be filed with the Hearing Clerk in response to comments filed in the initial 90-day period.

A request was filed for extension of the deadlines for filing comments and reply comments due to the complex nature of the Panel report and proposed monographs, the fact that the information evaluated by the Panel was not available until 30 days after their publication, and the fact that there had been an outbreak of flu at the requester's office. The request was denied because the 90-day comment period, which is already 1½ times longer than that usually provided for proposed regulations under Part 330 (21 CFR Part 330), provides ample time for comment.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), the data and information considered by the Panel was put on public display in the office of the Hearing Clerk, Food and Drug Administration (FDA), Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857, after deletion of trade secret information.

In response to the proposal, 27 comments and reply comments were received from 3 trade associations, 8 drug manufacturers, 3 consumer groups, and 13 consumers. The Commissioner, having reviewed the comments and reply comments, sets forth his conclusions under the following sections:

Section I containing the general comments and reply comments, as well as on the specific comments and reply comments on each of the three product categories.

Section II containing the Panel's recommendations for Category I, Category II and Category III conditions as well as Category III testing guidelines, all as modified by him on the basis of the comments and FDA's independent evaluation of the Panel's report. The Commissioner's conclusions will include a restatement of the Panel's recommendations and will constitute the Commissioner's adoption of the Panel's findings, as modified. In addition to substantive modifications in the Panel's findings, the restatement will include changes for clarity, for regulatory accuracy, and for reflection of any new data or information that has come to the Commissioner's attention. Gratuitous or unsupported statements will be excluded. The Commissioner's agreement with comments suggesting modification of the Panel's findings, and the Commissioner's own decisions to modify them, will be reflected in the Commissioner's version of these sections.

Section III containing the tentative final orders. All Category I conditions (generally recognized as safe and effective) decisions of the Commission, including modifications thereof due to agreement with the comments, will appear in the tentative final orders. The Commissioner advises that for clarity the format of the labeling section of the tentative final orders has been revised from that originally contained in the proposed monographs.

The Commissioner is aware that recent studies have implicated methapyrilene as a possible carcinogen or carcinogen synergist with nitrites in rats. The report concerns the finding of a 30-percent incidence of liver cancer resulting from the combined administration of methapyrilene and sodium nitrite. There is concern aroused by the nitrosation of tertiary amines because of the possibility that such reactions may occur in the human stomach (from ingested amines in foods and drugs and nitrites in food, as well as the high nitrite content of human saliva) and thus create a potential health hazard.

The studies implicating methapyrilene are too preliminary to support a definitive finding that methapyrilene is itself a carcinogen and must be removed immediately from all products in the OTC drug market.

However, after thoroughly reviewing all studies bearing on the carcinogenicity potential of methapyrilene, and in view of the fact that one study has shown evidence of at least a cocarcinogenic or synergistic effect, the Commissioner has concluded that the studies are sufficiently persuasive to warrant that methapyrilene be classified as Category II for use as an OTC nighttime sleep-aid. This issue is discussed at greater length later in this document.

FDA has requested and received assurance from the National Cancer Institute (NCI) that high priority will be given to methapyrilene testing in short term carcinogenicity screening tests developed at the Frederick Research Center; NCI has initiated a carcinogenesis bioassay on methapyrilene at the Frederick Research Center.

In the event that data from these other studies produce evidence that methapyrilene poses a health hazard as a carcinogen, the agency will take appropriate action to remove this active ingredient from the market, whatever its use, i.e., sleep-aid, antihistamine.

I. THE COMMISSIONER'S CONCLUSIONS ON THE COMMENTS AND REPLY COMMENTS

A. GENERAL COMMENTS

1. A comment urged the agency to explicitly recognize the legal status of the monographs issued under the OTC Drug Review as being interpretive, as distinguished from substantive regulations.

This subject was dealt with in paragraphs 85 through 91 of the preamble to the procedures for classification of over-the-counter drugs published in

the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), and the Commissioner reiterates the conclusions stated there.

2. Numerous comments from private citizens voiced concern over the false and misleading claims made for many of the products considered by this Panel and expressed support for the proposed monographs.

One of the purposes of the proposed monographs is, of course, to eliminate any exaggerated or false and misleading claims for these classes of products. Such support by consumers for the agency proposals is greatly appreciated.

3. A comment stated that FDA will have to modify the Panel's recommendations substantially if the final monographs are to be in accord with Executive Order 11821, which requires a financial impact assessment.

The combined annual sales of OTC nighttime sleep-aids, daytime sedatives, and stimulant products do not reach the minimum inflation impact limits necessary to invoke Executive Order 11821. Moreover, elimination of daytime sedatives, proposed elsewhere in this document, together with the cost of required testing for other classes of drugs does not approach the minimum limits necessary to invoke Executive Order 11821.

4. Two comments claimed that there is no provision in the law for Category III and that it is illegal per se. The gist of the comment is that Category III status is incompatible with continued lawful marketing of a product without an approved NDA.

This matter is presently in litigation. The Commissioner's position will be explained there.

5. One comment stated that the indications for the products should not be limited to the precise words as set forth in quotation marks in the proposed monographs. The comment argued that there are obviously other ways and other words that can be used to convey the same meaning as the phrases set forth in the proposed monographs and it would be unduly restrictive, unlawful and unconstitutional to prevent the use of such alternatives.

The Commissioner concludes that the limitation of terminology in the indications for these products is essential to assure their proper and safe use by the public. The Commissioner will permit alternative terminology only after approval of an appropriate petition to the agency under § 330.10(a)(12) (21 CFR 330.10(a)(12)) and publication of an amendment to an appropriate monograph. The rationale behind this policy was discussed in the Commissioner's response to comments in the antacid tentative final monograph published in the FEDERAL REGISTER of November 12, 1973 (38 FR 31260). The policy was further discussed in the amendment to the antacid monograph published in the FEDERAL REGISTER of March 13, 1975 (40 FR 11718), which restricts labeling to the exact terms approved by the Commissioner.

6. A comment stated that the Panel went beyond its charter in making statements concerning the advertising of the products under review, and that such statements regarding OTC drug product advertising were not only formulated with inadequate information but were also highly inappropriate for inclusion in a scientific report.

The Panel went beyond the limits of its charter in making statements with respect to advertising. However, the Panel members understood the limits of FDA authority when they did so and simply wished to make their views known to FDA and the Federal Trade Commission (FTC), which controls such advertising, that a coordinated effort was essential to assure compliance by the industry with the standards imposed by the OTC monographs. Since the Commissioner cannot act on this recommendation other than to bring the Panel's views to the FTC's attention, there is no need to reply to the adequacy of the data on the basis of which the Panel made it.

7. A comment noted that the Panel failed to differentiate between dosage levels of active ingredients on the basis of their salt forms and urged that this oversight be corrected.

The Commissioner agrees with the comment and concludes that where more than one salt form of an active ingredient has been placed in Category I or Category III, the dosage levels will be evaluated and expressed in terms of the concentration of the base.

8. A comment expressed concern with the increasing number of drugs being placed in Category III by the advisory panels, which, the comment suggested, are taking "the easy way out" by relieving themselves of the decisionmaking responsibility.

The comment identifies a real possibility but has no application here. In the case of OTC nighttime sleep-aids, little, if any, scientific study had ever been done on the active ingredients for the sleep-aid indication. These ingredients are all antihistamines and were marketed as nighttime sleep-aids to capitalize on the common side effect of antihistamines, i.e., drowsiness. By placing such ingredients in Category III, the Panel was in effect asking for effectiveness studies to be carried out, in many cases for the first time, to relate the known pharmacologic action of the ingredients to the indication for use for which they were being evaluated. Additionally, the Panel carefully set forth testing guidelines designed to permit movement to Category I. As for daytime sedatives, the Panel, in addition to putting specific ingredients in Category II, placed the entire class of products in Category III because it felt that so little research had been carried out that there was a serious question whether a target population exists who needs this class of products, and further, whether antihistamine ingredients are capable of performing a "sedative" or "calmative" function that would be safe for daytime use.

9. A comment expressed concern that no nighttime sleep-aid or daytime sedative ingredient had been placed in Category I and stated that "This continued attempt to restrict the marketing of OTC drugs, which was previously manifest in the OTC monograph on anti-diarrheal drugs and the monograph on skin antiseptics, is contrary to the original objectives set forth for these monographs." The comment quotes remarks of former Department of Health, Education, and Welfare (HEW) Secretary Weinberger and former FDA Commissioner Schmidt, generally predicting that the OTC Drug Review would not result in drastic curtailment in the availability of OTC products.

The quoted remarks of former Secretary Weinberger and former Commissioner Schmidt related to all OTC drug products, and did not imply a general rule in favor preserving as many products in each category as possible even if there were insufficient data to support the safety and effectiveness of the ingredients reviewed.

10. One comment expressed opposition to both prescription and nonprescription (OTC) nighttime sleep-aids and daytime sedatives on the grounds that they either create dependency or are ineffective. The comment urged that much stricter controls be imposed on all drugs of this type.

The Commissioner believes that the comment reflects misunderstanding of the very different and much milder physiological action of antihistamines, which are the active ingredients in OTC nighttime sleep-aids and daytime sedatives, compared to the more potent active ingredients used in prescription drugs of this type. These prescription drugs, because of their abuse liability, are subject to strict controls under the Controlled Substances Act (21 U.S.C. 801 et seq.). Antihistamines which are not regulated under that act, have generally been regarded as having low abuse potential and no ability to create dependency. The Commissioner concluded that while the effectiveness of antihistamines in existing sleep-aid and sedative products may well be questioned, as has been the case in this rule making proceeding, adequate clinical evaluation following the Category III testing guidelines should resolve such questions in the future.

The Commissioner advises that he will continually review any evidence of misuse or abuse. If information becomes available to suggest that further action is necessary to protect the public health, such action will be initiated.

The Panel has recommended and the Commissioner concurs that nighttime sleep-aids and stimulants be limited to not more than 14 days continuous use because symptoms requiring use for longer periods may indicate serious underlying disease. In such a case, the patient should consult a physician.

The Panel also recommended that the quantity of drug available in an OTC nighttime sleep-aid product container be limited to prevent abuse and misuse of OTC nighttime sleep-aids, as well as accidental ingestion of a lethal dose. The Commissioner has no authority to limit package size, but urges industry to comply voluntarily with the panel's recommendation as discussed in the report below.

The Commissioner has concluded in comment 68 below, based on the lack of a suitable target population and adequate studies proving safety and effectiveness, that daytime sedatives shall be Category II for safety and effectiveness. Therefore, the comment, as it relates to daytime sedatives, is moot.

11. Two comments objected to the Panel's recommendations that daytime sedative and nighttime sleep-aid packaging be designed to protect small children and that the quantity of the drug in the container be limited to prevent accidental ingestion of a lethal dose. The comment criticized the Panel for exceeding its mandate, since the Consumer Product Safety Commission, not FDA, is the agency charged by Congress with setting standards for safety packaging.

The Panel's suggestion is both logical and appropriate. Because the FDA does not regulate products under the Poison Prevention Packaging Act, the Panel's recommendations will be referred to the Consumer Product Safety Commission. Since the Commissioner has determined that daytime sedatives shall be Category II on grounds of safety and effectiveness and for lack of a suitable target population, the comment is moot as to those agents.

12. One comment expressed opposition to the Panel's statement at 40 FR 57317 on talc because it failed to distinguish adequately between high purity talc, used in cosmetics and pharmaceuticals, and mixed general dusts, generally referred to as "talc" and used in industrial situations. The comment maintains that talc can be an important, if not essential, pharmaceutic aid in the manufacturing of particular dosage forms. The proposed monograph permits the use of talc that does not contain asbestos, but the comment argues that the use of the term "talc containing asbestos" was an inappropriate term chosen by the Panel. Further, the comment charges that although the Panel conclusion was logical, the prelude to that conclusion does not properly represent published scientific data.

The Commissioner has reviewed the available data and concludes that the comment has raised a valid point in its reference to the term "talc containing asbestos." Contamination of talc by asbestos has in the past occurred, and the Panel cited several references on that point. Currently, however, FDA and a trade association are cooperating in the development of more sensitive techniques to detect any potential asbestos contamination. The Commissioner concurs with this effort and recognizes that talc that has no detectable asbestos contaminants is available for cosmetic and pharmaceutical uses.

The Commissioner disagrees with the charge that the Panel did not properly represent published scientific literature. The Panel may not have been sufficiently careful to distinguish between "cosmetic grade talc" and talc containing asbestos contaminants. That imprecision does not detract from the Panels's major concern, which was that no asbestos contamination be present in any of the products under consideration. High purity, or platy talc, however, is the only grade presently used by responsible firms in the manufacture of drugs, and improving methods of detecting asbestos fibers in talc will make it more feasible to guarantee that no asbestos contamination will occur.

Since talc is an inactive ingredient, it will not be categorized as I, II, or III, but talc in pharmaceutical preparations will be governed by the Commissioner's proposed regulation governing inactive ingredients published in the FEDERAL REGISTER of April 12, 1977 (42 FR 19156). This proposal would prohibit the use in pharmaceutical preparations of talc or any other inactive ingredient that is not listed in an official compendium as a pharmaceutic aid, or is not safe in the amount administered. Of course, asbestos contamination would render the talc unsafe and would be prohibited by the regulation.

13. A comment objected to the following statement in the Panel's conclusions at 40 FR 57297:

> The Panel concludes that approval of an active ingredient or combination of active ingredients for a particular indication should not be interpreted as unique to the active ingredient or to the combination. Labeling, package insert, or advertising shall not refer to such approval either directly or by inference as a unique or exclusive endorsement of such an ingredient or combination of ingredients.

The comment argues that, "because of the unnecessary concern, the Panel has attempted to impose an improper prior restraint on the First Amendment rights of the OTC manufacturer."

The panel's conclusion was that claims implying an exclusive endorsement by FDA of ingredients or combinations would be misleading and would, therefore, fall within the definition of misbranding under section 502(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(a)). The prohibition against introducing misbranded drugs into interstate commerce has been upheld as constitutional for over 60 years. See *Seven Cases* v. *United States*, 239 U.S. 510, 36 S. Ct. 190 (1915). Prohibiting such claims does not constitute a prior restraint against First Amendment rights, since the First Amendment does not protect statements that misbrand products. Such a restriction relates not to the general utterances or printing of inaccuracies regarding the approval of drugs for specific indications, but to references that offend against the drug in such a way as to misbrand the product. See *United States* v. *8 Cartons, etc.*, 103 F. Supp. 626 (W.D.N.Y., 1951); *United States* v. *Article of Drug*, 32 F.R.D. 32 (S.D. Illinois, N.D., 1963). There is, moreover, no prior restraint involved in the Panel's statement; a particular claim thought by FDA to be misleading for the reasons identified by the Panel would be proceeded against in a judicial action relating to the specific language used by the manufacturer.

The Panel's statement does not deny the right of manufacturers to refer to the report or monograph. It merely urges that they be truthful and state that such approval is not exclusive to their products. The Commissioner concurs with the Panel's statement.

14. A comment objected to the following general warning recommended by the Panel for OTC daytime sedatives and nighttime sleep-aids: "Do not take this product if you are presently taking a prescription or OTC drug without consulting a physician or pharmacist". The comment suggested that it be deleted in favor of specific drug interaction warnings where appropriate.

The question of whether to have general or specific drug interaction warnings was discussed in considerable length in the preamble to the proposed general conditions on OTC drugs published in the FEDERAL REGISTER on June 4, 1974 (39 FR 19880). In that document the Commissioner concluded that the proper way to handle possible drug interactions is to require that OTC drug labeling include a separate section, entitled "Drug Interaction Precautions," stating the specific or general interaction problem in-

volved with each drug, if any. The Commissioner continues to believe that a general drug interaction precaution on all OTC products will most likely be disregarded by the general public whereas a specific warning will have the intended impact. The Panel's recommendation of a general warning will therefore not be accepted; specific drug interaction warnings will instead be required where appropriate.

15. One comment urged the immediate removal of bromides from OTC drugs since those who rely on such medicines may be ignorant of the hazards posed by these products and may be placing their lives in danger with continued use.

The Commissioner agrees that ingredients that are not generally recognized as safe should be removed from the market as soon as possible. However, the Panel concluded and the Commissioner agrees that bromides are safe but ineffective at currently marketed dosage levels, and unsafe only at the higher dosage levels that would be necessary for them to be effective. Since there is no question of safety at the currently marketed dosage levels, the Commissioner can find no rationale for removal of these products before the completion of the OTC Drug Review process. However, the Commissioner notes that the manufacturer of one bromide-containing product with both nighttime sleep-aid and daytime sedative claims has reformulated the product to remove bromides.

16. A comment requested that all ingredients in OTC sleep-aid and stimulant drugs be conspicuously listed on the label of these products.

The Commissioner advises that section 502(e)(1)(A) of the act requires that the established name of each active ingredient appear on a drug product label. Certain other ingredients, whether active or not, are also required to appear on the label under this section. Although there is no authority under the law to require a declaration of inactive ingredients, this has frequently been suggested by OTC advisory panels, and inactive ingredients are sometimes included voluntarily by certain manufacturers.

The Commissioner favors the declaration of all ingredients including the inactive ones, and in the absence of authority to require the inclusion of inactive ingredients in OTC product labeling, issued the April 12, 1977 proposal setting forth the manner in which inactive ingredients must be declared if they are voluntarily included in the labeling by the manufacturer.

17. A comment stated that the Panel recommended that similar methodology be used in the evaluation of both OTC and prescription nighttime sleep-aids, as described in the Prescription Drug Hypnotic Guidelines (40 FR 57314; Dec. 8, 1975). The comment objected that these guidelines had not been furnished to the OTC drug industry and consequently cannot be commented on.

The Commissioner advises that the guidelines in question are properly indexed and have been on display with all other documents pertaining to this report in the office of the Hearing Clerk, FDA, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857, since January 4, 1976, as provided in the OTC drug review regulation (21 CFR 330.10(a)(2)). These guidelines are indexed and labeled as OTC Volume 050048. Copies are available on written request to the office of the Hearing Clerk.

It should be noted that these prescription drug guidelines were merely used as an aid in drafting the Panel's own testing guidelines and were given no special status.

B. GENERAL COMMENTS ON OTC NIGHTTIME SLEEP-AIDS

18. One comment stated that the Panel seeks to make all "sleeping pills" prescription drugs, which will greatly increase their cost.

The comment is mistaken; the Panel report and proposed monograph clearly recognize the usefulness and value of OTC nighttime sleep-aids and do not propose that they all be restricted to prescription use.

19. Two comments urged that sleep-aids be available only on prescription because of their potential for misuse.

The Commissioner has reviewed the data on abuse of OTC nighttime sleep-aids, and has not found sufficient evidence of pharmacologic potential for misuse or abuse of these agents to warrant placing OTC nighttime sleep-aids on prescription or recommending that they be subject to increased controls on prescription and distribution under the Controlled Substances Act.

Although there is little or no pharmacologic potential for abuse of the ingredients in OTC nighttime sleep-aids, the Commissioner is aware that some OTC products have appeared in the Drug Enforcement Administration's Drug Abuse Warning Network Reports. One possible explanation offered is that certain OTC nighttime sleep-aids, daytime sedatives and stimulants intentionally or unintentionally bear a strong physical resemblance in capsule or tablet size, shape, or color to controlled prescription stimulants, tranquilizers, hypnotics, and sedatives that are frequently abused and sold in illegal transactions. In fact, certain OTC products have even been marketed with trade names that closely resemble those of controlled prescription drugs. These look-alike/sound-alike drugs may also represent an attempt to benefit from such resemblance by implying some type of added efficacy or strength to a product. If such look-alikes present an opportunity for abuse, the Commissioner may consider initiating appropriate action under section 502(a) of the act.

20. A pharmacist commented that Dr. William W. Douglas in L. S. Goodmand and A. Gilman (eds.), "The Pharmacological Basis of Therapeutics," 4th Ed., McMillan, New York, p. 645, states that "while antihistamines * * * are generally ineffective in recommended doses, some singularly sensitive individuals may derive benefit." The comment objects to the idea of marketing antihistamines for sleep since only those singularly sensitive individuals will benefit.

The Commissioner notes that the passage referred to in the comment reads: "The tendency of certain antihistamines * * * to produce somnolence has led to their use as hypnotics. They are by no means as powerful or effective as the barbiturates, for example, but they may have value in selected patients. Antihistamines, particularly methapyrilene, are present in various proprietary remedies for insomnia that are sold 'over the counter.' While these remedies are generally ineffective in the recommended doses, some singularly sensitive individuals may derive benefit."

The Panel concurred with the conclusion that existing OTC dosage levels were not effective and recommended that methapyrilene be placed in Category III so that appropriate safety and effectiveness studies could be carried out at the higher dosage recommended by the Panel. Data supporting the effectiveness of the ingredients need not show that they are effective in all patients, just in a significant proportion of the target population (21 CFR 330.10(a)(4)(ii)). The Commissioner has reviewed the available data and concludes that the Panel was justified in its decisions. If the further testing recommended by the Panel fails to prove the safety and effectiveness of any antihistamine for use as a nighttime sleep-aid in a suitable target population, that ingredient will be reclassified as Category II and removed from the market 6 months after publication of the final order. The point is, of course, moot for methapyrilene since it has already been reclassified as Category II for safety.

21. A comment stated that the conclusions reached by the Panel demonstrate a prejudice against the OTC nighttime sleep-aid class of drugs and that judgment on the issues of safety and effectiveness should not be clouded by philosophical considerations.

The Panel members were aware of and sensitive to philosophical considerations. However, they did not base their decisions on those concerns. In fact, the Panel Chairman, Dr. Karl Rickels, specifically pointed out in his

speech at the December 4, 1975 FDA press conference on the report that:

> Although the Panel informally discussed the philosophical issues relating to drug abuse and misuse as well as chemical intervention in mood modification, we did not address these subjects in the report for two reasons. First, our mandate from FDA was based on much narrower grounds. We were asked to review the data placed before us and to determine if the active ingredients we reviewed could be generally recognized as safe and effective. Second, as constituted, our Panel simply did not have the expertise to discuss the philosophical and moral questions.

The comment offers no evidence, examples, or proof of bias on the part of the Panel. Far from being "biased" against OTC nighttime sleep-aids, the Panel stated in the preamble to the December 8, 1977 proposal at 40 FR 57296: "The Panel accepts that experiencing occasional sleep problems is a valid indication for OTC medication."

C. COMMENTS ON SCOPOLAMINE

22. A comment disagreed with the Panel's placement of scopolamine in Category II as a nighttime sleep-aid for reasons of lack of safety and efficacy and urged its placement in Category III. The comment points out that the Panel has held that it had insufficient data on the efficacy or safety of scopolamine at dosages currently employed but, at the same time, it had not adduced any evidence to show that it would not be effective or that it would produce untoward effects at those levels. This is particularly true in regard to the use of scopolamine in combinations with other ingredients for hypnotic purposes. There is already good documentation for the effectiveness of such combinations, according to the comment, although the comment acknowledged that factorial studies have not been performed to evaluate the contribution of individual constitutents. The comment states that such a situation argues compellingly for placement of scopolamine in Category III in combination sleep-aid products so that its potential benefits and risks as a component of OTC nighttime sleep-aids can be properly investigated.

The Commissioner concurs with the Panel's conclusion that scopolamine is presently marketed at ineffective dosage levels. The Panel advised that there are documented safety problems at what they perceived as the effective dosage level. The comment offers no new data to support effectiveness at the lower dosage level. In addition the comment points to no conclusive factual or theoretical evidence that scopolamine is effective at lower dosage levels in combination with other ingredients. The Commissioner concludes that should such evidence be produced, perhaps scopolamine might be generally recognized as safe and effective in that combination. If at some future time evidence is developed of effectiveness of scopolamine at lower levels in combination with antihistamines, a petition to amend the monograph can be filed.

D. COMMENTS ON DIPHENHYDRAMINE

23. A comment stated that sufficient data and information were submitted to the Panel to warrant the placing of diphendydramine at a level of 50 mg in Category I as an OTC nighttime sleep-aid.

The comment offered no new or additional information. The Commissioner concludes that additional data are necessary to support the classification of diphenhydramine as a Category I OTC nighttime sleep-aid. The Commissioner also concludes that two well-controlled clinical studies following the principles established in § 314.111(a)(5)(ii) are necessary to demonstrate the safety and effectiveness of diphenhydramine as an OTC nighttime sleep-aid. Both the 50-mg and 100-mg dosage levels should be studied with a careful comparison of side effects at both dosage levels.

24. One comment state that the reference material cited for diphenhydramine hydrochloride shows that 188 subjects were tested in 3 EEG studies, which demonstrated effectiveness at a 50-mg dose, and that, consequently, further EEG studies should not be required to place diphenhydramine hydrochloride in Category I as a nighttime sleep-aid.

The Commissioner agrees that, in view of the extensive EEG testing already done, additional EEG studies will not be required to demonstrate the effectiveness of diphendydramine as a nighttime sleep-aid.

E. COMMENTS ON DOXYLAMINE

25. A number of comments supported the safety of doxylamine succinate as an OTC nighttime sleep-aid and argued that it should be placed in Category I.

The Commissioner has reviewed all pertinent data available on the safety of doxylamine succinate, including that available to the Advisory Review Panel on Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products, whose recommendations and conclusions published in the FEDERAL REGISTER of September 9, 1976 (41 FR 38311).

The Commissioner has concluded in comment 26 below that testing is required to prove the safety and effectiveness of doxylamine succinate as an OTC nighttime sleep-aid. As part of these controlled trials, the side effects should be carefully monitored. A decision on the safety of doxylamine succinate as an OTC nighttime sleep-aid will be made after a benefit-to-risk evaluation of the controlled trials.

26. A number of comments urged that doxylamine succinate be generally recognized as effective as an OTC nighttime sleep-aid and objected to the proposed requirement of five additional studies as being excessive. Among the comments was one which pointed out that L. S. Goodman and A. Gilman (eds.), "The Pharmacological Basis of Therapeutics," 4th Ed. McMillan, New York, p. 132 (1970), states that doxylamine, one of the older antihistamines, has impressive hypnotic properties.

The Panel concluded in their report that doxylamine succcinate in a single dosage of 25 to a maximum of 50 mg per day at bedtime may be both safe and effective as an OTC nighttime sleep-aid. A minimum of at least five additional well-controlled studies, including at least three clinical and two EEG studies, were recommended to prove both safety and effectiveness.

The Commissioner concurs with the comments that five additional studies are excessive for this drug. The Commissioner concludes that two well-controlled clinical studies following the principles established in § 314.111(a)(5)(ii) and one EEG study are necessary to demonstrate the safety and effectiveness of doxylamine succinate as an OTC nighttime sleep-aid.

Testing requirements for phenyltoloxamine and pyrilamine are also modified to conform to the requirement of two well-controlled clinical studies and one EEG study to demonstrate the safety and effectiveness of these drugs as OTC Nighttime Sleep-aids.

F. COMMENTS ON METHAPYRILENE

27. Two comments objected to the placement of methapyrilene hydrochloride and methapyrilene fumarate in Category III with respect to safety. The comments cite the extensive marketing experience with methapyrilene both as a nighttime sleep-aid and as an antihistamine and the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products Advisory Review Panel's conclusion that methapyrilene is safe at dosages of up to 50 mg every 6 hours. The comments go on to point out the safety data presented to the Advisory Review Panel on OTC Nighttime Sleep-Aid, Daytime Sedative and Stimulant Products, the Panel's own conclusion in its final report that these drugs are probably safe, and its conclusion in its earlier draft of the final report that methapyrilene is in fact safe. The comments urge placement of methapyrilene hydrochloride and methapyrilene fumarate in Category I with respect to safety as a nighttime sleep-aid in dosages up to 50 mg.

The safety issue to which these comments are addressed is the propensity

of methapyrilene or its salts to cause anticholinergic side effects or adverse reactions, not to its role as a possible carcinogen or co-carcinogen. The Commissioner has indicated in the preamble to this document that preliminary data exist which tend to implicate methapyrilene as a carcinogen or co-carcinogen in rats. While the issue of carcinogenicity is being studied by the National Cancer Institute (NCI), as discussed in this document, the Commissioner has concluded that existing data justify classification of methapyrilene in Category II for safety. The Commissioner concurs with the comment that the safety of methapyrilene (apart from any carcinogenic potential) has been adequately demonstrated at doses up to 50 milligrams. He therefore concludes that no further safety testing would be required to monitor anticholinergic side effects or adverse reactions at doses up to or at doses of 50 milligrams. The data presented, together with the conclusions of the OTC Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products Advisory Panel, would amply justify this decision (41 FR 38312). The point is moot, however, since methapyrilene is in Category II due to its possible carcinogenic potential.

28. Two comments objected to the Panel's requirement for five additional well-controlled studies each to establish the effectiveness of methapyrilene hydrochloride and methapyrilene fumarate at a dosage of 50 mg as OTC nighttime sleep-aids. The comments cite the abundant data already presented to the Panel as well as four additional studies using an OTC nighttime sleep-aid-analgesic combination containing methapyrilene. The comments contend that the Panel's concern that dosages above 50 mg seem worth investigating is insufficient reason for failing to recognize the effectiveness of these drugs at the 50 mg level.

The Commissioner notes that the Panel's main concern with methapyrilene involved effectiveness, especially the dosage level at which it would be most effective. The Commissioner feels that, in view of both the data presented and the long and extensive clinical history of its sedative side effects, methapyrilene is probably effective as an OTC nighttime sleep-aid at a dosage of 50 mg. The point is moot, however, since methapyrilene has been placed in Category II for reasons relating to safety.

29. One comment stated that, since the references cited indicate that methapyrilene was tested by Dr. W. K. Noell in EEG studies of 100 subjects and found to be significantly better than placebo in time to "end of wakefulness" and in time to "onset of sleep", no further EEG studies should be required to place methapyrilene in Category I as a nighttime sleep-aid.

The Commissioner concluded in comment 28 above that effectiveness considerations for methapyrilene are moot since it has been placed in Category II for safety due to its possible carcinogenic potential.

G. COMMENTS ON OTC NIGHTTIME SLEEP-AID COMBINATIONS

30. One comment pointed out that the regulation dealing with safety of OTC drugs (21 CFR 330.10(a)(4)(i)) provides:

> Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

The comment maintains that proof of the low incidence of adverse reactions was submitted to the Panel in accordance with the regulation, which calls for "adequate tests by methods reasonably applicable to show the drug is safe." In those tests there was no significant difference between an OTC nighttime sleep-aid/analgesic combination and the placebo control. Proof of the "low potential for harm" under conditions of "abuse" consists, according to the comment, of the marketing experience of an OTC sleep-aid/analgesic combination product showing approximately 1 complaint for every 25 million tablets sold up to July 1973 and approximately 1 complaint for every 50 million tablets sold since July 1973.

The comment points out further that, as required by the regulation, material showing the safety of the OTC nighttime sleep-aid/analgesic combination has been published. The comment contends that every condition of the regulations for establishment of general recognition of safety of this combination product has been met and that the only reasonable conclusion is that 50 mg of methapyrilene individually and in any combination product as an integral drug must be considered as generally recognized as safe under the proper standard of the governing law and regulations.

As stated above in comment 27, the Commission has concluded that with respect to its propensity to cause side effects or adverse reactions, methapyrilene is safe for use as an OTC nighttime sleep-aid at doses up to 50 mg.

The Commissioner has no reason to believe that this safety would be any less when it is combined with an OTC analgesic product. these judgments concern only adverse reactions and anticholinergic side effects and not the possible carcinogenicity potential of methapyrilene which has resulted in its placement in Category II. Of course, this Category II classification includes combinations containing methapyrilene.

31. A comment stated that the Panel's recommendation to the Commissioner on combinations of nighttime sleep-aid ingredients is an inflexible and arbitrary prohibition on permissible combinations, is at variance with existing agency regulations for combinations of OTC drugs, and evidences a bias on the part of the Panel against OTC combination drugs. The regulations (21 CFR 330.10(a)(4)(iv)) state that:

> An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The comment argues that, since two drugs from the same pharmacological category may not be the same in a functional sense, the agency's position on OTC combination drugs should be consistent, whether the active ingredients come from the same or from different pharmacological classes. The Panel has approved combinations of an antihistamine and analgesic, subject to further testing and the identification of a suitable target population. It has not permitted combinations of two ingredients from the same pharmacological class.

The comment maintains that the general spectrum of pharmacologic activity may be very similar for several members of a pharmacologic class, but the intensity of effects will frequently vary with each compound. Also, where different chemical analogues in a class are present or where pharmacologic action is similar but chemical structure is not, different mechanisms of action may exist to achieve effects not possible when one of the drugs is used alone.

According to the comment, it is well-known that one can combine antihistamines to minimize sedation and maximize or maintain antiallergic activity. If this is so, the converse should be too, that is, one can maximize specific sleep-aid potency at low dosages and minimize unwanted other "antihistamine" side effects.

The comment also argues that all of the nighttime sleep-aid products considered in this review, including the

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combination products, are known and demonstrated to be extremely safe at labeled dosages. The position expressed in the comment is that the Panel's concern with possible enhancement, through the combination of single ingredients, of "toxic effects, allergic and/or idiosyncratic reactions, and possibly unrecognized and undesireable drug interaction(s)" is based on speculation alone, and not on any supporting evidence. The Panel's citation of the sulfonamides or "triple sulfas" as a justifiable exception to their ruling against combination of single class ingredients serves to undermine their argument since Lehr, in his important work, found not only that the combination of different sulfonamides achieved therapeutic potency while avoiding the problem with crystalluria, as noted by the Panel in its report, but also that such a combination actually lowered the incidence of untoward sensitivity reactions.

The comment argues that the Panel failed to provide documentation adequate to justify its failure to follow the regulations set forth for the OTC drug review on combination drugs, and that furthermore, one combination OTC nighttime sleep-aid under consideration which combines two antihistamines has an overwhelming record of safe public use. For these reasons, OTC combination nighttime sleep-aids containing two ingredients from the same pharmacologic class should be placed in Category III, and made available to the public while testing is being carried out to verify the effectiveness of the combination.

The Commissioner disagrees. The comment's justification for the inclusion of two antihistamines in a combination product is based on theoretical generalizations for which no documented evidence was submitted. The comment failed to cite any data to support the contention that the effectiveness of combinations can be maximized at low dosages while minimizing side effects.

A Category III classification for a combination of two antihistamines would require the submission of data tending to show that such a combination is safe and/or effective but which are insufficient to make a final determination. Such data have not, in fact, been submitted. Accordingly, combinations of two antihistamines must be classified in Category II.

32. A comment objected to the Panel's Category III classification of products containing methapyrilene and an analgesic that are offered for the relief of pain and to aid sleep. The Panel's decision was based on the fact that the antihistamine methapyrilene was independently classified in Category III as a nighttime sleep-aid, and on the lack of sufficient data to establish the existence of a meaningful target population requiring concurrent therapy from both ingredients. The comment contends that adequate and well-controlled studies demonstrate that the combination is, compared with placebo, effective in inducing sleep, improving the quality of sleep, and reducing pain. Combination drugs must, according to the comment, be evaluated as entities: If they accomplish their labeled purpose, they must be deemed effective, even if there is no evidence that the combination is more effective than any of its components.

The Commissioner agrees with the Panel's analysis and rejects the comment's position. The Panel's classification of methapyrilene in Category III for effectiveness as a nighttime sleep-aid precludes placement of a combination drug containing that ingredient in Category I. Although the comment is moot as to methapyrilene, it raises an issue that is involved in testing for any antihistamene/analgesic combinations used as OTC nighttime sleep-aids.

That a combination of an antihistamine and an analgesic is more effective than placebo in inducing or improving the quality of sleep is not necessarily evidence for the effectiveness of methapyrilene as a sleep-aid, for the effectiveness observed in the studies can as readily be attributed to the pain relief afforded by the analgesic component as to the soporific effects of the antihistamine. The promotion of sleep through the relief of pain is not a therapeutic effect properly associated with a "nighttime sleep-aid"; a nighttime sleep-aid exerts its therapeutic effect through a pharmacologic action that brings about or maintains drowsiness, not through the elimination of distractions that inhibit or interrupt sleep. Accordingly, a study of a combination antihistamine and analgesic product to establish the effectiveness of the combination as a nighttime sleep-aid must be designed to test the combination against its analgesic component alone in the indicated patient population. Only if the combination were successful in such a study could it be inferred that the antihistamine as a component of the combination is an effective nighttime sleep-aid.

Such success would not, however, demonstrate that the combination itself is effective for its intended therapeutic use for it would remain to show the existence of a significant patient population that requires concurrent therapy from an antihistamine for sleeplessness that is not caused by the distraction of pain, and from the analgesic, for sleeplessness that is. The two categories of patients are not self-evidently congruent: It may be that people who suffer sleeplessness for reasons other than pain are not the same people who suffer sleeplessness as the result of pain. Only where the two categories overlap are there patients who can benefit from concurrent therapy for the two independent conditions. It is the manufacturer's burden to demonstrate that the degree of overlap is such as to represent a significant target population. To evaluate the significance of such a target population, if it exists, requires a study in which patients reporting concurrent symptoms of sleeplessness that is not perceived as resulting from pain, and sleeplessness that is so perceived are administered the combination as well as each of its components separately. If the combination is more successful than either of its components in this patient population, then the existence of the target population has been established, and its significance can then be evaluated. None of the studies submitted to the Panel conform to this design. Therefore, they do not demonstrate the effectiveness of the combination in accordance with the combination drug effectiveness criteria of 21 CFR 330.10(a)(4)(iv) of the regulations. To meet these criteria, the factorial design testing recommended by the Panel and adopted by the Commissioner must be conducted.

The comment contends that the existence of the target population has already been demonstrated from market survey information indicating that significant numbers of people report "trouble sleeping due to pain." This misses the point: If the patient can in fact determine that his/or her sleep problems are due to pain, he will take an analgesic to relieve the pain, and thus promote his sleep. It is contrary to sound medical practice for such a patient to treat himself with a product that also contains a nighttime sleep-aid, which, by hypothesis, he does not need.

The comment also argues that patients are capable of determining whether they require both a nighttime sleep-aid and an analgesic, pointing to the Panel's statements that patients, through experience, are able to judge the dosage of analgesic that meets their needs. It does not follow, however, that a patient able to estimate how much of an analgesic he/or she needs to relieve pain is also capable of diagnosing sleeplessness that is due simultaneously to both pain and an unrelated sleep problem for which a sleep-aid is effective therapy. Moreover, even if patients could correctly diagnose such a condition it remains to be shown that such a condition actually exists. Only the factorial design studies recommended by the Panel can demonstrate whether it does and whether the combination can treat it effectively.

33. A comment argued that it is incompatible with the new drug provisions of the act for the Commissioner to require a combination drug product to be shown to be effective by com-

parison with each of its components. According to the comment, if the combination achieves its labeled therapeutic effect, it must be found "effective" within the meaning of the act regardless of whether the combination is no more effective than any of its components taken singly or whether a specific component is found not to be generally recognized as safe and effective. The product discussed in the comment is the combination of methapyrilene and an analgesic described in comment 32.

The Commissioner disagrees. The OTC Drug Review is a rule making proceeding pursuant to section 701(a) of the act. In such a proceeding, the Commissioner is not confined to making product-by-product determinations in accordance with section 505 of the act, but may apply the new drug definition by therapeutic class to ingredients found in more than one product. "Weinberger v. Hynson, Wescott and Dunning, Inc.," 412 U.S. 609, (1973); "Weinberger v. Bentex Pharmaceuticals, Inc.," 412 U.S. 645, 650 (1973); "USV Pharmaceutical Corp. v. Weinberger," 912 U.S. 655, 664-67, (1973).

The sections of the act cited in the comment deal with the definition of "new drug" and the requirements for a new drug application (NDA). These provisions do not directly bear upon the program for the classification by drug monograph of OTC drugs as generally recognized as safe and effective, although the option for a manufacturer to submit an NDA pursuant to the new drug provisions of the act is always open.

The OTC Drug Review regulation for combination drugs (21 CFR 330.10(a)(4)(iv)) provides that an OTC drug may combine two or more safe and effective active ingredients when each active ingredient makes a contribution to the claimed effect or effects and when the combination of active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients. These requirements necessarily include a prior determination of the safety and effectiveness of each active ingredient for the claimed indication for use. If an ingredient has been determined to be in Category III for the sleep-aid indication, it must follow that a combination product containing that ingredient is a Category III sleep-aid.

Evidence that a particular combination product is effective as an entity does not demonstrate that both components of the combination make a statistically significant contribution to effectiveness. The studies submitted to the Panel did not compare the marketed product with the individual ingredients in the formulation, and thus, did not substantiate the effectiveness of the antihistamine component as a nighttime sleep-aid. Since the Panel did not have sufficient independent evidence respecting the effectiveness of the antihistamine component as a sleep-aid to classify it other than in Category III, it could not properly conclude that the product should be classified in Category I as generally recognized as safe and effective as a fixed combination.

If substantial evidence exists that a product containing a combination of ingredients is generally recognized as effective as a fixed combination, then there should also be evidence tht each ingredient in that product is individually generally recognized as effective. No such evidence was submitted with respect to any analgesic/nighttime sleep-aid combination. Conversely, if it is determined that an ingredient is not generally recognized as effective for a particular indication, there can be no basis for concluding that a fixed combination product containing that ingredient is generally so recognized.

The contrary position taken in the comment not only repudiates the agency's combination drug policy, which has been applied for nearly a decade without serious legal challenge, but is also medically irrational. Pursued to its logical conclusion, the comment's reasoning would require the agency to approve as an effective nighttime sleep-aid a combination that contains not only agents that induce sleep and that promote sleep by relieving pain, but also antibiotics and any other ingredients unrelated to the induction or promotion of sleep, simply because they do not detract from the effectiveness of the sleep-aid ingredient itself in bringing about a state of drowsiness. The comment's position is erroneous both medically and legally.

34. A comment criticized the Panel's conclusion that studies on an analgesic/nighttime sleep-aid were invalid because they were not blind in the true sense. The Panel noted that the investigators received a list of test subjects indicating by the use of the letters A and B who received the placebo. The comment points out that these lists were in a sealed envelope marked "to be opened only at the conclusion of the study or in the event of an emergency." The comment therefore states that the judgments made by the Panel with respect to these tests were in error.

This fact was not made clear in the original data submitted to the Panel for review and has now been taken into account in the Commissioner's evaluation of the safety and effectiveness of analgesic/nighttime sleep-aid combination drugs.

35. A comment contended that seven studies presented to the Panel on a combination OTC nighttime sleep-aid/analgesic containing methapyrilene showed positive sleep induction activity. Since three of these studies involved patients with no pain, and since methapyrilene was the only sedative ingredient in the combination, the comment maintains that the sleep induction activity must be attributed to it. The comment points out further that these seven studies are discussed by the Panel in the December 8, 1975 proposal at 40 FR 57316 stating in part that "The manufacturer produced seven well-designed, well-controlled studies in support of his claim * * *. All seven studies were generally well done, * * *. They indicate clearly that the combination is more effective than placebo in inducing sleep, creating a better quality of sleep, and reducing pain."

The comment contends that in opposing the conclusion reached in these seven studies, the Panel makes several arguments which are not germane to a proper decision. The comment argues that the Panel either directly or by implication makes judgments about the relative effectiveness of the individual ingredients and rejects valid results, and insists on a factorial design study which is not well-suited to the demonstration of sleep-aid effectiveness.

The Commissioner disagrees. The Panel did not reject the conclusions of the studies in question but merely found them to be irrelevant because it was impossible to attribute the results to only one of the active ingredients. Testing a combination drug against its individual ingredients is the only way to make sure that an observed effect is due to one rather than all of the ingredients. Therefore, the Panel quite properly required a factorial design study so that the relative contribution, if any, of each of the active ingredients could be determined. While combinations containing methapyrilene are classified in Category II, the factorial design study suggested by the Panel will be retained in the testing guidelines for other combinations of analgesics and Category I or Category III antihistamines. (See part II. paragraph D. below—Data Required for OTC Nighttime Sleep-aid Ingredient Evaluation.)

36. One comment stated that the Panel's true reason for failure to give recognition of safety to OTC nighttime sleep-aid/analgesic combinations was grounded in bias against combination products. The comment contends that preference for single ingredient products because of "possible unrecognized and undesirable drug interaction(s)" is not a viable basis for denying general recognition of safety and effectiveness. Mere speculation based upon an abstract, theoretical generalization that perhaps some drugs might be rendered unsafe by the addition of further ingredients cannot

prevail against the concrete demonstration by adequate studies submitted to the Panel that a combination OTC nighttime sleep-aid/analgesic product specifically, under its recommended conditions of use, is in fact safe. Neither, then, according to the comment, is methapyrilene itself unsafe as it appears and is used in the combination product.

The comment is correct that theoretical considerations cannot be accepted in place of actual data. The Category III status of analgesic-nighttime sleep-aid combinations is not based upon a question of safety but upon whether there is a significant target population which requires analgesia and sleep induction concurrently. (See comment 32 above.)

37. A comment objected to the Panel's statement that "whether the combination of an analgesic and a nighttime sleep-aid enhances the effectiveness of either type of agent cannot be answered from the data reviewed." The comment states that there is no requirement that one ingredient in a combination enhance the activity of another. It is only required that there not be diminution of safety and effectiveness due to inclusion of another active ingredient.

The comment takes out of context and misinterprets the Panel's statement, which was part of an extensive discussion of the effectiveness of an analgesic/nighttime sleep-aid combination for a target population of individuals suffering from both pain and inability to sleep (40 FR 57316). The Panel, in an attempt to assist studies in this area, suggested that it might be possible that either the sleep-aid ingredient or the analgesic ingredient had an enhancing effect on the other ingredient. The Panel did not require a sparing or enhancing effect for the combination to exist, but merely suggested that such an effect would be beneficial if it could be proved.

38. One comment stated that, while much has been written about the interaction of marketed drug products, in every instance these reactions are related to the pharmacologic spectrum of the drug. At the present time, insofar as can be anticipated, the risk of interaction of antihistamines with other substances in our environment has been anticipated by the Panel in its requirements for labeling stating that an OTC nighttime sleep-aid product should not be used with other medications. The comment argues that, although it is possible that interactions presently unknown between antihistamines and some other drug may be identified at some future date, such theoretical possibility cannot stand as sufficient justification to proscribe the use of antihistamines either alone or in combination with analgesic ingredients.

The comment is valid and emphasizes the need for the Panel to justify every position taken. Based upon currently available information, the Commissioner concludes that the combination of an OTC nighttime sleep-aid with an analgesic presents no special or unique safety problems from the standpoint of drug interactions. (See comment 36 above.)

39. One comment was accompanied by four additional clinical studies not previously published or reviewed by the Panel. These studies used an analgesic/nighttime sleep-aid combination product consisting of aspirin, acetaminophen and methapyrilene fumarate. The comment contends that, based on these studies as well as the other available data, methapyrilene fumarate 50 mg and an analgesic/sleep-aid combination drug containing methapyrilene should be generally recognized as safe and effective for decreasing sleep latency and in providing better quality sleep, especially in the case of the analgesic/sleep-aid combination product for sleep disrupted by pain. The comment requests that both methapyrilene fumarate 50 mg and the analgesic/methapyrilene combination be placed in Category I as OTC nightime sleep-aids since all conditions of the applicable regulations (21 CFR 330.10(a)(4)(iv)) have been met. In addition, the comment objects to any further requirements to identify the target population of OTC analgesic/nighttime sleep-aid combinations as a waste of time, money, and research facilities.

The Commissioner finds that the above clinical studies do provide additional data, but still leave unanswered the basic questions of whether there is a significant target population for OTC analgesic/sleep-aid combinations and whether each ingredient in the product contributes significantly to its effects. The difficulty with these additional studies is that the final formulation product was not tested against the individual ingredients. Since the product was tested as a combination the new studies do not help answer the question as to relative effectiveness of the individual ingredients. Each ingredient must be tested alone, and in combination and evaluated against a placebo. The Commissioner notes that such combinations were also reviewed by the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products, whose recommendations and conclusions were published in the FEDERAL REGISTER of July 8, 1977 (42 FR 35346). That Panel concurred with the Advisory Review Panel on OTC Nighttime Sleep-aid, Daytime Sedative, and Stimulant Drug Products.

The Commissioner also concludes that a suitable target population must be demonstrated, that is, people suffering from concurrent pain and sleeplessness due to factors other than pain.

The Commissioner concurs with the Panel's finding that double-blind well-controlled factorial design testing as set forth in the testing guidelines is needed for combinations of this type. (See part II. paragraph D. below—Data Required for OTC Nighttime Sleep-aid Ingredient Evaluation.) Of course the specific combination mentioned by the comment, aspirin, acetaminophen and methapyrilene fumarate, has been placed in Category II due to the possible carcinogenic potential of methapyrilene. Consequently, the issue of what testing is appropriate in this case is moot.

40. One comment objected to the Panel's statement that "the Panel has insufficient information to identify a meaningful target population for OTC analgesic/nighttime sleep-aid combination products." The comment contends that the population has been established as "individuals who suffer from the minor painful conditions stated in the labeling together with resultant sleep impairment." The comment further contends that the target population for an OTC analgesic/sleep-aid combination has been identified (1) by unassailable logic, (2) by the conditions of use set forth in the labeling, (3) by recognition by the Panel itself in the statement at 40 FR 57316 that the "combination is recommended for nighttime use in patients suffering from a combination of pain and insomnia or from 'insomnia expectation'," (4) by medical studies submitted to the Panel and referenced in their report as Refs. 2, 3, 4, and 5 at 40 FR 57317, and (5) by market studies showing that significant numbers of people report "trouble sleeping due to pain."

The Commissioner has reviewed the items noted in the comment and is unable to reach the same conclusion. Merely discussing a target population does not make that population exist. Nor does labeling that identifies the intended conditions of use guarantee the existence of a signficant target population. The medical studies submitted to the Panel were rejected by it as inadequate, and the Commissioner concurs with the finding; the target population must be demonstrated by the factorial design recommended by the Panel.

The Commissioner concurs with the Panel's concern as to whether a significant population exists which suffers both from pain and sleeplessness that cannot be alleviated by an analgesic alone. As previously noted above in comment 39, the Commissioner advises that such combinations have been reviewed by the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products, as published

on July 8, 1977, and that that Panel concurred with the findings of the Advisory Review Panel on OTC Nighttime Sleep-Aid, Daytime Sedative, and Stimulant Drug Products.

H. COMMENTS ON OTC NIGHTTIME SLEEP-AIDS LABELING AND WARNINGS

41. A comment contended that the Panel made no findings of fact which would support any recommended change in labeling, that in every instance the Panel's recommended changes are based upón opinion and speculation but have no other foundation, and that there is, therefore, a lack of any evidentary base to support the Panel's recommendation with regard to the labeling of OTC nighttime sleep-aids. In addition, the comment states that the Panel's recommendations are made in the face of extensive industry experience in the marketing of OTC sleep-aids with existing directions and warnings.

The Panel's recommendations are well-documented, referenced, and supported. The Commissioner therefore rejects the comment as unfounded.

42. Comments objected to use of the term "nighttime sleep-aids," since use of the word "nighttime" might confuse persons wishing to use these products in order to sleep during the daytime.

The Commissioner thinks it is unlikely that those who sleep in the daytime will be confused by the terminology. The purpose of specifying "nighttime sleep-aid" is to make it clear that the product will make one drowsy, not just relaxed, and to minimize the possibility of persons taking the product for purposes other than that indicated.

43. Comments both supported and objected to the proposed limitation of indications and labeling claims for OTC nighttime sleep-aids to the terms "helps fall asleep" and "for relief of occasional sleeplessness." In those comments objecting to this restriction, the charge was made that the proposal is unduly restrictive, unlawful, and unconstitutional in that it prevents manufacturers from using truthful alternative wording.

The Commissioner believes that labeling terminology relating to indications for use is inseparable from the scientific and medical determinations made by the Panel and by FDA concerning the conditions under which a drug ingredient is safe and effective. If a manufacturer varies the terminology approved in the monograph, it is representing its product as safe and effective for a condition for which the product's ingredients have not been found to be safe and effective, or else it is assuming that the variant terminology means the same thing as the terminology approved in the monograph. To permit this practice would defeat the purpose of the OTC Drug Review. The Commissioner believes that the listed indications provide a concise description of those therapeutic effects that scientists recognize OTC nighttime sleep-aids to have, in language that is clear, accurate, and meaningful to the layman. If alternative wording or synonyms are desired, the agency may be petitioned for their inclusion in the monograph.

The Commissioner rejects the contention that limiting permissible labeling claims to those approved in the monograph is unlawful and unconstitutional because it prohibits use of truthful alternative wording. The purpose of the OTC Drug Review is to determine which claims are truthful and which are not, and ample opportunity is provided to settle the question through the OTC Drug Review and monograph amendment procedures.

44. A comment suggested that the claim "Helps you relax so you can fall asleep" should be placed in Category I for nighttime sleep-aids because it merely describes one of the requirements of a Category I ingredient.

The Commissioner finds that the term "relax" has definite tranquilizing or calmative connotations that do not properly relate to the OTC use of nighttime sleep-aids. Also, the use of such a term could result in confusion as to whether the product is a daytime sedative or a nighttime sleep-aid. The Commissioner, therefore, proposes to place this claim in Category II for nighttime sleep-aids.

45. A comment suggested that the claim "Reduced time to fall asleep" should be placed in Category I for nighttime sleep-aids because it simply describes one of the requirements of a Category I ingredient.

The Commissioner concludes that the claim for "Reduced time to fall asleep" is not fully synonymous with the requirements for Category I nighttime sleep-aid ingredients. The use of a nighttime sleep-aid should indeed "reduce" the time required for a person to get to sleep by providing the means for such sleep in the case of an individual who might otherwise remain awake. On the other hand, the unqualified claim "Reduced time to fall asleep" can easily be interpreted to support use of the drug by an individual who simply wishes to get to sleep faster than he normally would, but who might not be having any real sleep disturbance. While such use of nighttime sleep-aids may be appropriate, the Commissioner supports the Panel conclusion that it must be proven by further study. The claim therefore remains in Category III.

46. Several comments objected to the recommended warnings for OTC nighttime sleep-aids as too verbose and recommended that only those warnings that are absolutely necessary to make the product generally recognized as safe and effective and not misbranded be used. The comments observed that consumers do not read long-winded warning statements. One comment quotes FDA's statement published in the FEDERAL REGISTER of March 13, 1975 (40 FR 11717):

> It is also recognized that if labeling contains too many required statements, especially general statements of common sense, the impact of all warning statements on the label will be reduced. In addition, there is a space limitation on the number of statements that can appear on labeling.

The Commissioner agrees that the comment raises a reasonable point. The Commissioner has reviewed the recommended warnings and finds that in several cases they are too complex and lengthy for clear and easy understanding by the target population to whom they are directed. Accordingly, the Commissioner has revised several of the Panel's recommended warnings in the interests of conciseness, legibility, and clarity.

47. One comment stated that the proposed warning in § 338.50(c)(1): "For adults only. Do not give to children under 12 years of age" is redundant since both sentences are essentially the same. The comment, while agreeing with the basic warning, suggests that the second sentence be made optional.

The Commissioner agrees that the warning is redundant. However, the Commissioner concludes that the second sentence ("Do not give to children under 12 years of age") should be required since it defines the age group for which the drug is appropriate. The first sentence ("For adults only") should be deleted from the warning.

48. A comment objected to the proposed warning in § 338.50(c)(2): "Do not take this product if pregnant or if nursing a baby". The comment points out that the Panel did not cite any evidence that warrants this warning.

The Commissioner agrees with the Panel's concern that it is best that no drug be used during pregnancy, or while nursing, without the advice of a physician. However, in the absence of any data or information suggesting that this potential safety hazard exists from these drugs, the Commissioner concurs that the warning should not be required.

49. A comment suggested that the word "condition" in the first sentence of the proposed warning in § 338.50(c)(4) be changed to "sleeplessness" for the sake of clarity.

The Commissioner concurs with the comment. Since this wording clarifies the warning, the first sentence of the warning will be revised to read "If sleeplessness persists continuously for more than 2 weeks, consult your physician".

50. A comment recommended deletion of the second sentence of the pro-

posed warning in § 338.50(c)(4): "Insomnia may be a symptom of serious underlying medical illness" as being unnecessary, suggestive and possibly alarming to consumers.

The Commissioner finds that the intent of the warning in question is to inform consumers of the limitations on the usefulness of OTC nighttime sleep-aid drugs. This class of drugs is intended for short-term symptomatic relief in basically healthy individuals. Chronic sleeplessness is a sign of a serious underlying physical, emotional or psychological malady requiring professional medical attention. It is not the purpose of OTC drugs to deal with such medical problems. The Commissioner believes it is in the consumer's best interest to provide full disclosure to the public of all understandable and meaningful information relating to OTC drug usage. This warning is both clear and accurate, and will be retained.

51. A comment objected to the proposed warning for OTC nighttime sleep-aids: "If condition persists continuously for more than two weeks consult your physician. Insomnia may be a symptom of a serious underlying medical illness". The comment suggested instead the following warning: "Do not give to children under 6 or use for more than 10 days unless directed by physician". The comment maintains that this caution is sufficient since neither methapyrilene alone nor analgesic/nighttime sleep-aid combinations containing methapyrilene are subject to abuse in the manner assumed by the Panel, and there have been no findings of such abuse.

The Commissioner finds that abuse is not the issue dealt with by the warning in question. The Commissioner is concerned with misuse or overuse because of failure to understand the limits of OTC drugs. OTC drugs are for minor, self-limiting symptoms which can be self-diagnosed. The warning is designed to assist the user in determining when the limits of self-treatment have been reached. The Commissioner agrees with the Panel's warning.

52. One comment objected to the proposed warning for nighttime sleep-aids in § 338.50(c)(5): "Take this product with caution if alcohol is being consumed" on the basis that this is essentially a drug interaction warning. The comment claimed that there is no documentation of a potentially hazardous alcohol-drug interaction with any of the ingredients in this class of OTC drugs in the amounts used.

While the Commissioner is unaware of any documentation of any past adverse problems with the use of antihistamines as OTC nightime sleep-aids in connection with alcohol, he is aware of the additive depressant effect when antihistamines are ingested with alcohol. The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (September 9, 1976, 41 FR 38311) recommended an antihistamine-alcohol drug interaction warning. The Commissioner is also aware that such a warning is included in the labeling of prescription antihistamine drugs. The Advisory Review Panel on OTC Nighttime Sleep-aid, Daytime Sedative, and Stimulant Drug Products had documentation at 40 FR 57308 of an alcohol-antihistamine interaction in which deepened and prolonged sleep was reported. The Commissioner concludes that the alcohol warning should be retained in the OTC labeling of antihistamine drugs marketed as nighttime sleep-aids.

53. A comment objected to the proposed warning "Caution: This product contains an antihistamine drug" for OTC nighttime sleep-aids since this suggests that every known active ingredient in OTC drugs should be similarly listed. The comment maintains that there is no rationale for this caution and that it is consequently unjustified.

The Commissioner agrees that the Panel did not fully articulate the basis for its recommended warning. In fact, the Commissioner is unaware of any safety data to support the need for this warning at this time. Should an individual ingest a nighttime sleep-aid containing an antihistamine and a cold or allergy product containing an antihistamine, he would at most double the OTC dosage on a one-time-only basis. This has not been shown to be toxic or to have side effects serious enough to warrant such labeling. Based on extensive antihistamine data in the report of the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products Advisory Panel (September 9, 1976, 41 FR 38311) and the fact that OTC nighttime sleep-aids are for occasional use, the Commissioner concludes that the warning should be deleted.

The Commissioner also believes that as written the warning has no meaning to the consumer since it does not provide him with a clear choice of alternative actions.

54. A comment requested the omission of the proposed warning for OTC analgesic-nighttime sleep-aid combinations containig methapyrilene: "For adults only. Do not give to children under 12 years of age". The comment maintains that the Panel's statement that many children have an opposite reaction to drugs compared to that of adults is based on data with regard to diphenhydramine used in infants. The comment maintains that extension of this concern to methapyrilene and to the 6 to 12 year old age group is unsupported by any evidence. While the comment admits that general insomnia in children is not amendable to OTC treatment, it maintains that sleeplessness due to pain is properly treatable in children by an OTC analgesic-nighttime sleep-aid combination product.

The Commissioner disagrees with the comment that an OTC analgesic-nighttime sleep-aid combination would be useful in treating children with sleeplessness due to pain. As noted in comment 32 above, the purpose of such a combination is to treat pain and sleeplessness unrelated to the pain. The Commissioner concludes that insomnia in children should not be treated with OTC drugs. Insomnia does not routinely occur in children, except when it is associated with emotional or behavioral disorders. These conditions should be treated by a physician, and the availability of OTC medication might permit the parents to delay seeking professional help. For these reasons the Commissioner agrees with the Panel that all nighttime sleep-aids either alone or in combination should not be used in children under 12 years of age. As discussed in comment 47 above, the Commisioner has found that the second sentence of the adults only warning proposed by the Panel, "Do not give to children under 12 years of age" should be required. The first sentence "For adults only" should be deleted.

55. A consumer commented that OTC nighttime sleep-aids should bear a warning that these drugs should not be used by persons with glaucoma and that this warning should be in large letters so that it can be readily seen by persons with glaucoma.

The Commissioner notes that the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products Review Panel recommended (September 9, 1976, 40 FR 38311) the inclusion of this and some additional warnings for antihistamine drugs. In view of the expertise of that Panel with respect to the side effects of antihistamines, and after reviewing the basis for that Panel's recommendations, the Commissioner proposes to require the following warning for all OTC nighttime sleep-aids containing antihistamines: "Do not take this product if you have asthma, glaucoma or enlargement of the prostate gland except under the advice and supervision of a physician".

In view of the fact that this warning is of great importance to persons with glaucoma, who might have difficulty reading it, the Commissioner further requires that this warning be in type at least twice as large as that of all other warnings on the package.

I. Comments On OTC Nighttime Sleep-Aids Testing Guidelines

56. Several comments objected to the proposed requirement that sleep

laboratory studies be accomplished before nighttime sleep-aid ingredients can attain Category I status. The comments point out that there is considerable disagreement among experts in the field regarding the meaning and value, if any, of the EEG and polygraphic data obtained from sleep laboratory studies and that the statements and views of several noted experts contradict the Panel's position. One comment quotes Drs. Anthony and Joyce Kales as stating:

> Although considerable information has been amassed in sleep research regarding the physiological characteristics of sleep stages, we have repeatedly stated that we do not know the importance of any sleep stage. For example, the role of R.E.M. deprivation does not result in adverse physiological changes. Similiarly, the importance of increasing or decreasing stage-4 sleep with hypnotic drugs is also not established. [Kales, A., J. D. Kales, "Shortcomings in the Evaluation and Promotion of Hypnotic Drugs," *New England Journal of Medicine*, 293:826-827, 1975.]

Dr. G. W. Vogel is quoted as stating:

> It is concluded that the evidence does not support the hypothesis that R.E.M. deprivation is harmful, and does not support the hypothesis that schizophrenia is an eruption of the dream or R.E.M. state into wakefulness. [Vogel, G. W., R.E.M. Deprivation, III, "Dreaming and Psychoses," *Archives General Psychiatry*, 18:312-329, 1968.]

The comment then goes on to quote various sleep laboratory study experts who participated in a symposium on hypnotics in 1974 as making the following statements about sleep laboratory studies [as reported in Kagan, F., T. Harwood, K. Rickels, A. D. Rudjik, and H. Sorer, "Hypnotics, Methods of Development and Evaluation," Spectrum Publication, New York, 1975.]:

> Dr. Hauri—* * * During the past 20 years the EEG-defined sleep stages and the R.E.M.-NREM dichotomy have been the main focus of sleep research. This was based on the assumption that something as regular, predictive, and observed among all mammals as these sleep stages must have some basically meaningful place in the general scheme of sleep. However, we have not yet found the meaning. [page 24]—* * * Therefore to me, the ultimate test of a hypnotic is not the type of sleep, but the type of wakefulness it produces. [page 25].
>
> Dr. Greeman—* * * What is the physiological or clinical meaning of these polygraphic sleep findings? We are unable to attribute any meaning to acute REM suppression. When this effect was first described some scientists felt that the mechanism of action of sleeping pills had been discovered; hypnotics cause less REM sleep, so the sleeper, upon awakening, has had less dramatic mental activity during sleep and feels that he has "slept like a log". Others looked upon REM sleep suppression as an undesirable side effect. The early, uncontrolled studies of experimental deprivation of REM sleep had shown dramatic effects, now known to be due to the fact that awakenings were so frequent that the subjects were total sleep deprived as well as REM deprived. Despite considerable research we are not positive that REM sleep has any function, although any state with this degree of organization must have some physiological purpose.
>
> Dr. Morgan—* * * Methods for evaluating hypnotics have changed little in 20 years. Newer objective techniques such as the use of the electroencephalogram have increased our knowledge of sleep but have not improved the evaluation of hypnotic efficacy.

Finally, the comments object to the Panel's statement at 40 FR 57296 that "The drug should not interfere in an unusual manner or to an unusual degree with physiological EEG patterns characteristic of normal sleep," since as one comment contends "that the alterations in EEG pattern have not been demonstrated to reflect deleterious effects to generate a consensus within the community of researchers in sleep." The comment requests deletion of this testing requirement.

The Commissioner recognizes that sleep laboratory testing and the exact meaning of electroencephalogram measurements and their relationship to sleep are the subject of much scientific controversy. They do, however, represent one of the few truly objective measurements available for testing this class of drugs. Since the only alternatives available are such subjective measurements as having someone watch the test subject to determine sleep onset, or asking the subject about the quality or duration of his sleep, and since no better alternatives were offered by the comments, the Commissioner concludes that EEG and/or sleep laboratory test results are of value in determining the overall effectiveness of these drugs and should be included in testing to establish their safety. The Commissioner wishes to emphasize that the results of such tests will be evaluated as one component of the test results from sleep laboratory and clinical testing. As noted in comments 24 and 29 above, such tests will not be required for some ingredients.

57. A comment objected to the Panel's requirement for safety testing of nighttime sleep-aids (December 8, 1975, at 40 FR 57313). The Panel stated that "Safety should be evaluated using the current requirements for preclinical testing in animals as defined in 21 CFR 312.1(a)(2)6.a." The comment contends that this was a testing requirement applicable to "New Drugs for Investigational Use" (21 CFR 312.1), and should be required only for those OTC ingredients which have not been subjected to extensive clincial studies or with which there has not been extensive clinical experience, and not to OTC ingredients, such as those reviewed by this Panel, which have a long history of safe consumer use. The comment points out further that the Panel stated in several places in their report their belief that antihistamines are basically safe as OTC nighttime sleep-aids, and that their safety is not in question at the dosage recommended by the Panel. The comment also asks that the requirement for preclinical animal testing be deleted in view of the extensive safety data on antihistamines that have been submitted to the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products.

The Commissioner concurs with the comment and will not require that OTC nighttime sleep-aid ingredients be subject to preclinical testing specified in 21 CFR 312.1. Preclinical testing in animals is required to conclude that a drug is relatively safe to initiate clinical testing in humans. In the case of the OTC nighttime sleep-aid ingredients, such testing would serve no useful purpose since these drugs have been used in humans for as long as 25 to 30 years without any serious safety hazard.

The Commissioner concludes that most ingredients in OTC nighttime sleep-aids are basically safe and merely require some additional proof of effectiveness. Specific effectiveness or safety testing requirements are set forth where necessary for each ingredient.

58. One comment requested clarification of the following Panel statement at 40 FR 57313 about effectiveness testing for approved claims for nighttime sleep-aids: "Regarding effectiveness, a number of important variables must be considered: (1) Sleep latency (time required to fall asleep), (2) number of awakenings, (3) total time spent awake, (4) sleep duration, (5) sleep quality, as estimated by the sleeper, (6) sleep stages and cycles evaluated by EEG and polygraphic criteria, and (7) side effects."

The comment requested clarification as to whether all of these variables must be investigated, irrespective of the claim made for the ingredient. It also argued that except for item 7 (side effects) only those variables directly pertaining to the claim being contemplated for the ingredient should be investigated.

The Commissioner notes that the Panel wanted all these variable tested to yield a complete picture of a drug's effectiveness. Ideally all could be measured in the same test, but some factors can be measured by separate tests. The Commissioner concurs with the Panel that each of these variables should be tested to obtain a complete profile of the drug. (The exception is item 6, which, as noted in comments 24 and 29, will not be required for some ingredients.)

59. A comment stated that the Panel was apparently of the opinion that some special advantage will accrue from laboratory sleep studies of the

antihistaminic drugs proposed for use as nighttime sleep-aids, as evidenced by a statement at 40 FR 57313 that: "On the other hand, objective sleep laboratory studies have obvious advantages to assess objectively and exactly continuous measures of sleep, thus providing exact measures of sleep latency, sleep duration, number of awakenings, and other variables of interest." The comment further objected to the EEG monitoring as unnecessary since these same measures of sleep would be observed by a trained nurse-observer in a clinical trial.

The Commissioner is unaware of any evidence demonstrating that a trained observer can provide monitoring and measurement of variables over an extended time period as accurately as scientific instruments with recording capabilities. The Panel is correct in viewing results from EEG monitoring as an advantage since the problem with previous studies was the softness or lack of objectivity of the data. Accordingly, the Commissioner concludes that where laboratory sleep studies are helpful to a determination of general recognition of effectiveness or safety, they will be retained. Additional clinical studies where sleep is documented by a trained nurse-observer may also be required for some ingredients.

60. One comment objected to the proposed testing requirement that the duration of the nighttime sleep-aid studies "may vary from 1 to 2 weeks." The comment proposed that the length of the studies should depend on and vary with the nature of the protocol.

The Commissioner notes that the normal length of time for OTC nighttime sleep-aid use is not to exceed 2 weeks. It is therefore reasonable to require that testing be done within that same basic length of time. The Commissioner realizes, however, that there may be protocols developed which would require slight deviation from this guideline. The Commissioner concludes that such deviation will be permitted, on an individual basis, if adequate scientific justification is submitted.

61. A comment objected to the Panel's requirement at 40 FR 57313 that studies of nighttime sleep-aids "establish an optimal dosage for the target population for which it is intended under conditions which more closely resemble actual OTC use." The comment states that "it would not be profitable to attempt to precisely define 'optimal dosage'" in light of the heterogeneity of the target population and suggests that the choice of dosage level to be investigated must remain with the manufacturer. The comment proposes that the word "suitable" be substituted for the word "optimal" in the Panel's statement.

The Commissioner disagrees with the comment. The term "suitable" is too imprecise and would defeat the basic purpose of the OTC drug monographs. The function of the OTC drug monographs is to delineate to the extent possible, in light of the present state of the art, the safest and most effective dosage level. Therefore, the Commissioner concludes that since the "optimal dosage" is the smallest dosage that shows both the desired effectiveness and safety, it is exactly this dosage level that should be determined.

62. Another comment objected to the Panel's statement at 40 FR 57313 regarding the objectives of clinical studies of nighttime sleep-aids. The comment specifically objected to the requirement that these studies "determine any preferences the subjects may have between 2 nights (drug versus placebo)" since this can only be satisfied by the performance of crossover studies in which both placebo and drug are tested within a short interval.

The comment is correct that a crossover design study is required to determine subject preference between the drug and the placebo, and that ideally the interval between the drug and the placebo test should be rather short. While this may present some difficulty, it is extremely imnportant to have this subject preference data as part of the overall evaluation of safety and effectiveness of these drugs, since the placebo effect is extremely high in all drugs of this type. The Commissioner agrees with the Panel and will retain the requirement.

63. One comment requested clarification of the following statement at 40 FR 57313 regarding the types of population to be studied for nighttime sleep-aids: "A greater variety of populations differing as to age, sex, diagnostic categories, social class, treatment setting, previous treatment, etc., may be studied." Specifically, the comment wishes clarification of whether the first sentence implies that a large variety of populations "must" be studied.

The Commissioner finds that, taken in context, the requirement is suggestive, not mandatory.

64. One comment objected to the requirement that a factorial design test is necessary to determine the effectiveness of each ingredient, or placebo, on the grounds that such a requirement is unjustified, academically oriented research, and not sanctioned under the law. The comment points out that no factorial design studies were required for testing of antacid/analgesic combinations products in the OTC Antacid monograph. The comment contends that all that is required to justify the combination is evidence of a pharmacologic contribution. The comment further points out that the Panel has stated that: "If a combination contains an analgesic and a nighttime sleep-aid, both of which are safe and effective when used alone, it is convenient to combine the ingredients in a combination for the treatment of concurrent symptoms. The Panel would recognize the combination as safe and effective (effective as both a nighttime sleep-aid and as an analgesic in a significant proportion of the population having both sleeplessness and pain at the same time)." The comment contends that these conditions have been met by data submitted to the Panel, and therefore urges that a combination of methapyrilene and aspirin, acetaminophen or salicylamide be placed in Category I.

The Commissioner disagrees. The factorial design testing is a practical method of determining if each ingredient does in fact contribute significantly to the combination. In any case, the comment would no longer apply since methapyrilene, and consequently the entire combination, has been placed in Category II for safety.

65. A comment stated that, while the Panel's general description of a suitable target population for nighttime sleep-aids (those with mild or occasional sleep disturbances) was appropriate, clinical studies should not be constructed in such a way that subjects would be tested only on those nights when they happened to experience a spontaneous sleep disturbance.

The Panel did not feel that individuals with induced or chronic sleeplessness were ideal subjects for testing these drugs. The Panel in its report, in fact, rejected testing of chronic insomniacs at a mental institution because they were not normal individuals suffering from occasional sleeplessness. The Commissioner fully agrees with the Panel that these drugs should be tested on the same basic target population in whom they are intended for use. The comment is therefore rejected, and the requirement will be retained.

66. One comment was made regarding the Panel's statement at 40 FR 57313: "Females of childbearing age may be included if results of animal reproductive and teratologic studies are satisfactory. However, the Panel believes that new drugs not intended for lifesaving use should not be used in women known to be pregnant or who are nursing a baby." The comment questioned both the meaning of the first sentence and the necessity for conducting the reproductive and teratologic studies in every case for the ingredients being considered as OTC nighttime sleep-aids in view of the vast clinical experience with them.

The Commissioner agrees that it is not appropriate to use pregnant or nursing women in the studies requested by the Panel. The Panel was merely

expressing its concern and general feeling with regard to the use of pregnant or nursing women and women of childbearing age as subjects in any but the most critical research. However, there is no data or information that would indicate any reason to exclude from these studies women of childbearing age. The Commissioner concludes that animal reproductive and teratology studies are likewise unnecessary in view of the vast clinical experience with these drugs and their well-known clinical profiles.

67. One comment objected to the Panel's requirement that for studies of OTC nighttime sleep-aids "The investigators should be experienced in evaluating drugs affecting the central nervous system; and in the conduct of clinical trails; they should have ready access to the target population group for whom the nighttime sleep-aid may be indicated." The objection was based on the limited number of investigators who would be available under this restriction, and the comment requested the agency to broaden the description of investigator to include at least competent clinical pharmacologists and others qualified by virtue of training and experience to conduct such studies.

The Commissioner wishes to emphasize that the purpose of this requirement is to ensure competent, well-designed and well-conducted studies and not to develop a small cadre of selective individuals to carry out the studies. While such competence is often shown by previous experience and by access to the target population, it is the opinion of the Commissioner that this should not be made a requirement, and the Testing Guidelines will be modifed to reflect this. The Agency will review the adequacy of all tests on their own merits.

J. GENERAL COMMENTS ON OTC DAYTIME SEDATIVES

68. One comment stated that the Panel's factual findings require the Commissioner to place daytime sedatives in Category II and order them removed from the market on grounds of both safety and effectiveness.

The Panel recommended that the Commissioner place four antihistamine ingredients in Category III on the ground that the available evidence would not permit a final classification in Category I or II. The comment objected to this classification because Category III status would authorize the marketing of OTC antihistamine daytime sedatives for 3 additional years when the Panel found no evidence of benefit from them. The Panel concluded that antihistamine daytime sedatives may cause drowsiness, but that "There is little or no evidence that such drugs possess anti-anxiety psychotropic properties comparable to those demonstrated in clinical studies with prescription tranquilizers." "Any anti-anxiety psychotropic activity, if it exists, most likely would be related to the 'drowsiness' effect of the antihistamine." Antihistamine daytime sedatives make the user sleepy, they do not affect mood, or reduce anxiety, as do some prescription tranquilizers. For this reason they are ineffective as daytime sedative agents and, therefore, the comment argues, the Commissioner should place them in Category II.

The comment also stated that, in addition to being ineffective, daytime sedatives should be placed in Category II because they are unsafe. The Panel has noted its concern "with a possible danger in 'treating' simple and transient variations in normal mood and behavior with OTC products containing antihistamines." According to the Panel, "There is also possible danger that because of excessive sedation, individuals with normal anxiety-like symptoms will involuntarily and unwittingly suffer reduced alertness, ability to concentrate and motor coordination." Thus, according to the comment the drug might be unsafe if its user were to drive or cook, and for this additional reason the Commissioner should place all antihistamine daytime sedatives in Category II.

The Commissioner notes that the Panel decision as to whether daytime sedatives should be placed in Category II or III was not unanimous. The majority of the Panel was doubtful that there were adequate "benefits inherent in the changes claimed to be produced by OTC daytime sedatives" (40 FR 57318). They were unable to determine any deomonstrable indications for which OTC daytime sedatives are useful, and felt that further testing would be necessary to prove the existence of a suitable target population, as well as the safety and effectiveness of OTC daytime sedatives. The majority wished to allow maximum opportunity to prove these factors, even though they expressed doubt that a suitable target population could be delineated, or that effectiveness apart from drownsiness could be shown. Thus, they placed antihistamine OTC daytime sedatives in Category III. The minority of the Panel found no clear evidence of effectiveness and no sharply defined indications. In addition, they were concerned that the proposed clinical trials, if properly conducted, would probably take 4 to 6 years to prove effectiveness. They indicated that this interval would constitute an extraordinary length of time to market a group of drugs not deemed effective at present dosage levels, and potentially hazardous to ambulatory patients at higher doses. The minority would have classified OTC daytime sedatives as Category II.

The Commissioner believes that maximum opportunity should be offered to all interested parties to come forward with supporting data. However, for several reasons, the Commissioner is unable to support the continued marketing of OTC daytime sedatives while testing is carried out.

Before any drug can be generally recognized as safe and effective, a suitable target population must be defined, as required in 21 CFR 330.10(a)(4)(ii). A suitable target population would include those persons who require treatment for tension and other symptoms of anxiety on a short-term or intermittent basis. "Tension" or "nervous tension" is not a single disease entity, but is a component of the anxiety syndrome.

The Commissioner concludes, based on recent data, that the mode of action of prescription anti-anxiety drugs does not involve inducing drowsiness; drowsiness is not only unrelated to the anti-anxiety effect of these drugs, but is an undesirable side effect of these anti-anxiety agents.

In contrast, the only effect of antihistamine drugs is to make one drowsy or sleepy, not to calm him or reduce anxiety. The drowsiness, while it serves as a logical basis for permitting antihistamines to be marketed as OTC nighttime sleep-aids provides no benefit for patients who would use these products during the day when they need to be alert.

Since this is the case, the Commissioner rejects the premise that proving that an antihistamine makes one drowsy constitutes proof of effectiveness in treating symptoms of anxiety. For these reasons, the Commissioner concludes that there are no suitable OTC indications for these drugs and no identifiable target population and that, therefore, OTC antihistamines cannot be generally recognized as safe and effective as daytime sedatives.

69. One comment stated that, since the bromides and scopolamine are not safe and effective as daytime sedatives and since the antihistamines cause drowsiness without "calming" the user, all daytime sedatives are ineffective and should be removed from OTC sale.

The Commissioner has reviewed, and concurs with, the findings of the Panel that scopolamine and the bromides should be placed in Category II (not generally recognized as safe and effective or misbranded) and in due course they will be removed from the market.

The major class of drugs reviewed for use as OTC daytime sedatives is the antihistamine group. In its discussion of OTC nighttime sleep-aids, the Panel concluded that some antihistamines are probably useful in producing drowsiness and sleep due to a general, nonspecific central nervous system (CNS) depression. But as discussed in comment 68 above, this nonspecific CNS depression is not effec-

tive in reducing tension or other symptoms of anxiety and the drowsiness caused by antihistamines can be hazardous in patients whose daytime activities require mental alertness and coordination such as driving a car or operating machinery.

After reviewing all available data, the Commissioner concludes that antihistamines as well as scopolamine and the bromides should be classified as Category II for lack of effectiveness and safety at marketed OTC dosage levels.

70. A comment pointed out that the Panel has failed to recognize the effectiveness of any ingredient as a daytime sedative and expressed the feeling that the Panel's requirements for proof of effectiveness are largely due to a general bias against this class of drugs. The comment contends that, taken in their entirety, the studies required are unreasonable.

The Commissioner disagrees. There are very few studies on the effectiveness of antihistamines as daytime sedatives or calmatives. The available data on the sedative effects of antihistamines relate to their effectiveness in promoting sleep, an effect very different from that of a daytime sedative. The studies suggested by the Panel would require 4 to 6 years to complete, and the Commissioner has concluded that OTC daytime sedatives cannot be permitted on the market during that period of time. The reasons for this decision have been discussed in the response to comment 68 above.

71. One comment stated that OTC daytime sedative ingredients found to be unsafe should be removed from the market.

The Commissioner emphasizes that any ingredients found to be unsafe will be removed from the market. However, the Panel concluded and the Commissioner agrees that the ingredients placed in Category II are presently marketed at levels too low to result in any serious safety concern. If such a situation did exist, the Commissioner would act outside the usual OTC Drug Review administrative process as he did for the halogenated salicylanilides as published in the FEDERAL REGISTER of October 30, 1975 (40 FR 50527). The Commissioner appreciates the support of the drug industry in this OTC Drug Review process and notes that the major drug manufacturer of the bromide salts in the United States has removed these ingredients from its product.

As noted above in comment 68, the Commissioner has concluded that OTC daytime sedatives, in current OTC dosages, may cause drowsiness that can be hazardous in persons trying to adhere to a normal daytime routine. The Commissioner has concluded that these products should be classified in Category II on grounds of both lack of safety and lack of effectiveness. He further concludes, based upon the current available data, that there is not a demonstrated, sufficient hazard to health to initiate action outside the normal OTC Drug Review administrative process.

72. One comment alleged that Category III was illegal, and that, for this reason, FDA has no authority to sanction the marketing of OTC daytime sedatives in the absence of an approved new drug application.

This position was answered in the reply to comment No. 4 of this preamble. The matter is currently in litigation, and the Commissioner's position will be explained there.

73. A comment stated that, even if the Commissioner decides that Category III is authorized by statute, this is not an approriate case for permitting the marketing of a drug which is not generally recognized as safe and effective. The comment argues that it has been almost 4 years since the agency notified manufacturers of daytime sedatives of the OTC Drug Review, and requested evidence on safety and effectivenes. Having failed to produce any reliable evidence up to this time, the comment argues, it is unlikely that these manufacturers will generate evidence showing safety and effectiveness in 3 additional years. The comment goes on to state that there is no justification for marketing these drugs pending final testing if, as the panel found, these drugs confer no benefit.

The Commissioner believes that the comment has misinterpreted the original call for data. There was no requirement for testing imposed at that time, merely a request to submit, for review and evaluation, published and unpublished data and information pertinent to the designated Category of OTC drugs. The Panel, after 3 years of deliberation, determined that further studies would have to be carried out on daytime sedatives. This was only an advisory opinion and manufacturers were not required to begin testing. Testing is required only when a final monograph is published in the FEDERAL REGISTER.

In addition, the comment has incorrectly interpreted the findings of the Panel, at least those of the majority. The Panel questioned whether the existence of a target population could be proven and having insufficient data to positively disprove the existence of this population placed this drug in Category III. The Panel requested information showing the existence of a population, but a minority of the Panel argued that there could be no identifiable target population for OTC daytime sedatives and hence there was no basis for a Category III classification. It is the Commissioner's view that the conclusions of the minority are better reasoned and supported. The Commissioner concludes that the time frame projected for completion of the studies, 4 to 6 years, is too long to permit OTC daytime sedatives to remain on the market when no target population has been clearly defined and where there is no proof of effectiveness. Therefore, the Commissioner has concluded that OTC daytime sedatives should be classified in Category II as discussed above in comment 68.

74. One comment stated that the Panel's statement at 40 FR 57322 expressing concern over advertising of OTC daytime sedatives and recommending a ban on advertising during the testing period should be rejected by the Commissioner as being biased and without scientific merit and beyond the Panel's charge. The comment contends that the concept of allowing the Panel to recommend that advertising for daytime sedatives be banned is totally repugnant to and inconsistent with the cooperation being given by the industry, consumers, and the agency in the conduct of this OTC Drug Review.

The OTC Drug Review Panels are advisory, and as such do not issue binding rules or regulations. They are, however, free to comment on any scientific or policy issue that they have considered in the course of their review. The Commissioner welcomes their suggestions and comments even in cases such as this, where he has no authority to implement their recommendations. The Commissioner advises that he will bring the Panel's concerns to the attention of the Federal Trade Commission, which has the responsibility for regulating OTC drug advertising.

75. Another comment supported the Panel's conclusion that, if a person has simple nervous tension every day for longer than 2 weeks, then he is likely to be taking an OTC daytime sedative for a condition which requires medical intervention.

Since the Commissioner has determined that all OTC daytime sedatives shall be Category II, the comment is moot.

76. A comment stated that "simple nervous tension" is defined by current medical standards, and that the Panel has acknowledged that many persons experience tension at some time and most have learned to deal with it. The comment takes the position that "simple nervous tension" is an OTC indication for the symptomatic relief of a mild degree of tension in the normal functioning individual with periods of episodic stress, and that these symptoms do not require prescription drugs.

The comment states further that the target population for daytime sedatives in a modern environment is very large. The person manifesting

severe symptoms and unable to cope with minor stresses obviously requires medical supervision and is not an appropriate candidate for OTC medication. On occasion almost all persons are subject to stress requiring symptomatic relief of simple nervous tension, and these individuals should have a readily available mild medication for relief of the symptoms of stress that do not require a physician's or psychiatrist's attention.

The comment contends that the symptomatology of simple nervous tension is measurable in a target population by objective studies utilizing known techniques for measuring mood, discomfort, and life crises.

The Commissioner disagrees that the term "simple nervous tension" is a well-defined medical entity. The Commissioner is unaware of any data or information that supports this statement, nor does the comment provide any definitions, references, or other supporting data. The comment does not spell out what these symptoms are nor what techniques could be used to measure them. Although tension is one of the components of anxiety, the syndrome of "simple nervous tension" has not been clearly associated with the clinical syndrome known as "anxiety," according to data submitted to FDA. Nor has the syndrome of "simple nervous tension" been defined in any medical literature. Tension is only a component of the anxiety syndrome; it does not exist alone as a disease entity.

After reviewing all available data, the Commissioner concludes that there is no target population of persons who could benefit from OTC daytime sedatives. Individuals with true anxiety and accompanying tension should be treated with appropriate anti-anxiety therapy by a physician. Persons with normal episodic tenseness should probably not be treated with drugs at all, and the drugs currently available as daytime sedatives have no effect on symptoms of anxiety and tension. Their only effect is to make one drowsy, and there is no data that show that drowsiness or sleepiness acts to relieve tension. For all these reasons, the Commissioner has concluded that the claim "occasional simple nervous tension" and the class of daytime sedatives used to treat it should both be classified as Category II.

K. COMMENTS ON OTC DAYTIME SEDATIVES LABELING AND WARNINGS

77. Comments both supported and opposed the Panel's recommendation that labels for Category III daytime sedatives contain the following warning: "Warning: This product has not been demonstrated to be effective to the satisfaction of the Food and Drug Administration." One comment urged that a similar warning be placed on the label of all drugs in Category III since consumers have a right to adequate and accurate information about drugs they use.

The Commissioner disagrees. Daytime sedatives, or for that matter most drugs placed in Category III, have been on the market for many years. Classification in this category permits them to remain on the market for a brief additional period while evidence is developed to permit their final classification into either Category I or Category II. To require an effectiveness warning on products while these questions are being resolved would be misleading since such a warning implies a total absence of data on the effectiveness of products. Additionally, there may be minor questions about safety, labeling, or combinations with other ingredients which have not been resolved (e.g., the product may cause minor irritation, have a minor side effect or be longer acting when combined with another ingredient) that require Category III classification but that are too minor to make such a warning appropriate. Finally, the Commissioner is concerned that labeling of this type might cause a useful ingredient to be dropped and not tested purely for economic and not scientific reasons. This would defeat the very purpose of Category III, that is, to encourage testing of products using modern experimental methods within a certain time.

Accordingly, the Commissioner concludes that such a warning is inappropriate. However, since the Commissioner has classified daytime sedatives as Category II, the point is moot as to them.

78. On comment urged that labeling for OTC daytime sedatives be made larger and clearer to permit easier reading of labels by senior citizens.

The Commissioner notes that the Fair Packaging and Labeling Act and its implementing regulations currently require that the labeling of all OTC drugs be clear and legible. The Commissioner sees no need to specify the exact size and style of type for all labeling for particular OTC products, but he agrees with the intent of the comment. He urges that labeling for any OTC products whose population may include substantial numbers of senior citizens or people with impaired vision be designed to ensure adequate size and clarity of all print. However, since daytime sedatives are classified as Category II, the comment is moot.

79. A comment stated that use of the term "daytime sedative" to describe a class of products for simple nervous tension or nervous tension headaches is confusing and may be misleading as these products are not intended as sleep-aids. The term "sedative" by its very definition suggests sleep. "Daytime calmative" was suggested as a far more appropriate term to distinguish these products from sleep-aids and more potent prescription tranquilizers.

The Commissioner agrees that the use of the term "daytime calmative" is more appropriate for a class of drugs indicated for use in relieving tension during periods of normal daytime activity. But, as discussed in Comment 68 above, the Commissioner has concluded that none of the ingredients reviewed by the Panel for use in OTC daytime sedatives effectively relieve tension during periods of normal daytime activity and that all ingredients submitted as daytime sedatives should be classified in Category II. Therefore, the comment is moot, and the term "daytime sedative" will be retained in this document.

80. One comment objected to the Category II classification of the following daytime sedative labeling claims: "Nervous tension headaches", "nervous irritability", "simple nervous tension due to everyday overwork and fatigue", and "calmative". The comment stated that these claims are equivalent to or explanatory of the recommended Category III claim "occasional simple nervous tension". The comment stated further that the other phrases objected to by the Panel, namely, "a relaxed feeling", "calming down and relaxing", "gently sooth away the tension", and "resolving that irritability that ruins your day", appear to constitute promotional claims rather than labeling and are thus not within the purview of the Panel.

The Commissioner concurs with the Panel that the claims for "nervous tension headaches" and "nervous irritability" are not equivalent to the recommended Category III claim of "occasional simple nervous tension" in that they imply a special type of problem or tension from a particular source. They will remain in Category II.

The Commissioner is also concerned about the phrase "simple nervous tension due to everyday overwork and fatigue". It refers to factors that are in and of themselves unlikely to cause nervous tension. OTC daytime sedatives do not relieve fatigue and, in fact, may increase such fatigue by their pharmacological mode of action. Therefore, the Commissioner concurs with the Panel's Category II recommendation for this phrase or similar phrases which attempt, albeit unsuccessfully, to describe the cause or source of tension.

The Commissioner concluded above in comment 76 that the claim "occasional simple nervous tension" should be classified in Category II since this term does not refer to a well-defined medical entity. As discussed in comment 79 above, the Commissioner will

retain the Panel's Category II recommendation for the term "calmative".

The comment's contention that the other phrases objected to by the Panel are promotional claims and consequently not within the Panel's purview is rejected. The Commissioner concludes that any labeling for an OTC product is within the Panel's purview. In addition, it is entirely correct for a Panel to recommend against the use in labeling of any term or phrase that they consider misleading or medically imprecise, even if such a claim has previously been limited to advertising.

81. One comment objected to the proposed warning "Do not take this product if pregnant or if nursing a baby" recommended for use on daytime sedatives, on the basis that the Panel did not cite any specific evidence supporting the need for this warning.

The Commissioner agress with the Panel that it is best that no drug be used without the advice of a physician during pregnancy or while nursing. However, a decision to require a label warning against the use of a particular drug or class of drugs during that period must be based on a substantial reason to believe that an actual safety hazard would result from such use. In view of the lack of such data the Commissioner must concur with the comment. However, since all ingredients used as daytime sedatives have been classified as Category II, the point is moot.

82. Another comment objected to the following general warning recommended by the Panel for OTC daytime sedatives: "Do not take this product if you are presently taking a prescription or OTC drug without consulting a physician or pharmacist", and suggesting that it be deleted in favor of specific drug interaction warnings where appropriate.

The question of whether to have general or specific drug interaction warnings was discussed at considerable length in the June 4, 1974 proposed general conditions on OTC drugs, and that discussion will not be repeated here. Based on that discussion, the Commissioner has concluded that the proper way to inform the consumer of potential drug interactions is to require that the labeling include a separater section headed "Drug Interaction Precautions." The Commissioner realizes that such interactions may be somewhat complicated. He is concerned, however, that a broad general warning would have no impact and would not be in the consumer's best interest, since the user would not be alerted to specific drug/drug or drug/disease interactions that could in certain circumstances be life threatening. The Commissioner supports specific warnings where appropriate, but since all daytime sedatives are Category II, the point is moot.

83. One comment objected to, and requested the deletion of, the proposed warning: "Take this product with caution if alcohol is being consumed" for daytime sedatives as being inappropriate for this class of OTC drugs. The comment expressed ignorance of any documentation by the Panel of potentially dangerous alcohol drug interactions with any OTC daytime sedatives at marketed doses, and pointed out that other FDA OTC Drug Advisory Review Panels have not required a warning regarding the same OTC ingredients.

The Commissioner concluded in comment 52 that such a warning should be required for OTC nighttime sleep-aids since the depressant effect of alcohol when combined with the antihistamines would be additive. This same additive effect would be especially hazardous when daytime sedatives are consumed with alcohol. The Commissioner concludes that an alcohol warning would be appropriate for daytime sedatives. However, since all daytime sedatives are Category II, the point is moot.

84. One comment pointed out that the two sentences in the proposed daytime sedative warnings, "For adults only. Do not give to children under 12 years of age," are redundant. The comment suggested that the second sentence in the warning be made optional.

As noted in comment 47 relating to OTC nighttime sleep-aids, the Commissioner concurred that the warning is redundant and deleted the first sentence of the warning. However, any discussion of warnings is moot since this entire class of drugs is Category II.

L. COMMENTS ON OTC DAYTIME SEDATIVES TESTING GUIDELINES

85. One comment con0Pi136°tended that the time provided for Category III testing of OTC daytime sedatives, in view of the acknowledged necessity for developing methodology in this area, is so confining as to be prejudicial.

The Commissioner concluded in comment 68 that all daytime sedatives should be classified Category II. The Commissioner concludes that it is inappropriate to discuss any further testing for safety and effectiveness of daytime sedatives and will delete any discussion of testing guidelines for this class of drugs from this document.

86. One comment objected to the safety testing requirement proposed for daytime sedatives since, with respect to safety, it is obvious that those drugs, which are antihistamines, will possess the same properties as antihistamines in the same dosages for other OTC drug indications.

The comment is correct in stating that antihistamines have the same properties when used in the same dosages whether used as daytime sedatives or for other indications. A number of safety issues such as impairment of motor function, reduced alertness and impairment of sensory performance are not problems when these drugs are used as OTC nighttime sleep-aids. Reduced alertness is important, however, when these ingredients are used in patients conducting normal daily activities. It becomes extremely important to determine the degree to which antihistamines might impair an individual's ability to react to motor traffic, operate machinery, cook, or deal with everyday hazards.

The Commissioner has concluded, however, that antihistamines are not appropriate for use as daytime sedatives and that safety testing guidelines should therefore not be included in this document.

87. Comments objected to the following statement on effectiveness testing of OTC daytime sedatives at 40 FR 57322: "The Panel doubts, however, that any such effectiveness can be differentiated from the placebo effect." The comment contends that the Panel's conclusion is arbitrary and biased in face of the well-recognized calmative effects of the ingredients used in this class of products.

The Commission disagrees that the calmative effects of antihistamines are well-recognized. The sedative effects may be evident, but there is no conclusive evidence that these drugs have any calmative action. The Panel's remark was intended to point out that, while these ingredients were placed in Category III to permit definitive testing of their calmative effects, the Panel, based on its review of antihistamine mechanisms of action and the available data, had serious doubts as to the potential success of such testing. The Panel did not intend to display bias, but to point out quite clearly the difficulties in the development of data required to prove the effectiveness of these ingredients as daytime sedatives.

The Commissioner proposes to place OTC daytime sedatives in Category II and concludes that testing guidelines should therefore not be included in this document.

88. One comment objected to the requirement that the qualifications of investigators be provided to FDA before beginning studies on Category III daytime sedatives.

While agreeing with the Panel's statement that studies be conducted by qualified investigators, the Commissioner concurs with the comment that there is no demonstrated need for preclearance of investigators. However, since the daytime sedatives have been classified as Category II, the point is moot.

M. GENERAL COMMENTS ON OTC STIMULANTS

89. A comment stated that caffeine preparations should be removed from the OTC market because a stimulant should be used in disease states only where a stimulant is recognized as a therapeutic necessity. At the present time, most people are using it to replace sleep.

The Commissioner notes that the Panel was composed of medical experts who were of the opinion that there exists a suitable healthy adult target population which can benefit from the occasional use of safe and effective OTC stimulant drugs. The Panel did not recommend their use in disease states. The Panel emphasized that such products are for occasional use only and never for more than 1 to 2 weeks except under the advice and supervision of a physician. The Commissioner concludes that stimulants should be used only to temporarily help restore mental alertness or wakefulness when experiencing fatigue or drowsiness.

90. A comment stated that stimulants containing caffeine are dangerous. The person who comment urged that they be packed in glass, tin, or plastic containers with safety caps since his pet dog died after eating a number of caffeine tablets packaged in a cardboard box.

The Commissioner, after reviewing all pertinent data, finds no evidence that stimulants containing caffeine in currently marketed OTC drug products are dangerous to humans and finds no reason to prohibit their being packaged in cardboard containers.

The Commissioner advises that the issue of whether these drugs may be safely packaged in cardboard containers would, of course, be within the jurisdiction of the Consumer Product Safety Commission, which administers the Poison Prevention Packaging Act.

91. One comment stated that according to J. M. Ritchy *in* L. S. Goodman and A. Gilman, eds., "The Pharmacological Basis Therapeutics," McMillan, N.Y., 4th Ed., p. 359, 1970, caffeine's main action is to allay drowsiness and fatigue and that this action may be brought on by the administration of 150 to 200 mg of caffeine. The comment then stated that most of the OTC preparations, if taken as suggested, will not elicit a pharmacological response.

The Commissioner notes that the Panel was aware of the Goodman and Gilman citation and used this reference as well as a variety of additional data in arriving at their decision that the administration of 100 to 200 mg of caffeine not more often than every 3 to 4 hours does elicit a pharmacological response and that this dosage range is suitable for use as an OTC stimulant drug. While narrower, the activitiy range suggested by J. M. Ritchy in Goodman and Gilman coincides with that arrived at by the Panel. The Commissioner finds no basis for revising the dosage schedule proposed by the Panel.

92. One comment stated that caffeine-containing stimulants do not belong on the OTC drug market because their dosage is only equivalent to a strong cup of coffee or tea.

The Commissioner disagrees with the comment. While the consumer may derive the same stimulant effect from drinking beverages containing caffeine, the Panel recognized and the Commissioner concurs that there is a suitable target population which can benefit from the occasional use of safe and effective OTC stimulant products containing caffeine. It is the Commissioner's view that some individuals, for a variety of reasons, may prefer the tablet or capsule form of this drug to the beverage, and thus should have such a choice available to them.

N. COMMENTS ON OTC STIMULANT COMBINATIONS

93. A comment requested that the classification of ammonium chloride as a single active ingredient for use in stimulant drug products be deleted for the following reasons:

a. There has been no submission of such a drug product to the Panel for their evaluation.

b. There is no labeling of any pharmaceutical product relying on ammonium chloride as a stimulant.

c. There has been no claim of efficacy made for this ingredient other than as a diuretic agent.

The comment expressed concern that the listing of this ingredient in the stimulant area will cause confusion.

The Commissioner notes that a submission was made to the Panel on a stimulant that declared among its active ingredients ammonium chloride. While the Panel was well aware that this ingredient has some use as a diuretic, it was not specified to them whether any stimulant properties were being attributed to it in the product in question. They had no alternative, therefore, but to consider it and classify it with respect to stimulant activity. The classification of it in Category II for one type of use of course is not intended to reflect on its safety and effectiveness for other uses. The Panel clearly points out in their report that they deferred review of ammonium chloride as a diuretic to the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. The comment is therefore rejected.

94. One comment stated that the combination of caffeine and ammonium chloride is safe and effective as an aid in the relief of premenstrual symptoms of swelling, weight gain, and fatigue. The comment stated that the purpose of the caffeine is to alleviate the mental and physical fatigue which commonly accompanies water retention during the premenstrual period. The comment also states that the report does not indicate what evidence, if any, was considered or relied upon to make the determination that the combination of caffeine with ammonium chloride is irrational, and that there is no indication in the report or in the evidence before the Panel to show that due consideration was given to a need for concurrent treatment of water retention and fatigue in premenstrual women.

The comment urges that the recommendation of the Panel with respect to the combination of ammonium chloride and caffeine for OTC use to relieve the symptoms of swelling, weight gain, and fatigue which occur during the premenstrual period be set aside and that only the pertinent recommendation for caffeine be accepted. The comment then urges that final classification of the combination be deferred until the Advisory Review Panel on OTC Miscellaneous Internal Drug Products has had an opportunity to review the effectiveness of ammonium chloride as a diuretic agent.

The Commissioner advises that the Panel, based on its expertise and the data reviewed on caffeine, stated that if found no acceptable evidence that this combination of ingredients would be effective in relieving fatigue. The Panel further stated at 40 FR 57327 that caffeine alone could be expected to increase rather than cause any decrease in the nervousness associated with premenstrual tension. Since the comment offers no additional data to refute the Panel's findings, the Commissioner rejects the comment and will retain the Panel's classification of this combination. In the event that the Advisory Review Panel on OTC Miscellaneous Internal Drug Products classifies this combination differently in light of new or additional data, the Commissioner will reopen the issue.

O. COMMENTS ON OTC STIMULANTS LABELING AND WARNINGS

95. A comment stated that the indications for stimulants as set forth in the proposed monograph omit any references to the perfectly valid use of such products to ward off anticipated drowsiness. Although the Panel's recommended dosage directions acknowledge the usefulness of such products in preventing the return of drowsiness by the allowance for repeat doses every 3 to 4 hours, there is no provision for general prophylactic use.

The Commissioner advises that while the Panel recognized that OTC stimulants could safely and effectively be used to restore mental alertness or wakefulness when fatigue or drowsi-

ness was being experienced, the Panel found no basis for recommending general prophylactic use of OTC stimulants. In fact, any recommendation for general prophylactic use would run directly counter to the Panel's recommendation that these products are only for occasional use. "General prophylactic use" would imply very regular long term use at any time that an individual felt he might conceivably become fatigued. Neither the Panel nor the Commissioner has any objections to the ready availability of OTC stimulants for use when needed; in fact, they support it. The Commissioner concludes, however, that it would be irresponsible to recommend that an OTC drug be consumed regularly because the user might or might not experience the symptoms for which it is recommended. Using the same logic, one could recommend "general prophylactic use" of an antacid or laxative every day on the chance that one might experience the need for it at some later time during the day. The Commissioner rejects the comment as inappropriate.

96. One comment objected to the following warnings: "*Caution:* Do not exceed recommended dose since side effects may occur which include increased nervousness, anxiety, irritability, difficulty in falling asleep and occasionally disturbances in hearing rate and rhythm called palpitations" and "*Contains caffeine.* Do not take this product with large amounts of caffeine-containing beverages such as coffee, tea or cola drinks". The comment argued that these warnings are unnecessary since the established name of the drug, caffeine, must appear on the principle display panel of the product label and since the public, as a result of its vast experience with coffee, tea, and cola drinks, is well aware of the side effects of excessive caffeine intake. The comment states that these warnings are excessive since they are based solely on the Panel's opinion and since the dosage of those products is only approximately equivalent to a single cup of coffee.

Even though the public is familiar with caffeine, the Panel felt and the Commissioner concurs, that the public is not aware of all the possible side effects of excessive caffeine consumption. The Commissioner concludes that the warning, "*Caution:* Do not exceed recommended dose since side effects may occur which include increased nervousness, anxiety, irritability, difficulty in falling asleeep and occasionally disburbances in heart rate and rhythm called palpitations", alerts the consumer to the possible specific effects of excessive caffeine consumption, and he invites further comment on this warning. Since individuals could inadvertently overdose themselves with caffeine if they ingested it from several different sources simultaneously, the Commissioner concludes that the other Panel recommended warning is necessary, but further clarifies it to read: "The recommended dose of this product contains about as much caffeine as a cup of coffee. Take this product with caution while taking caffeine-containing beverages such as coffee, tea or cola drinks because large doses of caffeine may cause side effects as cautioned elsewhere on the label". The Commissioner concludes that this proposed warning will have more meaning to the consumer than the warning originally recommended by the Panel, and he is interested in receiving further comment on this warning.

97. One comment stated that the warning "For occasional use only. If fatigue or drowsiness persists continuously for more than two weeks, consult a physician" is unnecessary since it is based on speculation and not on findings of fact as to its need and, in addition, it tends to state the obvious.

The Commissioner finds that fatigue or drowsiness, especially when experienced for 2 weeks or more, may be symptomatic of a number of serious disorders requiring the attention of a physician. This is common medical knowledge and sound common sense, not mere "speculation" as the comment suggests. As to the comment's contention that this warning states the obvious, the Commissioner agrees. However, many if not most warnings serve that purpose, and they remind people of important facts which, while obvious to many, might be overlooked by some. The comment is therefore rejected. The Commissioner concludes that the warning should be retained.

98. One comment objected to the following proposed warning for OTC stimulant drugs: "*Caution:* Do not exceed recommended dose since side effects may occur which include increased nervousness, anxiety, irritability, difficulty in falling asleep, and occasionally disturbances in heart rate and rhythm called palpitations" on the basis that it is too long and may cause concern among consumers.

The comment further states that there is no need for the label to reiterate the possible side effects of higher than normal doses, and states this warning is more appropriate for prescription package insert labeling. In addition, the comment expresses concern that the layman would fail to understand the terminology and be frightened unnecessarily even to the point that he might not take the medication but would consult a physician needlessly. The comment also raises the possibility that some consumers might develop psychosomatic side effects after reading about them. Consequently, the comment proposes that this warning be revised to simply read: "Do not exceed recommended dose".

The Commissioner finds after reviewing all pertinent data that the more specific warning is more informative to the public. The Commissioner believes that the consumer should be fully informed and that the consumer has a right to full disclosure of the reasons behind label warnings and the possible consequence of ignoring those warnings. The Commissioner concludes that a more specific warning should therefore be retained.

99. A comment proposed that the second sentence of the following warning proposed for OTC stimulants be made optional since it is redundant: "For adults only. Do not give to children under 12 years of age".

The Commissioner concluded in comment 47 relating to nighttime sleep-aids, that the warning is redundant. The Commissioner concludes that this warning is likewise redundant for OTC stimulants. The second sentence "Do not give to children under 12 years of age" should be required; the first sentence should be deleted.

100. One comment objected to the proposed warning in § 340.50(c)(4) for products containing caffeine: "Do not take this product with large amounts of caffeine-containing beverages such as coffee, tea of cola drinks". The comment argues that it is unnecessary and recommends its deletion since the Panel did not cite any situations where consumers are harmed by taking OTC products containing caffeine or by consuming beverages containing caffeine. The comment points out that the Panel recognized that a toxic dose of caffeine is much higher than the dose recommended for OTC use.

The Commissioner advises that the intention of the warning proposed by the Panel is to alert individuals to the danger of possible overdosage or overstimulation through consumption of caffeine from a number of different sources. While the toxic dose of caffeine is much higher than the recommended OTC dose, overstimulation could occur in some individuals through the ingestion of the drug from multiple sources, e.g., OTC stimulant drugs plus coffee, hot or iced tea, or cola beverage, within a short period of time. The comment is therefore rejected.

The Commissioner concluded in comment 96 that such a warning is necessary, although is should be clarified.

101. Comments expressed general agreement with the Panel's proposed warning for caffeine-containing stimulants but pointed out that many products besides the three mentioned in the warning, namely, coffee, tea and cola drinks, also contain caffeine, e.g., cocoa, chocolate candy and icings, and some OTC and prescription drugs.

The—comments suggest the following alternative wordings for this warning:

"Contains caffeine: Do not ingest more than (leave blank—to be filled with proper dosage) without advice of your physician."

or

"Contains caffeine: Do not ingest this product with large amounts of caffeine-containing food or drug products without the advice of your physician."

or

"Contains caffeine: Do not take this product with large amounts of caffeine-containing foods, beverages or medication."

The comments recommend this more general language for the warning as being more effective in informing the consumer than the originally proposed language, which merely identifies a few food products. The comments point out that the original language would only serve to lull the user into a false sense of security and frustrate the purpose of the proposed rule since there are other food products and OTC drugs that contain caffeine and that are not identified in the original warning.

The Commissioner acknowledges that there are other sources of caffeine than the three examples given in the Panel's proposed caffeine warning. He notes, however, that these examples were selected as being the largest and most likely sources of additional caffeine by users of OTC stimulants. The Commissioner further notes that these comments do not disagree with the need for this warning but merely object to the specific examples of those beverages.

The Commissioner concluded in comment 96 that such a warning is necessary, but that it needs clarification.

102. One comment challenged the Panel's statement that the "teratogenicity of caffeine can be detected in rats if sufficiently high doses are given; these are of the order of 250 mg/kg and would be equivalent to 100 cups of coffee contining 125 mg of caffeine each." The comment contended that the statement was erroneous and "implied that there is no possible teratogenic hazard to developing embryos." It argued that caffeine may be teratogenic in humans as doses producing malformations in animals are only slightly greater than those consumed by women and that consequently there is an inadequate safety margin. The comment also cited human retrospective studies implicating caffeine with problem pregnancies and low birth weight.

Several animal studies were cited in the comment to show that caffeine is teratogenic at doses consumed by humans (Refs. 1 through 5). The contention is made that the studies indicate that birth defects occurred at 30 to 50 mg/kg doses and that this dose range is a level to which "a small minority of pregnant women is likely to be exposed." This contention is based on the assumption that a 100-lb. (46 kg) pregnant woman drinks between 10 and 20 cups of coffee daily, each containing 125 mg of caffeine and producing dose levels of 3 mg/kg of caffeine per cup, or a total of between 30 and 60 mg/kg of caffeine. An undocumented source is quoted in the comment as asserting that 9 percent of coffee drinkers average seven or more cups daily.

The Commissioner notes that since 1974 the Select Committee on GRAS Substances of the Federation of American Societies for Experimental Biology (FASEB) has been reviewing the safety of caffeine as a food additive for FDA's Bureau of Foods. This group is aware of the studies cited in the comment and has included the results of these studies as part of its review of caffeine. The FASEB Committee submitted a tentative report to FDA in November 1976 and held a public hearing on the report in September 1977. The FASEB Committee then reconvened to evaluate the additional information obtained at the hearing. A final report on the safety of caffeine as a food additive will be submitted to FDA within the next few months. FDA's Bureau of Foods is about to begin a laboratory study in animals to assess whether the animal teratology studies reviewed by FASEB can be replicated.

While the comment states that the animal studies indicate that birth defects occurred at 30 to 50 mg/kg doses, the Commissioner notes that these animal studies do not show consistent malformations at doses up to 75 mg/kg. The comment quotes the FASEB report, "Tentative Evaluation of the Health Aspects of Caffeine as a Food Ingredient," as concluding that "At doses greater than 75 mg/kg teratogenic effects are apparent in animal studies" (Ref. 6). In three mouse studies at 50 mg/kg of caffeine, only one "uniquely deformed" fetus occurred (Refs. 3 and 4). At test doses of 100 mg/kg and above, malformations were reported in these studies.

The results reported on the teratogenicity of caffeine in animals vary for a given dose of caffeine (Ref. 5). This variability has been attributed to species differences, strain differences, the source and form of the caffeine tested by different investigators, the stage of embryonic development at which caffeine was administered, the rate of caffeine administration, the route of caffeine administration and differences in caffeine metabolism between species and strains. In studies in mice and rats cited in the comment, caffeine was administered orally as well as by other routes. Teratogenic effects in the oral studies varied with the time period over which the dose was administered, the gestational period when administered, the strain of animal, and the method of oral administration (intubation or feeding). Oral doses at which teratogenicity occurred ranged from 100 to 500 mg/kg.

Differences between species and strains of test animals are also reflected in the variability of the lethal dose of caffeine. In most instances, the dose administered in animal teratology studies approximated the lethal dose. The available acute toxicity data (Ref. 6) show that the oral LD_{50} of caffeine in the mouse is 132 mg/kg. The oral LD_{50} in the rat varies from 192 to 296 mg/kg, and one study reports 1,050 mg/kg.

The doses which produced teratogenicity in animals were in the lethal range, approximately 100 to 300 mg/kg. In man, the ingestion of large doses of caffeine up to 10 g (200 mg/kg) has caused convulsions and vomiting with complete recovery in 6 hours (Ref. 9). The acute human lethal dose of caffeine is unknown but appears to be greater than 200 mg/kg. It should be pointed out that a dose of 10 g of caffeine is the amount of caffeine contained in 70 to 100 cups of coffee. The 200 mg/kg dose in man is a high toxic dose but apparently not a lethal dose. It may be that humans are less sensitive to caffeine than the mouse or rat. No caffeine-related teratogenic effects have been reported in humans. The comment failed to consider in its evaluation of the teratogenic potential of caffeine that the daily consumption of 10 cups of coffee, which is estimated in the comment to contain 20 to 30 mg/kg of caffeine, is taken over a period of several hours and not in a single dose. In the animal studies, the teratogenic doses, which approximated the lethal dose, were administered as a single dose.

The comment also cited human retrospective studies. One such study was claimed to report that 13 of 14 heavy coffee drinkers (seven or more cups of coffee per day) had problem pregnancies, including miscarriages and stillbirths (Ref. 7). Another study was claimed to indicate that coffee consumption was associated with an increased incidence of low birth weight infants (6.6 percent as compared to 4.2 percent of the controls), but that no association with birth defects was noted (Ref. 8).

The Commissioner has examined the results of three human studies (Refs. 7, 8, and 10). Two of these three studies were summarized in the comment and mentioned above. The Commissioner finds many discrepancies between the comment's summary of these two studies and the published reports. The comment's summary of one of the reports stated that 13 out of 14 heavy coffee drinkers (seven or

more cups of coffee a day) had problem pregnancies, including miscarriages and stillbirths. The study (Ref. 7) actually states that these 14 women were part of a group of 800 women from whom a survey team received replies to a questionnaire. Most of the 800 women were noncoffee, nonalcoholic beverage drinkers. About 200 of these women (about 25 percent) reported problem pregnancies. It is apparant that the 14 women who reported drinking 7 or more cups of coffee daily were part of the 200 of 800 women reporting problem pregnancies. The remaining 186 women with pregnancy problems were noncoffee drinkers. The published report is an incomplete study and the survey team agreed that their study by no means pointed to coffee as the cause of the problem pregnancies.

In the second study summarized in the comment (Ref. 8), the comment stated that coffee consumption was associated with an increased incidence of low births weight in infants (6.6 percent as compared to 4.2 percent in the controls). The comment noted that the report did not find an association between caffeine and birth defects. In this study, 5,200 women were asked to describe their coffee consumption during pregnancy as none, seldom or frequent. Other parameters, such as maternal age, parity, socioeconomic status, body weight, etc., were not considered by the investigators. The questions asked of the women did not require a quantitative answer, i.e., the number of cups of coffee consumed daily. The answers were subjective. The investigators concluded that because of other variables that were not considered it was questionable whether a direct causal relationship existed between coffee conumption and low birth weight. In addition, the investigators studied the association between coffee consumption and shortened gestation period and found no relationship. It is also interesting to note that in the two human studies cited by the comment, the investigators did not inquire whether any drugs, in addition to the coffee, were taken by the women during pregnancy.

The third human study examined by the Commissioner (Ref. 10) was cited in a report prepared for the FDA's Bureau of Foods by FASEB (Ref. 6), "Tentative Evaluation of the Health Aspects of Caffeine as a Food Ingredient." This study was not cited by the comment, although the FASEB report was mentioned in the comment in relation to animal studies. In this study, the investigators considered the association of drugs taken by women during pregnancy with the incidence of malformed infants delivered by these women. Caffeine, as a drug, was one of the ingredients compared with the incidence of malformations.

In this study, the ingestion of caffeine, as an ingredient in analgesics, by 458 mothers of malformed infants was compared with the ingestion of caffeine by 911 mothers of normal infants. Virtually all of these women (1,333 out of a total of 1,369) had taken one or more durgs during pregnancy. The investigators carefully checked the prescribed and self-administered drug histories of these women for the period of their pregnancies. They also eliminated bias in the selction of the mothers with abnormal infants and the mothers with normal infants. Statistical comparisons were made between caffeine used during the whole period of pregnancy and caffeine used during the first trimester. The data showed that 2.4 percent of mothers with abnormal infants had taken caffeine during the whole period of pregnancy as compared to 1.5 percent of mothers with normal infants. This difference was not statistically significant. The data on the use of caffeine during the first trimester of pregnancy show that the durg was ingested by 0.2 percent of mothers with malformed infants as compared with 0.7 percent of mothers with normal infants. FASEB concurred with the author's conclusions that there was no association between caffeine used as a drug and abnormalities in offspring.

The Commissioner wishes to emphasize that the concern of the Advisory Review Panel on OTC Nighttime Sleep-aid, Daytime Sedative, and Stimulant Drug Products was with the use of caffeine as a stimulant and not as a food ingredient. The Panel recommended caffeine as a stimulant at an oral dose of 100 to 200 mg not more often than every 3 to 4 hours. The highest single dose recommended, 200 mg (4 mg/kg), is 50 times less than the toxic dose of 200 mg/kg in man. The highest total daily dose that would be received if 200 mg were taken every 3 hours for 24 hours would be 1,600 mg (32 mg/kg). This total dose is approximately 6.3 times less than the toxic single dose of 200 mg/kg. An individual who continuously takes a stimulant for 24 hours is clearly ignoring the recommended labeling that restricts the product by the label caution: "For occasional use only. If fatigue or drowsiness persists continuously for more than 2 weeks, consult a physician". It can be assumed that under usual circumstances an individual will sleep for at least 6 hours. During the 18-hour waking period, a total of 200 mg could be taken six times, i.e., 1,200 mg or 24 mg/kg which is approximately 8.3 times less than the known toxic single dose of 200 mg/kg. An important consideration that further increases the margin of safety is the fact that the total dose of 24 mg/kg of caffeine is taken in fractionated doses of 4 mg/kg. In animal studies in which the total daily dose was fractionated, the incidence of teratogenicity decreased (Ref. 5). In man, a direct causal relationship between caffeine and malformations has not been reported in the years that caffeine has been consumed in coffee, tea, and beverages.

In an evaluation of caffeine ingestion and its relation to teratogenicity, animal studies alone cannot be the overriding consideration when information on human experience with the drug is available. The Commssioner finds the comment's interpretation of the studies on coffee consumption by pregnant women at variance with the data and conclusions of the studies. Long usage of caffeine and retrospective studies have not revealed a teratogenic effect in humans. These facts must be considered regardless of demonstrated teratogenic effects of high doses of caffeine in animals. The relationship between the dose of caffeine necessary to elicit a teratogenic effect in animals and the number of cups of coffee that a human would have to drink to approximate this dose must be a consideration. Even a lower teratogenic dose of 100 mg/kg in animals represents 40 cups of coffee containing 125 mg of caffeine per cup. From human experience, it appears that man may be a species that is less sensitive to caffeine than the mouse or rat. It has been suggested that humans are protected by the rapid metabolism of caffeine, with only 1 percent excreted unchanged (Ref. 11).

After a review of the available data, and in view of the fact that caffeine is a naturally occurring substance present in widely consumed foods and is also used as a food additive, the Commissioner is deferring any regulatory action until he has carefully reviewed the final findings of the FASEB Select Committee and the results of the FDA caffeine teratology study.

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All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the calls for data published in the Federal Register of August 22, 1972 (37 FR 16885) and May 25, 1973 (38 FR 13763). The volumes are on public display in the office of the Hearing Clerk, Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

For the convenience of the reader, the Commissioner includes the following tables summarizing his conclusions regarding the categorization of single active ingredients and combination of ingredients:

Categorization of Single Ingredients

Ingredient	Nighttime sleep-aid	Daytime sedative
Antihistamines:		
Diphenhydramine hydrochloride	[1]III	[2]II
Doxylamine succinate	[1]III	[2]II
Methapyrilene fumarate	II	II
Methapyrilene hydrochloride	II	II
Phenyltoloxamine dihydrogen citrate	[1]III	II
Pyrilamine maleate	III	II
Bromides:		
Ammonium bromide	II	II
Potassium bromide	II	II
Sodium bromide	II	II
Scopolamine compounds:		
Scopolamine aminoxide hydrobromide	II	II
Scopolamine hydrobromide	II	II
Miscellaneous compounds:		
Acetaminophen[3]	II	II
Aspirin[3]	II	II
Salicylamide[3]	II	II
Thiamine hydrochloride	II	II
Passion flower extract	II	
Niacinamide		II

Ingredient	Stimulant
Caffeine	I
Ammonium chloride[4]	II
Ginseng	II
Vitamin E	II

[1]These ingredients have not been marketed previously as OTC nighttime sleep-aids. Therefore, according to 21 CFR 330.13 (41 FR 32580, August 4, 1976), marketing of these ingredients as OTC nighttime sleep-aids is prohibited prior to determination by the Commissioner that they are generally recognized as safe and effective, or a new drug application for the product has been approved.

[2]Ingredients have not been submitted as daytime sedatives and would not be appropriate for such use.

[3]Referred to OTC Internal Analgesics Panel for evaluation of analgesic claims.

[4]Referred to OTC Miscellaneous Internal Drug Products Panel for evaluation of diuretic claim.

Ingredient	Nighttime sleep-aid	Daytime sedative
Combinations containing 2 antihistamines	II	II
Combinations containing more than 2 antihistamines	II	II
Combinations containing bromides	II	II
Combinations containing scopolamines	II	II
Combinations containing analgesics	III	II
Combinations containing thiamine hydrochloride, passion flower, or vitamins	II	II

Ingredient	Stimulant
Combinations containing diuretics	II
Combinations containing ginseng	II
Combinations containing vitamin E	II

II. The Commissioner's Conclusions on Nighttime Sleep-Aids

A. General Discussion

Sleep is generally defined as a regularly recurrent, easily reversible behavioral state characterized by relative quiescence and a greatly increased threshold of response to stimulation from the environment. In recent years it has been shown that a series of well-defined changes in brain wave patterns and other physiological changes regularly accompany behavioral sleep. These polygraphically recorded patterns are now useful in determining exact time of sleep onset and minute-by-minute changes in sleep stages. It appears justifiable at this point to add to the above behavioral definition of sleep that normal sleep must be accompanied by the usual well-determined sequence of polygraphic patterns.

The Commissioner concludes that experiencing occasional sleep problems is a valid indication for OTC medication. Sleep problems amenable to help by OTC products would fall into two broad categories: (1) Occasional difficulty in falling asleep (an increase in sleep latency), and (2) occasional difficulty in remaining asleep (an increase in number of awakenings, total time awake after sleep onset, or early morning awakening). Normal sleep patterns vary considerably and a person should take OTC medication only when his pattern deviates widely from his usual pattern.

Patients with severe or chronic insomnia are not candidates for self-medication; they should consult their physicians. Severe insomnia can be defined as sleep difficulty serious enough to interfere regularly with a person's normal waking activities. Chronic insomnia is sleep difficulty occurring every night or almost every night for at least several weeks.

An OTC nighttime sleep-aid, then, is a substance which helps an individual fall asleep or is used for the relief of occasional sleeplessness. Possible uses for such products, if demonstrated by adequate testing, would be to reduce time taken to fall asleep, number of awakenings, or early morning awakening or any combination of the above circumstances if these circumstances (delayed sleep, frequent awakenings, light sleep, or reduced duration of sleep) interfere with the normal sleep pattern of the individual.

B. Safety and Effectiveness

The Commissioner concludes that the following criteria apply to establish the safety and effectiveness of nighttime sleep-aids.

The active ingredient must be safe in the doses suggested on the labeling. The demonstration of safety should be based on current criteria used to evaluate centrally acting drugs. This includes the guidelines for testing the safety of nighttime sleep-aids. (See part II, paragraph D, below—Data Required for OTC Nighttime Sleep-Aid Ingredient Evaluation.) The general guidelines used in the introduction of drugs for prescription use should also be followed in assessing safety. Drugs that are suspected of causing mutations and/or cancer should not be authorized for OTC use.

Because these drugs are intended for nighttime use, their action should not persist into the daytime hours, or beyond the intended period of sleep, so that no interference with normal motor or sensory performance is encountered during the waking state.

The drug should be effective without causing undue disturbance in the period after sleep, such as depressed motor or sensory activity, including reduced ability to perform simple motor tasks. The drug should not interfere in an unusual manner or to an unusual degree with physiological EEG patterns characteristic of normal sleep. There should be a low potential for allergic manifestations and for idiosyncratic responses to the drug. The margin between an effective and a toxic dose should be large, and the desired effect should be produced ordinarily with a single dose; occasionally a repeated dose may be needed. The drug should not be habit-forming or addicting. There should be no serious toxicity that would result from ill-advised or inadvertent chronic use of the drug.

Determination of effectiveness of an OTC nighttime sleep-aid can be made to some extent by subjective reports from patients or subjects, and by nurses' observations, but are made more accurately by all-night sleep laboratory recordings. Preferably, several methods should be used, such as all-night sleep recordings in a small number of subjects combined with subjective reports in a large number of subjects, to make certain that a potential sleep-aid does improve sleep as verified both by objective criteria and by reports of improved sleep by the subjects themselves. The Commissioner has included later in this document guidelines for evaluating the effectiveness of a nighttime sleep-aid. (See part II, paragraph D, below—Data Required for OTC Nighttime Sleep-Aid Ingredient Evaluation.)

In accordance with current practice, the packaging of such drugs should be designed to protect small children. The Panel recommended that the quantity of the drug available in an OTC nighttime sleep-aid product container be limited to prevent accidental ingestion of a lethal dose. The Commissioner has no authority to limit package size, but will refer the Panel's recommendations to the Consumer Product Safety Commission. He urges industry to comply voluntarily with the Panel's recommendation and notes that the problem of accidental poisonings in children led to the adoption of a similar voluntary package size restriction for children's aspirin (32 FR 3440).

The Commissioner is concerned that OTC nighttime sleep-aid may also be involved in some accidental poisonings. He therefore urges industry to voluntarily limit package size to a sublethal dose, but in any event to no more than 2 week's supply.

LABELING

The Commissioner has included discussions on labeling elsewhere in this document. (See part II. paragraph C.1. below—Category I Labeling, paragraph C.2. below—Category II Labeling, and paragraph C.3. below—Category III Labeling.)

C. CATEGORIZATION OF DATA

1. *Category I conditions under which OTC nighttime sleep-aids are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredients

The Commissioner concludes that none of the submitted active ingredients can be generally recognized as safe and effective and not misbranded as OTC nightime sleep-aids.

Category I Labeling

The Commissioner has reviewed the Panel report and has concluded that the following changes in Category I labeling should be made based on submitted comments and additional data. The general drug interaction warning has been deleted in favor of specific warnings where applicable. (See comment 14.) The contraindication of antihistamines in pregnancy and lactation has been deleted as being without scientific basis. (See comment 48.) The recommended general warning "Caution: This product contains an antihistamine drug" has been deleted as having no meaning to the consumer. (See comment 53.) The first sentence of the adults only warning has been deleted since it is redundant; the second sentence is more definitive. (See comment 47.) The word "condition" has been changed to "sleeplessness" in the 2-week use limitation warning for the sake of clarity. (See comment 49.) The Commissioner concludes that a warning should be added contraindicating the use of antihistamines in persons who have glaucoma, asthma, or enlarged prostate. (See comment 55.)

The Commissioner concludes that the following labeling shall be Category I for nighttime sleep-aid active ingredients generally recognized as safe and effective and not misbranded:

a. *Indications.* (1) "Helps fall asleep".

(2) "For relief of occasional sleeplessness".

(3) "Helps to reduce difficulty in falling asleep."

b. *Warning.* (1) "Do not give to children under 12 years of age". The Commissioner concludes that since all of the studies reviewed by the Panel dealt with adults, not enough data are available on these drugs for use in children. Also, there are insufficient data on how children will react, especially in light of the fact that many children have an opposite reaction to that of adults. For example, it is possible that children may be more easily stimulated rather than sedated with antihistamines used as nighttime sleep-aids (Ref. 1).

(2) "If sleeplessness persists continuously for more than 2 weeks, consult your physician. Insomnia may be a symptom of serious underlying medical illness". The Commissioner is concerned that consumers should be informed of the limitation of usefulness of OTC nighttime sleep-aid drugs. This class of drugs is intended for short-term occasional sleeplessness experienced by basically healthy individuals. Continuous use of an OTC nighttime sleep-aid for more than 2 weeks may be indicative of a serious underlying physical, emotional or psychological disturbance requiring professional medical attention.

(3) For products containing an antihistamine: (i) "Take this product with caution if alcohol is being consumed". The Commissioner concludes that the depressant effects of anithistamines and alcohol are addictive and could create a greater soporific effect than is desirable.

(ii) "Do not take this product if you have asthma, glaucoma or enlargement of the prostate gland except under the advice and supervision of a physician". This warning should be in type at least twice as large as all other warnings on the package. The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (September 9, 1976), recommended the inclusion of this warning for antihistamines because of the atropine-like effects associated with this class of drugs. While the Advisory Review Panel on OTC Nighttime Sleep-Aid, Daytime Sedative and Stimulant Drug Products did not recommend such a warning, the Commissioner concludes that this same warning should apply to anithistamines when used as nighttime sleep-aids. This atropine-like or anticholinergic effect could be hazardous in patients with glaucoma and could lead to difficulty in urination in those individuals with an enlarged prostate. In asthma, the antihistamines may cause drying of the bronchial secretions, making expectoration of the secretions more difficult and thereby increasing obstruction of the airway.

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2. *Category II conditions under which OTC nighttime sleep-aids are not generally recognized as safe and effective or are misbranded.*

Category.II Active Ingredients

The Commissioner concludes that the following OTC nighttime sleep-aid active ingredients cannot be generally recognized as safe and effective or are misbranded:

Bromides: Ammonium bromide, potassium bromide, and sodium bromide.

Methapyrilene hydrochloride and methapyrilene fumarate.

Scopolamine compounds: Scopolamine aminoxide hydrobromide and scopolamine hydrobromide.

Miscellaneous compounds: Acetaminophen, aspirin, passion flower extract, salicylamides, and thiamine hydrochloride.

a. *Bromides (ammonium, potassium, sodium).* The Commissioner concludes that ammonium bromide, potassium bromide and sodium bromide are not safe in therapeutic dosage levels as OTC nighttime sleep-aids because of toxicity and possible teratogenic effects. The Commissioner further concludes that at the dosage levels presently marketed these ingredients are

not effective as OTC nighttime sleep-aids. Ammonium, potassium, and sodium bromides are similar in their pharmacological action and will be discussed as a group.

Bromine was discovered by Balard in 1826 and introduced into medicine in the salt form in the treatment of epilepsy in 1843 by Laycock. Its application as a hypnotic by Behrend dates back to 1864 (Ref. 1). The toxicity of bromides was noted in the 19th century. Wuth in 1927 reemphasized the toxicity of bromides which had been ignored for almost 100 years (Ref. 2). The barbiturates replaced bromides in the treatment of epilepsy, and bromides came to be used mainly as hypnotics and sedatives in the early 20th century.

By the late 1920's, bromides were widely prescribed and sold OTC as sedatives and hypnotics. Modern case reports about bromide toxicity recall their widespread use and importance before barbiturates, and the so-called "minor tranquilizers" such as meprobamate replaced them to a very large extent in the 1950's (Ref. 3). With the availability of more prescription drugs, the use of bromides shifted primarily to OTC use, although cases of poisoning still result from prescribed drugs. The OTC preparations have become the largest source of bromide use today in medicine. They are seldom recommended by physicians although toxic effects have resulted from prescriptions containing bromides within the past 10 years (Ref. 4).

Bromide, the negatively charged ionic form of bromine, is the drug we are concerned with in this discussion. Its close chemical relation to the chloride ion should be noted. Both chlorine and bromine are chemical elements included in a group known as the halogens. Special analytical methods are needed to detect bromide ion in the presence of chloride ion in biological fluids (Refs. 5 through 11). Bromides are ordinarily given by mouth and are efficiently absorbed. At high doses, subjects complain about gastrointestinal irritation, even when the drugs are given after meals, and some physicians in the past recommended that the bromides be given daily in three divided doses (Ref. 12). Divided doses cut down the intensity of gastrointestinal irritation, but serve no other purpose. A daily dose, if it could be tolerated without gastrointestinal irritation, would maintain therapeutic levels of bromide in the body. Absorption of a single oral dose is complete in 2 to 3 hours according to a study with radioactive bromide (^{82}Br) (Ref. 13). Peak plasma levels are reached about 30 to 45 minutes after a single oral dose (Ref. 14).

Distribution of bromide is the same as distribution of chloride, except for certain relatively minor differences. Like chloride, bromide distributes through the extracellular space, which is approximately 21 percent of total body weight. For a 150-lb (70 kg) man, the chloride or bromide extracellular space is approximately 15 liters. This space includes interstitial fluid and blood plasma. Large amounts of bromide appear in the salivary glands and also in gastric juice, where hydrogen bromide is formed. Bromide secretion by the gastric mucosa is analogous to that of chloride. Formation of hydrogen bromide contributes to the gastric discomfort experienced by chronic users of bromides. Like chloride, bromide enters the red blood cells in appreciable amounts. Monovalent inorganic anions like chloride or bromide are not bound to any considerable extent to plasma protein, so that plasma determinations of these two ions refer to free halogen.

The total halogen concentration in the extracellular space, as measured in the plasma, is predominately chloride and is normally about 99 to 105 milliequivalents per liter (mEq/L). In cases of poisoning by bromide, the chloride concentration may appear to go up, and this may be a clue to bromide poisoning. Usually bromide simply replaces part of the chloride, and standard laboratory tests report both ions as chloride.

Bromide does not penetrate cells in the brain to a greater extent than chloride, nor has there been found any qualitatively different distribution in brain tissue. It is assumed that bromide acts directly on the central nervous system (CNS), but not much information is available about the mechanism of its action. This is due, in large part, to the fact that bromides have been less widely used in the modern era in which more sophisticated ways of monitoring central nervous system function have been introduced.

At least 80 percent of the elimination of bromide proceeds via the kidney. Both chloride and bromide ions are cleared from the kidney by simply filtration, and then each is partially reabsorbed by the tubules of the kidney. The renal clearance of bromide is slightly less than that for chloride because the bromide ion is reabsorbed from the renal tubules somewhat more efficiently than chloride (Ref. 16). If chloride intake is kept constant and enough bromide is given, it is possible to reach high steady state levels of bromide. If bromide intake is maintained constant and chloride intake is reduced, there will be a more rapid increase in the body concentration of bromide. The half-time for elimination of bromide from the body is about 12 days, on the average, for persons with normal kidney function assuming that sodium chloride intake remains constant (Ref. 13).

The maintenance dose of bromide, about 0.9 g per day, if taken from the start of dosing, would produce no ill effects, because almost 6 weeks would elapse before effective concentrations would be attained in the body fluids. This rate of accumulation is much too slow, since no one taking the drug on his own volition would wait that long for symptomatic relief; thus, large doses have to be taken initially to produce an effect rapidly. If dosage continues at the same high initial rate, cumulative poisoning would soon occur. At a moderate dose of 1 g 3 times a day, the minimal effective blood concentration of 50 mg/100 ml is only attained after a week. After 3 weeks of continuous administration at the same rate, the blood level rises to 110 mg/100 ml, a blood concentration likley to produce toxic effects such as rashes, mental disturbances consisting of impaired thought and memory, dizziness and irritability (Ref. 17).

The body content of bromide may increase to a toxic level if the dosage is greater than the required maintenance dose and/or the renal elimination is below the expected level. At a steady rate, where intake equals output, the blood level will be just below the toxic range. If the rate of elimination were reduced, not unusual in older persons, the new steady state blood level of bromide would be a toxic concentration.

The blood serum concentration associated with toxicity is usually reported as 150 mg bromide per 100 ml or above. But cases of toxicity have occurred with serum levels of 50 mg/100 ml, and some patients have tolerated blood levels higher than 150 mg (Ref. 18).

To use these drugs chronically without monitoring the patient's chloride balance and blood serum bromide is not safe medical practice since small changes in chloride intake or small changes in kidney function can lead to severe poisoning.

In 1927 Wuth (Ref. 2) stated, "Taking into account the interaction of bromides and chlorides, it is evident that if these individual variations of chloride intake are not considered it is merely a matter of luck whether bromide treatment is successful or not, or whether it does or does not lead to intoxication."

Depression of the central nervous system occurs with therapeutic amounts of bromides. With low doses an individual becomes drowsy. Larger doses produce impairment of central function causing difficult speech, difficulty in thinking, and impaired memory.

There has been considerable argument about the effects of bromides on motor preference, but very little research has been done. In a "semi-blind" study by Uhr and collaborators (Ref. 19), several tests of motor coordination, including simulated auto-

mobile driving, tests of memory, and behavioral profiles, were studied comparing a placebo, meprobamate and bromide. One group was not told what they were ingesting and the other group receiving different amounts of bromide were told that they were all ingesting the same amount. This is a bizarre design. In the doses used, 5 to 8 g of bromide per day, there were no major deficits in performance produced by the bromides.

Jellinek and his associates (Ref. 18) inquired about the effects of bromides on human subjects as one increased the blood levels from sedative to mildly toxic ranges. The study was designed so that bromide levels of about 100 to 200 mg/100 ml of serum would be achieved and monitored in normal and psychotic subjects. Physical and psychological examinations were carried out during the course of the study. By giving daily doses of 50 mg of sodium bromide per kg body weight to all subjects, 78 normal subjects attained a mean serum bromide level of 148 mg/100 ml (range 120 to 200). However, a mean of 134 mg (range 98 to 186) was attained in 20 psychotic subjects.

In the normal subjects only sedative effects were noted. "Sounder and increased sleep" and some loss of concentration were noted. Skin rashes were seen in 2 of the 78 subjects. Some moderate tremors of the tongue, slightly increased patellar reflexes, and subjective feelings of "unsteadiness" were noted. Psychological tests showed that (6 subjects) had reduced ability to concentrate. Sixteen subjects volunteered the information that they had developed a sexual indifference. Of the 20 psychotic patients with blood levels comparable to those for normal subjects, 2 showed sluggish or fixed pupillary reactions to light. Except for these, there was "generally a picture of sedation and even of some therapeutic effect."

In the same study (Ref. 18), in a second group of 28 psychotic patients, doses of 75 to 100 mg/kg body weight of sodium bromide were given daily. A mean blood serum level of bromide of 228 mg/100 ml was obtained (range) 175 mg to 310 mg). Sixteen subjects were dropped from the study after the fifth week because of various toxic signs. These signs included positive Romberg test (six subjects), bromoderma (two or possibly three), unsteadiness and/or dizziness in four, sleepiness or similar symptoms in eight, and a few miscellaneous toxicities. "An exacerbation of psychotic symptoms was not prominent" in this whole group of 28 subjects.

The Commissioner notes that the conclusion reached by the authors is that bromide therapy does not uncover psychotic behavior, but that psychotic patients generally show the same kinds of symptoms reported for normal subjects who are intoxicated. It is suggested by the authors that at blood levels below 200 mg bromide/100 ml of serum an additional factor is at work in cases where "bromism" or "bromide psychosis" has been reported.

Various types of skin rashes are seen in cases of bromide toxicity. The diagnosis is often missed because the possibility of bromide ingestion is not considered by the physician (Refs. 20 and 21). Because these reactions occur in only 1 to 10 percent of subjects taking bromides, it is likely that they represent an allergic reaction to the drug.

A single oral dose of bromide is not effective, because it takes a few days to achieve a thereapeutic concentration in the extracellular fluid. This means that the sedative activity will be persistent and not transitory, as is intended when a hypnotic (sleep inducer) is used to induce sleep. Because bromides cannot induce sleep promptly after a single dose and must be used for several days and because these ingredients then have a continued pharmacological action, the Commissioner concludes that bromides should not be indicated as OTC sleep-aids. Sleep is not induced, says Sollman (Ref. 1), but is made possible by the calming action: ". . . the bromides tend to produce a mental calm, aloofness progressing to lassitude. These predispose to sleep which can be resisted."

The Commissioner notes that contraindications to bromide therapy have been listed repeatedly (Ref. 22). These include: (1) Anorexia: Vomiting and diarrhea induced by taking of bromides can easily deplete the body's chloride content, thus making chronic bromide intoxication more easily produced, (2) Alcoholism: Bromides enhance and prolong symptoms of hangover and intoxication, (3) Congestive heart failure: Usually patients with cardiac failure are on a restricted salt diet, so that intoxication with bromides will occur more readily than in normal dubjects, and (4) Kidney disease: Excretion of bromides is likely to be reduced more than in the normal individual and toxicity is to be anticipated.

Depression of the entire central nervous system is the usual pharmacological effect, except that the medulla is not depressed until very high drug concentrations are achieved. Psychic functions are depressed and spinal reflexes are diminished. Muscle tone is lowered. Large doses lessen arterial tension, lower body temperature, depress sexual drive, and cause somnolence, loss of coordination and sluggish reflexes. Psychic phenomena may include hallucinations of auditory or visual type, depression, or maniacal excitation. The neurological examination usually, but not always, shows a symmetrical distribution of altered function. This is useful in distinguishing between a central lesion and intoxication.

There has been discussion in the literature about the distinction between true schizophrenia and the apparent schizophrenia exhibited by some patients with bromide intoxication. Clearing up of the symptoms and their nonrecurrence as the intoxication disappears are useful indices. Some authors, for example, Levin (Ref. 23), claim that they can distinguish the two types of patient by the content of their hallucinations.

Neurological symptoms are commonly observed in cases of poisonings. Weakness was most common in one study of 27 cases (Ref. 24). It can involve a single extremity and thus mimic a central nervous system tumor or cerebrovascular accident. Sleepiness and stupor were also common. The state of consciousness was depressed in 14 of the patients, varying from drowsiness to coma. Thirteen patients were incontinent. Twenty has abnormal reflexes. Ataxia with the appearance of intoxication was the most common cerebellar sign; coarse tremor of the hands or tongue was seen in seven patients. Slurred speech was also common. Psychic manifestations included extreme excitement (12 cases), emotional instability, confusion, disorientation, and incooperativeness. In 12 cases, the average bromide concentration was 239 mg/100 ml of blood serum. Most of these patients had bronchopneumonia and/or urinary tract infection. The two deaths were due to pneumonia, a frequent cause of death in comatose patients.

"Ocular bobbing" is an intermittent conjugate downward deviation of the eyes in the absence of any reflex lateral eye movements. It is ordinarily caused by destruction of part of the brain. The sign is also seen in cases of bromism where there is a lateral deviation of the eyes as well as the downward movement.

Animal studies have pointed to the possibility that bromides may be teratogenic (cause abnormalities in the developing fetus) (Ref. 26). In studies carried out on animals with chronic bromide intake such that the concentration in the body was about as great as in human subjects on therapeutic doses, there appeared to be mental retardation as evidenced by reduced learning ability in offspring (Ref. 27). In this case, the bromide was given to pregnant rats from the 4th to 12th day of gestation at a total dosage of 192 mg of bromide per kg.

A woman who had previously had two normal children delivered two boys, 1.5 years apart, while taking bromides. Both boys showed growth retardation and reduced head size. One was described as a "true microcephalic" (Ref. 28).

It is clear that bromides cross the placenta readily. Cases of bromide intoxication have occurred in newborns. A girl born after 40 weeks of gestation weighed only 2,020 g (4.45 lb), was irritable and difficult to feed in the postnatal period and developed slowly (Ref. 29). At age 2.5 years, she showed retarded mental and motor development and was below the 10th percentile in height, weight, and skull circumference. The mother had taken large amounts of a bromide-containing preparation all through gestation to relieve headaches.

A 7-day-old girl entered a children's hospital with lethargy, poor sucking reflex and a blood serum bromide level of 365 mg/10 ml (Ref. 30). The mother, a nurse, took 1 quart of an OTC bromide preparation the day before delivery and had apparently taken lesser amounts during her 39-week pregnancy. On the 6th post partum day, the mother was found to have a serum bromide of 320 mg/100 ml. Both mother and infant recovered in this case, even though the blood levels were quite high.

A case of bromism with skin rash present was detected in a premature male infant (Ref. 26). Ten days after delivery, skin lesions began to appear and penicillin treatment was started. The penicillin did not affect the rash, and it was suggested that the mother's milk be tested for bromide. The milk contained 120 mg bromide per 100 ml. The child was cured by substituting cow's milk.

There are numerous case reports of bromide poisoning in infants (Ref. 31).

In summary, the Commissioner concludes that because the mode of action of the bromides involves displacement of chloride, a normal body constituent, and because this displacement takes many days to occur after ingestion of many of the "recommended" doses, the bromides cannot be considered for the use of occasional symptoms of sleeplessness. The mode of action involves a disturbance in the body's salt balance which requires the therapeutic level of the drug to be very close to the toxic level. In addition, bromides readily cross the placental barrier which might result in teratogenic effects such as mental retardation of the offspring. The Commissioner concludes that there is no indication for which bromides should be available on the OTC market. The risks involved in the uncontrolled use of bromides as nighttime sleep-aids are too great to permit general availability in the OTC market (Refs. 32 through 37).

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B. METHAPYRILENE FUMARATE AND METHAPYRILENE HYDROCHLORIDE

As noted in the preamble to this document, the Commissioner is aware that recent studies have implicated methapyrilene as a potential carcinogen or carcinogen synergist with nitrites in rats. Based on his review of these studies and other available data, the Commissioner has concluded that methapyrilene cannot be generally recognized as safe and is therefore classified in Category II. The data are not sufficiently definitive, however, to support a firm conclusion that methapyrilene is itself a carcinogen and must be removed immediately from all products in the OTC market. Should such data be developed, the Commissioner will consider what further action is appropriate.

The information on which the Commissioner's conclusion is based is as follows:

One investigator has reported on a series of experiments on the combined administration of several test chemicals with sodium nitrite to rats. The chemicals selected for study were tertiary amines for which he had evidence of nitrosamine formation under

defined test tube or in vitro conditions. The particular nitrosamines produced in a number of these reactions are the potent carcinogens, dimethylnitrosamine (DMN) and diethylnitrosamine (DEN).

With the combined administration of methapyrilene and sodium nitrite to rats for 90 weeks, the investigator observed a 30 percent incidence of liver cancer and concluded that this effect resulted from the in vivo formation of DMN. (Refs. 1 and 2).

The Commissioner has reviewed the toxicity studies in NDA's in the agency's files, as well as the nitrosation potential of methapyrilene and the carcinogenicity of DMN. Based on this review, it appears that methapyrilene itself rather than DMN may be primarily responsible for the response reported by Dr. Lijinsky. This opinion is based on the following considerations:

(1) Nitrosation potential of methapyrilene and other tertiary amines.

(2) Estimated total dosages of DMN based on in vitro reaction results vs dosages of DMN producing a carcinogenic response.

(3) Disparity in tumorigenic response of a number of tertiary amines vs. methapyrilene, as reported in Lijinsky's papers.

(4) Liver pathology and tumor types reported for test chemical-nitrite studies yielding DMN as the nitrosation product and for DMN itself.

(1) *Nitrosation potential of methapyrilene and other tertiary amines.* N-nitroso compounds are produced by the acid-catalyzed reaction of nitrite with certain nitrogen compounds, e.g., secondary or tertiary amines, alkylureas, and amino acids. For nitrosation to occur, nitrite is usually first converted to nitrous acid, and then to an active nitrosating species, e.g., nitrous anhydride, nitrosyl halide, or nitrous acidium ion. The amount of nitroso-compound produced will depend partly on the nitrosation kinetics.

The kinetic equations and rate constants for nitrosation of amines are based on experiments performed at 25° C. From the tabulation of these data the generalization has been derived that the ease of nitrosation increases as the basicity of the amine decreases. From information developed to date, which includes the rate constants for 14 secondary amines, one tertiary amine and 13 amides, it has been concluded that compounds that do not yield N-nitroso derivatives under the conditions used in the development of these rate constants would probably not be nitrosated in vivo.

The rate of reaction for some tertiary amines has been estimated, from which it has been postulated that in vivo nitrosation of simple tertiary amines probably will not prove important biologically. When trementhylamine and triethylamine, 1.0 molar (M) each, were reacted with 50 millimolar (mM) nitrite at pH 3.4, 25° C for 4 hr, the yield of DMN and DEN was 0.1 to 0.2 micromolar (*u*M). This nitrosation rate was estimated to be 10,000 times slower than that for dimethylamine. Also, *N*-methylpiperidine was nitrosated at least 10,000 times slower than the secondary amine piperidine.

In a review article discussing the formation of *N*-nitroso compounds, Mirvish points out that studies on 12 tertiary amine drugs produce yields of volatile nitrosamines of less than 1 percent except for tolazamide, oxytetracycline, and aminopyrine under defined conditions (e.g., 37° C, pH 3.4, 4 hrs). To achieve comparable yields for most of the tertiary amines, it was necessary to employ extreme conditions (heating at 90° C for several hours with high nitrite concentration).

Table 1 below shows the in vitro nitrosamine yields for some of the compounds reported in the Lijinsky study. The most easily nitrosated compounds are aminopyrine, dimethylphenylurea and oxytetracycline. The yields for methapyrilene, chlorpromazine and lucanthone indicate that these compounds are poor nitrosators. It is concluded that the latter three compounds would probably not be nitrosated to DMN to any marked degree in vivo.

The in vivo nitrosation rate would be dependent upon the concentrations of both the amine and nitrite, the rate of absorption of nitrite, the conversion of available nitrite to nitrous acid, and other stomach contents such as inhibitors and catalysts. The yields of DMN from methapyrilene at 37° C in vitro have been determined to be:

150 mM $NaNO_2$ + 30 mM amine→ 9μg/ml; 0.7 percent

40 mM $NaNO_2$ + 10 mM amine→ 0.6μg/ml; 0.08 percent

In the study included in the Lijinsky paper the concentrations of nitrite and methapyrilene in the drinking water were:

30 mM $NaNO_2$ + 4 mM amine

The yield probably would be considerably lower than those above. In the in vivo situation, the availability of nitrite would be reduced to a significant extent. It has been shown that residual nitrite in rats 10 minutes after intubation was 12 percent in an empty stomach and 30 percent when nitrite was intubated after feeding. By 20 minutes, the residual nitrite values were 0 percent and 4.4 percent, respectively.

In vitro-in vivo nitrosation relationships may be inferred from several studies in the literature. Dimethylamine, trimethylamine, and trimethylamine oxide are more readily nitrosated than methapyrilene. Both di- and trimethylamine have been shown to yield nitroso derivatives at 25° C. At temperatures above 25° C, the nitrosation potential of trimethlyamine oxide is equal to or greater than trimethylamine, depending upon the amine-to-nitrite ratio. However, the results of studies of the amine-nitrite administration for each of these compounds indicate there was not sufficient in vivo nitrosation to induce a tumorigenic response. Chronic feeding of rats with trimethylamine + nitrite (each 0.5 percent in the diet) did not induce tumors after 1 year (Ref. 3). Another study using Swiss and Strain A mice, in which the induction of lung adenomas was used to detect and estimate the presumed in vivo formation of Nitroso compounds, dimethylamine at 2 to 7 grams per kilogram in food, did not show a positive response (Ref. 4). Also, other studies in the literature, reviewed by Mirvish, indicate that only readily nitrosatable compounds are sufficiently nitrosated in vivo for tumors to be induced (Ref. 3). No liver tumors were observed following the combined administration of trimethylamine oxide and nitrite for 50 weeks (Refs. 1 and 2).

Conclusion: Methapyrilene would not be sufficiently nitrosated under the conditions of Lijinsky's experiment to produce a positive response attributable to DMN.

(2) *Estimated total dosages of DMN based on in vitro reaction results vs dosages of DMN producing a carcinogenic response.* Assuming an in vivo nitrosation rate equal to the in vitro rate at the greater amine and nitrite concentrations, as shown in Table 1 below, the total nitrosamine dosage has been estimated for some of the compounds included in the Lijinsky study. In effect, it is an "idealized" estimate. For methapyrilene the total DMN dosage administered to the rats in the Lijinsky study over the period of 90 weeks is estimated to be 16.2 mg.

In addition to total dosage, the amount of each individual dose must be taken into account, i.e., the higher the individual dose, the shorter the animal survival time. The total dosage for a tumorigenic response is considerably lower than doses compatible with a good survival rate. Taylor et al., for example, reported a high tumorigenic response (18/18) at a total dosage of 120 mg of DMN. In the Taylor study the 4-milligrams-per-week dosage of DMN is in the range of dosages producing carcinogenic effects with only short-term exposure and is considerably greater than the estimated 0.18 mg per week of DMN that would have formed in vivo at the in vitro rate of nitrosation given in Table 1 (Ref. 5).

A dose-response study by Terracini et al. (Ref. 6) is used for comparison in Table 2 below. Terracini reports that a diet of DMN was fed for 104 weeks and that the 5 ppm level gave a total dosage of 54 mg. It can be seen from

the table that at 2 ppm the tumor incidence was about 3.8 percent.

The total dosage at this level has been estimated as 22 mg. Thus at a dosage greater than the estimated 16.2 mg of DMN given the rats in Lijinsky's experiment there was a tumor yield only one-eighth (⅛) that reported by Lijinsky. At the 5 ppm dose (54 mg) the total dosage is greater than three times that of the estimated DMN intake in Lijinsky's study, but the tumor response is approximately one-third (⅓).

It is concluded that the estimated total DMN dosage based on in vitro nitrosation rates (even at concentrations of methapyrilene and nitrite five times greater than in the Lijinsky study) would not be sufficient to produce a 30-percent carcinogenic response.

(3) *Disparity in tumorigenic response of a number of tertiary amines vs. methapyrilene, as reported in Lijinsky papers* (Refs. 1 and 2). Based on the nitrosation rates in Table 1 below and the total nitrosamine dosage, the predicted biological response would be: aminopyrine greater than dimethylphenylurea greater than oxytetracycline greater than methapyrilene greater than or equal to chlorpromazine. However, dimethylphenylurea, with a total dose greater than three times that of methapyrilene, produced a 6.9-percent liver tumor yield vs. 30 percent for methapyrilene. Chlorpromazine produced only a 3-percent tumor yield, although the estimated total nitrosamine intake is 62 percent that of methapyrilene. Perhaps the greatest discrepancy in results was seen with lucanthone, a compound which shows an in vitro yield of nitrosamine comparable to methapyrilene. The nitrosamine, DEN, is also a potent liver carcinogen. The combined administration of lucanthone and nitrite resulted in only 2 liver tumors (6.9 percent). On the other hand, lucanthone without nitrite showed a highly significant carcinogenic response with a 30-percent liver tumor yield.

Except for methapyrilene and oxytetracycline, the tumor yields are consistent with the results reported for DMN by Terracini et al. Although the results with oxytetracycline appear aberrant, i.e., low total dosage of DMN producing a high (16.7 percent) tumor yield, the in vitro yield data at greater concentrations of drug and nitrite show oxytetracycline to be a fairly good nitrosator. The toxicity of oxytetracycline itself might contribute to the result also, since it is known that oxytetracycline can cause changes in liver enzymes.

Conclusion: When compared with biological response and nitrosation rates of other DMN yielding amines as well as with lucanthone, the 30 percent carcinogenic response for methapyrilene is too great to be attributable to DMN.

(4) *Liver pathology and tumor types reported for test chemical nitrite studies yielding DMN as the nitrosation product and for DMN itself.* The tumors reported for dimethylnitrosamine are those of the liver and the kidney. Short-term exposure of up to 4 weeks at dosage levels ranging from 6 mg to 42 mg DMN yielded kidney tumor incidences of 20 percent to 100 percent (Ref. 6). In a chronic dose range study, Terracini et al. found that the incidence of liver tumors falls rapidly when the dietary concentration of DMN is reduced from 50 to 5 ppm. Although no kidney tumors were found in rats receiving 5 ppm DMN for up to 104 weeks (54 mg), eight liver tumors were seen, consisting of 2 sarcomas and 6 hepatocellular carcinomas (Ref. 6).

Taylor et al. reported that all rats receiving DMN developed Kupffer cell sarcomas of the liver (hemangi- oendotheliomas) (Ref. 5). The authors state:

> The fact that DMN did not produce hepatocellular tumors is not consistent with commonly reported results. The difference in response could be due to a number of variables, such as strain of rat, influence of different diets, immediate and cumulative doses, and life-span after receiving DMN. This disparity may be due to differences in diagnostic interpretation of these tumors. Perhaps better documentation of tumors reported in future literature would be in order. Certainly, there should be some unanimity reached on classification of these tumors of liver origin, especially in view of the many metabolic studies involving DMN.

The hemangioendotheliomas were reported as similar to those produced in a previous experiment in rats fed aminopyrine or heptamethylenenimine together with nitrite.

A second finding in Taylor's paper relates to the combined administration of aminopyrine, sodium nitrite, and carbon tetrachloride to rats. Both Kupffer cell sarcomas and hepatocellular tumors were observed. Although rats receiving similar dosage of carbon tetrachloride alone did not show any tumors, a report in the literature states that hepatocellular carcinomas were observed in Wistar, Osborne-Mendel and Japanese rats following CCl_4 administration (Ref. 7).

Taylor et al. view the DMN-CCl_4 as follows:

> From our studies, it appears that the Kupffer cells are more responsive to the action of DMN than are liver cells themselves; however, hepatocytes did respond to the carcinogenic stimulus in the presence of CCl_4. The inducement of mitosis in liver cells by CCl_4 provides a situation not unlike that reported in many instances where carcinogenesis is greatly enhanced by mitotic activity of target cells. Besides alteration of mitotic states, the effect of CCl_4 on liver cell enzymes and membranes that influence the metabolism of DMN is no doubt of great importance also in the initiation of these tumors.

With methapyrilene and nitrite, Lijinsky reports the following types of liver tumors:

5 liver cholangiocarcinomas
3 hepatocellular carcinomas
1 liver hemangioendothelial sarcoma.

Eight of the nine tumors are types that Lijinsky has never observed with DMN in his laboratory rats, and the cholangiocarcinomas have never been reported as a DMN-induced tumor in rats. In short, only one animal showed the tumor type that has been reported by Lijinsky as the only tumor that DMN induced in his many rat studies.

In addition, Lijinsky reports that in the methapyrilene experiment, almost 50 percent of the animals not having liver tumors showed necrotic and other degenerative changes in the liver.

This finding is supported by data in the FDA files, which show methapyrilene to be a hepatotoxic agent at dosage levels comparable to those used by Lijinsky. The toxicity was explored to the greatest extent by a firm proposing to market a combination product. In three subchronic studies, rats were intubated 5 days per week for 30 administrations of either methapyrilene alone or the proposed combination containing methapyrilene. At 60 mg/kg, methapyrilene showed bile duct proliferation and a variety of degenerative and regenerative changes in all animals. Hepatic cord cell changes were characterized by increase in size, binucleate forms, increased nuclear and nucleolar sizes, and mitoses. At 20 mg/kg the changes were present in all males and 6 of 10 female rats, although they were reported as milder.

The firm which submitted the NDA was sufficiently concerned about liver toxicity to have an examination of the slides by four pathologists. The histopathology was summarized by comparing the findings of liver toxicity with those associated with toxins such as those in certain poisonous plants, i.e., the senecio. These plants contain pyrrolizidone alkaloids, a number of which have been reported to be liver carcinogens.

It is concluded that the major tumor type in the Lijinsky study (cholangeocarcinoma) has never been reported as having been induced by DMN in rats. Although hepatocellar carcinoma (the other tumor type observed by Lijinsky) has been reported in rats, he has never observed it as a DMN-induced tumor type in the Sprague-Dawley rat in his laboratory. Hemangioendothelioma, the only tumor type attributed to DMN in his previous studies, was observed in only one animal.

The liver pathology and tumor types reported in the Lijinsky study are not, in fact, unlike that produced by the

senecio alkaloids. The liver pathology caused by methapyrilene is also similar to that of the senecio alkaloids.

This overall analysis thus suggests that the tumorigenic response in Lijinsky's experiments was induced by a chemical other than DMN. At this point the nitrosamine cannot be ruled out completely. If it has a role, however, it is one of a synergist as with the CCl_4 studies mentioned above.

There are two complicating factors which preclude a stronger statement on the carcinogenic potential of methapyrilene: the negative results of the short-term tests and the possiblity of a synergistic effect of one or more nitrosamines.

The utility of short-term tests in detecting compounds as suspect carcinogens is still undergoing exploration, but the available results suggest that methapyrilene is not a direct-acting carcinogen. The National Cancer Institute has arranged for the study of methapyrilene in short-term tests which are being considered for a carcinogenesis screen. These tests are (1) salmonella typhimurium test, (2) in vitro neoplastic transformation, (3) the mouse lymphoma system, and (4) DNA repair utilizing primary heptocytes.

Reports received and evaluated by the FDA to date include the results of the first two tests listed above (Ref. 8).

(1) *Salmonella typhimurium mutagenicity test.* The salmonella/microsome test uses bacteria as sensitive indicators of DNA damage and mammalian liver extracts for conversion of carcinogens to their active mutagenic forms. With this test system there is a high correlation between mutagenicity and carcinogenicity: 90 percent of carcinogens tested were mutagenic.

Seven dosage levels of methapyrilene hydrochloride were tested with and without metabolic activation systems in five salmonella tester strains. The activation systems were both uninduced and induced S-9 liver preparations from rats, mice, and Syrian hamsters. No mutagenic response was observed in any of the tests, including the various combinations of bacterial strain and S-9 preparation.

In addition, tests were run with methapyrilene hydrochloride reacted with nitrite prior to exposure to the tester strains. In this series of tests similar to those mentioned above, a sixth bacterial strain was added. Here, too, no mutagenic response was observed in any of the series of tests.

(2) *Hamster in vitro neoplastic transformation system* (Ref. 9). This test system, being developed at the Frederick Cancer Research Center, has shown promise based on approximately 100 compounds which have been studied. A number of the carcinogens which showed negative responses in the different mutagenicity test systems have shown a positive response in this system. Included in this category are some of the heavy metals. The second encouraging aspect of this test system is the fact that neither false positive results nor spontaneous transformations have been observed to date.

The protocol for the methapyrilene studies was in two parts. In the first part, nine dosage levels of methapyrilene were tested with and without metabolic activation (hamster liver S-9 fraction). In these series no transformed colonies were observed. The second part of the protocol allowed for the in vitro nitrosation reaction at a 5:1 molar ratio of nitrite to methapyrilene. The reaction mixture was bioassayed with and without metabolic activation: A positive response was observed at the highest dosage of the methapyrilene-nitrite reaction mixture only with metabolic activation.

In this study, nitrite rather than methapyrilene alone seems to be the key element to the neoplastic transformation response. One could assume that sufficient nitrosamine was formed from the reaction to evoke the positive response.

These negative findings in in vitro systems must be tempered with the following comments: Although the bacterial system has shown a high correlation between mutagenicity and carcinogenicity, a number of hepotocarcinogens have not shown positive responses, e.g., carbon tetrachloride, chloroform, the halogenated hydrocarbon pesticides DDE and dieldrin, safrole, and several hypocholesteremic agents. Since the liver pathogenesis shown by methapyrilene appears to be similar to these compounds, it is not surprising that a negative response was observed.

The interesting feature of the bacterial study was the negative response observed following exposure of the tester strains to the in vitro methapyrilene-nitrite reaction products, one of which should have been DMN. The literature states that the potent carcinogen dimethylnitrosamine (DMN) is weakly positive in the Salmonella system. Apparently, insufficient DMN was formed in the in vitro nitrosation reaction to produce a positive response.

The neoplastic transformation system is in a relatively early stage of development at the Frederick Cancer Research Center. Thus the number of compounds tested is limited. Since DMN has shown a positive response in other transformation systems, it could be the agent responsible for the positive response that was observed in this test.

The other carcinogenic compounds listed above as showing a negative response in the bacterial system have not yet been explored in this transformation system.

It is concluded that short term test data suggest that methapyrilene is not a direct-acting carcinogen. The mechanism of carcinogenesis might be similar to other hepatocarcinogens showing a negative response in the short term tests.

In summary, Lijinsky concludes that the finding of a 30-percent incidence of liver cancer resulting from the combined administration of methapyrilene and sodium nitrite for 90 weeks is due to the in vivo formation of DMN. There is concern aroused by the nitrosation of tertiary amines because of the possibility that such reactions may occur in the human stomach (from ingested amines in foods and drugs and nitrites in food, as well as the high nitrite content of human saliva) and thus create a potential health hazard.

This analysis, however, suggests that the carcinogen in Lijinsky's experiment was methapyrilene rather than DMN.

1. Methapyrilene would not be sufficiently nitrosated under the conditions of Lijinsky's experiment to produce a positive response attributable to DMN.

2. The estimated total DMN dosage based on in vitro nitrosation rates (at concentrations of methapyrilene and nitrite that are five times greater than in the Lijinsky study) would not be sufficient to produce a 30-percent carcinogenic response.

3. When compared with biological response and nitrosation rates of other DMN yielding amines as well as with lucanthone, the 30 percent carcinogenic response for methapyrilene is too great to be attributable to DMN.

4. An evaluation of liver pathology and tumor types reported for test chemical-nitrite studies yielding DMN as the nitrosation product and for DMN itself indicates that the results are of a severity that is greater than can be attributed to DMN-induced carcinogenesis. The possibility of synergism cannot be excluded, however, since a mechanism similar to that reported for CCl_4 could account for the tumorigenic response.

TABLE NO. 1

	Concentration Amine mg/ml	Concentration $NaNO_2$ mg/ml	Temp.	Time (hr)	pH	N-Nitroso compounds	Yield of NO-compound ug/ml	Yield of NO-compound % Theoretical
Methapyrilene	5	10	37°	4	3.4	DMN	9	0.7
Dimethylphenylurea	1.6	2.8	37	3	3.5	DMN	33	4.2
Chlorpromazine	5	10	37	4	3.4	DMN	10	0.88
Oxytetracycline	8	16	37	4	3.0	DMN	20	15.0
	1	1	37	2	3.2	DMN	0.5	0.3
Aminopyrine	0.25	0.25	37	2	3.2	DMN	33	40
Lucanthone	5	10	37	4	3.6	DEN	10	0.7

Table No. 2

Nitrosation product in vitro		Concentration in water (%) Test Chem	Nitrite	Treatment period(wks)	Total dose per animal: Test Substance (gm)	Nitrite (gm)	Estimated nitrosamine (mg)	Liver tumors # Animals	Liver tumors %	Reference
Methapyrilene	DMN	0.1	0.2	90	9	18	16.2	9/30	30.0	Refs. 1 and 2
Dimethylphenylurea	DMN	0.1	0.2	50	5	10	51.2	2/29	6.9	"
Chlorpromazine	DMN	0.1	0.2	50	5	10	10	1/30	3.3	"
Oxytetracycline	DMN	0.1	0.1	60	6	6	3.0	5/30	16.7	"
Aminopyrine	DMN	0.1	0.1	30	3	3	396.0	29/30	96.7	"
		0.025	0.025	50	1.25	1.25	165.0	26/30	86.7	"
Trimethylamine oxide	DMN	0.08	0.2	50	4	10	---	0		"
Dimethyldodecylamine	DMN	0.18	0.2	80	14	16	---	1/24	4.2	"
	NO-N-MDC[1/]									
Lucanthone	DEN	0.14	0.2	50	7	10	14	2/30	6.7	"
		0.14	---	50	7	---	---	6/21	30.0	"
DEN[2/]					64 mg/kg		ca 30	11/20	55.0	Ref. 10
DMN		2 ppm		60			21-22	1/26	3.8	"
		5 ppm		60			54	8/74	10.8	"
		20 ppm		60			216	15/23	65.2	"
		50 ppm		60			540	10/12	83.4	Ref. 10
DMN		0.4%		30			120	18/18	100	Ref. 5

1/ Nitroso-N-methyldodecylamine(NO-N-MDC)--another nitrosation product that has not been shown to produce liver tumors. There was, however, a 20.8 percent incidence of kidney and bladder tumors in rats that may be attributable to NO-N-MDC.

2/ DEN produced esophageal and liver tumors, as well as tumors of the nasal cavity.

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The Commissioner further concludes that data other than those related to the carcinogenicity issue discussed above are inadequate to prove that methapyrilene hydrochloride and methapyrilene fumarate are safe and effective as OTC nighttime sleep-aids in appropriate dosages (equivalent to 25 to a maximum 100 mg of the base) in a single dose at bedtime. Although classification of these ingredients in Category II makes such additional testing unnecessary at this time, if they were classified in Category III, further testing for both safety and effectiveness would be necessary.

The Commissioner has prepared the following chart comparing the dose of the base, and of the hydrochloride and fumarate salts, based on the fact that their molecular weights are in the ratio of 1(base):1.1(hydrochloride):1.5-(fumarate):

Comparison of dosage of methapyrilene (base) to the hydrochloride and fumarate salts

Base	Hydrochloride (ng)	Fumarate (ng)
25 mg	27.5	37.5
50 mg	55	75
75 mg	82.5	112.5
100 mg	110	150

In the following discussion the dose will be expressed in terms of the base unless otherwise stated:

Most studies have been performed with the hydrochloride salt whose weight is close to that of the base. The ingredients have been marketed as OTC sleepaids containing 10 to 26 mg per tablet or capsule. The Commissioner notes that the recommended dosage of the various OTC preparations (25 to 50 mg) is substantially below the 100 mg dose at which patients receiving the drug for various allergies experienced drowsiness (Ref. 11). There is some evidence of effectiveness at a bedtime dose of 50 mg (Refs. 12 and 13) but others report drowsiness only at 100 mg (Ref. 11). Since these ingredients have been classified in Category II because of their possible carcinogenicity potential, any further discussion of the testing required is unnecessary.

Methapyrilene was introduced clinically by Feinberg and Bernstein 1 year after diphenhydramine (Ref. 14). Its antihistaminic and antianaphylactic activity was verified in experimental animals and its antiallergenic activity documented in a varied series of 253 patients, whose average dose was 50 mg orally 1 to 4 times daily; a few patients received 100 mg doses, but such a dose was frequently not well tolerated. In this apparently uncontrolled study, side effects were noted in approximately 25 percent of the patients. Sedation was the most common side effect, occurring in 48, or 19 percent, of the patients studied. The degree of sedation was not as great as that produced by diphenhydramine, but equaled or exceeded that of tripelennamine.

Kierland and Potter (Ref. 15) compared methapyrilene with diphenhydramine and tripelennamine in 126 dermatologic patients. Doses, given 3 or 4 times daily, were usually 100 mg of methapyrilene and 50 mg of the other two drugs. Improvement was comparable with the three drugs. Drowsiness was observed in 10 of the 126 patients receiving methapyrilene, 3 or 47 with diphenhydramine and 1 of 44 with tripelennamine, although the authors noted that the degree of drowsiness was more marked with diphenhydramine than with either of the other drugs.

The Friedlanders (Ref. 11) also verified antiallergic effectiveness of methapyrilene in 85 of 117 patients. Dosage was usually 100 mg 4 times daily for adults and 25 to 50 mg daily for children. One or more side effects, generally mild, occurred in about 25 percent of the patients, usually at the 100 mg (adult) dose level, and were frequently obviated by reduction in dosage to 50 mg. Of special interest was that drowsiness was observed in 19, or 16 percent, of the patients studied.

The classic paper on the hypnotic effects of methapyrilene offered in evidence for its effectiveness as a nighttime sleep-aid is the study of Straus et al. (Ref. 12). In that study the authors compared 50 mg of methapyrilene with 100 mg of phenobarbital and placebo under double-blind conditions in 54 male insomniac patients in a Veterans Administration hospital. The experimental design called for each patient to receive each medication 6 times for a total of 18 nights in 3 weeks (a few nights were missed). Drug administrations were randomized, except that no drug succeeded itself. Evaluations of effectiveness consisted of objective (graded by nurses observing the patients hourly during the night) and subjective (as reported by the patients to a physician the next day) reports of three criteria: Falling asleep (sleep latency), staying asleep and overall evaluation. A 4-point scale was used, ranging from 0 (no sleep response) to 3 (excellent sleep response). The data indicate that both methapyrilene and phenobarbital were more efficient than placebo in their hypnotic effect. The nurses' observations found methapyrilene more effective than phenobarbital in inducing sleep (but the patients cound not distinguish between the two compounds); in overall evaluation the patients favored phenobarbital (but the nurses could not differentiate between the two); and for staying asleep, neither patients nor nurses could distinguish between them. The authors concluded that the two drugs exerted approximately equal hypnotic effects, in each case significantly greater than that of the placebo. It should be noted that phenobarbital, with its known slow onset of action, is not the ideal barbiturate hypnotic; secobarbital or pentobarbital would have been better choices for comparison. Nevertheless, the study does provide data demonstrating hypnotic effectiveness of methapyrilene in 50 mg doses.

In another study, Shapiro (Ref. 16) used methapyrilene from 1 to 66 days as a sedative in 33 hyperactive children ranging in age from 4 weeks to 12 years. The drug produced sleep and relaxation of hyperactive states during the daytime in 24 of 31 children, with nausea experienced by one child only. Nowhere in the article is the dosage defined.

Noell et al. (Ref. 17), in a daytime EEG study with over 3,000 Air Force volunteers, found that of 33 antihistamines studied, methapyrilene 50 mg ranked eighteenth in time to "end of wakefulness" and fifth in time to "onset of sleep." In both of these effects methapyrilene scored significantly better than placebo but nearly as well as secobarbital 100 mg.

Feinblatt and Ferguson (Ref. 13) compared methapyrilene niacinate, methapyrilene hydrochloride and placebo in a double-blind study involving 53 patients with insomnia. The dose of each methapyrilene salt was 50 mg (calculated as methapyrilene base). Both were considerably more effective than placebo, inducing "satisfactory sleep" in 37 (70 percent) of the 53 cases, "partial relief" in 9 (17 percent) and failing in 7 (13 percent).

More recently, Teutsch et al. (Ref. 18) used subjective responses to evaluate sleep following pentobarbital 100 mg, diphenhydramine 50 mg, methapyrilene 50 mg or placebo in 150 patients in two Veterans Administration hospitals. The four preparations, in identical capsules, were administered by a nurse-observer on each of 4 consecutive nights of randomized program. Next morning the patients reported to the nurse how well they had slept, the time taken to fall asleep, how long they had slept, and how the sleep compared with their usual night's sleep at home. For all response variables, both pentobarbital and diphenhydramine were found significantly better than placebo when evaluated by the subjective question, "How long did you sleep?" In one of the two hospitals, methapyrilene was superior to placebo while in the other hospital it was not.

The Commissioner is aware of instances of poisoning, either accidental or suicidal, with methapyrilene. For example, fatalities have included a 15-

month old girl who developed hyperpyrexia, cerebral edema, upper nephron nephrosis and uremia (Ref. 19), and an adult suicide who died in convulsions (Ref. 20). Examples of nonfatal cases include a 20-month-old child (Ref. 21) and two adults (Ref. 22), all manifesting convulsions, and a pregnant female with a toxic psychosis mimicking eclampsia (Ref. 23).

A number of additional studies in which methapyrilene was used in combination with salicylamide and scopolamine (Ref. 24) have been reported. The Commissioner concludes that the evidence clearly supports a positive effect: methapyrilene in these combinations almost certainly is able to produce drowsiness, EEG shifts, and reduced sleep latency. These effects are probably present but not strong with 50 mg of methapyrilene and since this appeared to the Panel to be a relatively safe drug, doses of 75 mg or 100 mg seemed to them to be worth evaluating (Ref. 24).

The Panel reviewed all data available to it which bore on the safety of methapyrilene, and concluded that methapyrilene salts were probably safe and might be effective at appropriate doses for use as an OTC nighttime sleep-aid. At that time, there were no published studies that showed methapyrilene to have any carcinogenic or co-carcinogenic potential. Since this was the case, the Panel directed its attention toward the EEG and clinical studies necessary to prove effectiveness and establish an optimum dosage range. The Panel voiced early in the report its conclussion that the antihistamines "are basically safe as OTC nighttime sleep-aid products * * * approval of these preparations is based on demonstration of effectiveness" (40 FR 57294).

The Panel recommended clinical studies to evaluate effectiveness of dosages of 50 to 100 mg in which anticholinergic and other side effects were to be monitored. The Panel stated its conclusion: "Should anticholinergic or other side effects prove not serious in these additional (clinical) studies, and should these studies in dosages of 50 mg and possibly up to 100 mg prove methapyrilene to be effective, i.e., significantly better than placebo in improving sleep in one or more sleep parameters, this drug could be moved from Category III to Category I" (40 FR 57310).

In sum, the Commissioner concurs with the Panel's findings relating to aspects of safety and effectiveness of methapyrilene other than carcinogenicity, which the panel did not address. However, since the Commissioner has determined that methapyrilene is Category II because of its possible carcinogenicity potential, any further discussion of the studies required for effectiveness, or safety not related to the carcinogenicity issue, is unnecessary.

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c. *Scopolamine compounds.* The Commissioner concludes that scopolamine, scopolamine hydrobromide, and scopolamine aminoxide hydrobromide are not safe at dosage levels which might possible be effective as OTC nighttime sleep-aids. Although there are insufficient data available for OTC nighttime sleep-aid products concerning the effectiveness of scopolamine alone in producing sleep, the Commissioner concludes, on the basis of the reported toxicity associated with these compounds, that doses high enough to be possibly effective as OTC nighttime sleep-aids are not safe. In the dosages currently used, the Commissioner concludes that these ingredients are ineffective as OTC nighttime sleep-aids.

Scopolamine (L-hyoscine) occurs naturally as an alkaloid of belladonna. It is chemically and pharmacologically similar to atropine. Scopolamine in clinical doses (0.5 to 1.0 mg, orally or parenterally) normally causes drowsiness, euphoria, amnesia, fatigue, and dreamless sleep (Ref. 1). Meyers and Abreu (Ref. 2) suggest that differences in the therapeutic potencies of atropine and scopolamine may produce dissimilar effects in the brain.

Selected doses of either drug produce sedation in animals. Large doses of scopolamine (1.0 to 1.5 mg/kg) produce persistent excitement and larger doses produce transient excitement followed by deep sedation (Ref. 2). The sedative effects of scopolamine in man appear with doses of 0.3 to 0.6 mg whereas 2.0 mg or more of atropine are required to produce sedation, amnesia, and drowsiness (Ref. 3).

The belladonna alkaloids are absorbed rapidly from the gastro-intestinal tract, more so from the intestine than the stomach (Ref. 4). They also

enter the circulation when applied locally to the mucosal surfaces of the body. Only limited absorption occurs from the eye and the intact skin, but in the lung atropine can be absorbed sufficiently from inhaled smoke to produce extrapulmonary effects such as blockade of peripheral symptoms due to cholinergic stimulation (Ref. 5).

Only about 1 percent of an oral dose of scopolamine is eliminated in the urine. Much of the alkaloid is thought to be destroyed by enzymatic hydrolysis, particularly in the liver.

Tolerance to scopolamine apparently occurs, although experimental evidence for it is sparse. Studies in mice suggest that tolerance occurs when scopolamine is given chronically to antagonize pilocarpine-induced hypothermia (Ref. 6). Tolerance did develop to scopolamine's effects in a behavioral situation in which chronic doses were injected into rats (Ref. 7). However, other workers have found no tolerance to scopolamine in mice when the drug was given chronically and then withdrawn to test the effects of pilocarpine (Ref. 8).

Studies in humans strongly suggest that chronic scopolamine administration (10 mg/kg intramuscularly) produces tolerance in the central nervous system as well as some involuntary (autonomic) effects (Ref. 9). Tolerance is noticed particularly in patients with parkinsonism, who may eventually receive daily doses of scopolamine that would result in toxic levels, if given to patients receiving the drug for the first time (Ref. 10).

Habituation and true addiction probably do not occur, although the literature on this aspect of scopolamine's actions is also sparse. In patients with parkinsonism who are suddenly withdrawn from large therapeutic doses, vomiting, malaise, sweating, and salivation have been known occur (Ref. 1).

The side effects with therapeutic doses are mainly of importance because of their subjective unpleasantness to the patient and include the following: (1) Dryness of the mouth, (2) blurred vision, (3) photophobia (abnormal visual intolerance of light), and (4) cardiac effects (tachycardia, bradycardia, arrhythmias, and palpitations). These are the most common side effects, and can rarely be completely avoided with the doses required to obtain significant therapeutic benefit (Ref. 11). Tolerance to the side effects, as with the therapeutic doses, apparently occurs.

Other side effects which sometimes occur include the following: (1) Acute glaucoma (increased intraocular pressure); (2) constipation, which can progress into complete obstruction of the bowel; (3) urinary retention, when enlargement of the prostate is present; (4) anhidrosis (lack of sweating), which may produce heat intolerance and in some cases can seriously impair body temperature regulation in individuals in a hot environment (children are especially sensitive to this effect); (5) hypersensitivity reactions, particularly skin rashes, and occasional edema (swelling) of parts of the mouth and throat; (6) ataxia, manifested by stumbling or difficulty in walking, which may be seen with therapeutic doses in susceptible individuals; and (7) toxic psychoses (hallucinations, agitated delirium, belligerence, violence), which may occur, particularly when scopolamine is combined with bromides or methapyrilene and taken in high doses (Refs. 12 and 13). In a report involving scopolamine given as a premedication before surgery, 20 percent of the patients given 0.2 to 0.6 mg intravenously became delirious postoperatively (Ref. 14).

It has been reported that the sedation, tranquilization, and amnesia produced by scopolamine are useful in many circumstances, including labor, delirium tremens, toxic psychoses and maniacal states (Ref. 1). In these conditions, the drug is almost always combined with agents which produce analgesia and sedation. However, when given alone in the presence of pain or severe anxiety, scopolamine may induce outbursts of uncontrolled behavior.

As indicated earlier, therapeutic doses of scopolamine normally cause drowsiness, euphoria, amnesia, fatigue, and dreamless sleep. The same doses, however, occasionally cause excitement, restlessness, hallucinations, or delirium instead (Ref. 1). These atypical reactions may be idiosyncratic (unusual, infrequent, genetically caused reactions). They resemble the central effects of toxic doses of atropine, and occur regularly after large doses of scopolamine.

Infants, young children, and old people are especially susceptible to the effects of an overdose of scopolamine. The symptoms of poisoning develop soon after ingestion of the drug. The mouth becomes dry and burns; swallowing and talking are difficult; and there is marked thirst. The vision is blurred, and photophobia (sensitivity to light) occurs. The skin is hot, dry, and flushed. A rash may appear especially over the face, neck, and upper part of the trunk. The body temperature rises and may reach 109° F. or higher in infants. The pulse is weak and very rapid, but in infants and old people the increased heart rate may not occur. Palpitations are prominent, and the blood pressure is elevated. Urinary urgency and difficulty in urination are sometimes noted.

The patient is restless, excited, confused, and exhibits weakness, giddiness, and muscular incoordination. Walking and talking are disturbed. Nausea and vomiting sometimes occur. The behavioral and mental symptoms may suggest an acute organic psychosis. Memory is disturbed, orientation is faulty, hallucinations are common, and mania and delirium often occur. In some cases of scopolamine poisoning, a mistaken diagnosis of acute schizophrenia or alcoholic delirium has been made, with the individuals being committed to a psychiatric institution for observation and treatment (Ref. 13). The entire syndrome often lasts 48 hours or longer. Depression and circulatory collapse occur only in cases of severe intoxication; the blood pressure declines, respirations become inadequate, and finally respiratory failure occurs after a period of paralysis and coma.

Fatalities from scopolamine are rare, but sometimes occur in belladonna poisoning in children. In these cases, the cause of death is apparently uncontrolled fever. Of all the potent alkaloids, atropine is usually stated to be more toxic than scopolamine, but the evidence for this is inconclusive; persons have survived doses of 500 mg of scopolamine. In the case of atropine, doses of 1,000 mg have been survived. The best antidote for scopolamine is physostigmine 2 to 3 mg subcutaneously every 2 hours as needed (Ref. 15).

As with any depressant drug, the actions of scopolamine can be expected to enhance the effects of or be enhanced by other depressants such as alcohol (Ref. 16), barbiturates, narcotics, or tranquilizers. The drug has also been shown to produce an acute psychotic reaction when combined with marijuana (Ref. 17).

The following study plus many other studies suggest a "depressant" effect of scopolamine in animals which could be extrapolated to a depressant, or sedative, effect in humans. The dosages used cannot accurately be compared to those used in humans, but they do demonstrate that all of scopolamine's effects in animals are in the range of 0.01 to 10.0 mg/kg when given by injection.

Longo (Ref. 18) studied the effects of atropine and scopolamine on the encephalogram of the rabbit. The two alkaloids produced a sleep pattern (slow synchronous activity) while blocking the "awakening reaction." scopolamine was 10 to 15 times more active than atropine in this regard. The generally classified EEG synchronization is "dissociated" from the behavioral effects of the drug in that the animal is apparently alert during the time that the EEG indicates a sleep pattern. This is known to be a characteristic of antimuscarinic central action.

The bulk of the literature on scopolamine's effects in man concerns its actions as an antimotion sickness and antiparkinsonism drug. This literature

really indicates nothing more than the fact that scopolamine somehow depresses those areas of the brain involved in motion sickness (e.g., the cerebellum, semicircular canals and associated structures, and/or the medullary emetic centers) and in parkinsonism (basal ganglia and extrapyramidal system), and that the doses used are similar to those which appear to be effective in producing drowsiness.

The number of papers which document the sleep-inducing effect of scopolamine is surprisingly small, and many of these are reviews which assume the sedative effect of scopolamine, or simply refer again and again to the few papers available.

Very early reports in the European literature document the use of scopolamine hydrobromide in producing amnesia during labor when given in doses of 1/100 gr (0.6 mg) intravenouly. This preceded its use in combination with morphine to produce "twilight sleep" as a form of obstetrical analgesia with amnesia. Orkin et al. (Ref. 19) have studied atropine and scopolamine as preanesthetic medications and have found that smaller quantities of thiopental and meperidine are required to produce unconsciousness when scopolamine (0.4 to 0.6 mg intravenously) is given as a preanesthetic medication. One of their conclusions was that "scopolamine in 0.4 to 0.6 mg doses (intravenously) is almost as hypnotic as 100 mg of meperidine."

Tesoriere (Ref. 20) has also confirmed the "depression of the cortex" and amnesic effects in patients being prepared for surgery. The "common dose" of 0.32 to 0.43 mg (intravenously) can severely depress the older patient and must be used with caution.

Ostfeld and Aruguete (Ref. 21), in an often cited study, reported that 0.8 mg of scopolamine injected subcutaneously can impair performance in behavioral tests involving the ability to focus attention, to recall objects and words, and to maintain an attentive set. They also noted that whereas the administration of atropine was accompanied by a rise in pulse rate, scopolamine administration was followed by a decrease in such rate. Finally, the subcutaneously administered scopolamine appeared to induce sleep, hallucinations, and mental disorientation more frequently than 10 mg of atropine administered orally.

Eger (Ref. 4), in a very complete review, reaffirmed the central nervous system effects of scopolamine, and noted that scopolamine is some 5 to 15 times more potent in producing drowsiness than atropine.

Environmental conditions and subjective attitudes greatly influence the response to scopolamine. Although these factors have not been extensively studied, a few examples are available (Ref. 22): (1) The pain of labor can cause the response to amnesic doses of scopolamine to change to a state of delirious excitment and restlessness, often to such a degree that restraints are necessary; (2) the loss of a night's sleep can markedly increase the psychotomimetic effects of scopolamine; and (3) in high ambient temperatures the central effects of scopolamine are significantly accentuated. The mechanism for this last effect is unclear.

The Commissioner concludes from the available literature that scopolamine has central depressant effects in animals, and that in appropriate doses it produces drowsiness and sleep in humans. However, there is a serious lack of sufficient data on the central effects of scopolamine over a wide range of doses in man.

(1) *Scopolamine hydrobromide.* There are products presently on the OTC market promoted for sleep which contain 0.25 mg of scopolamine hydrobromide per unit dose as part of a combination of ingredients. The Commissioner concludes that this ingredient is not effective as a nighttime sleep-aid in doses presently marketed, and that at higher, possibly more effective doses it would not be safe.

Although scopolamine hydrobromide has central depressant effects in animals, the evidence for it's hypnotic effect in humans is mainly anecdotal on the basis of the drug's early use in Parkinsonism and motion sickness. One source, also anecdotal, states that an oral dose of 0.3 mg has "little soporific effect" (Ref. 23). However, the Commissioner is aware that no clinical studies of the effects of scopolamine hydrobromide alone on sleep onset or duration of sleep were located.

As mentioned earlier, there is evidence which suggests an alarming frequency of side effects when scopolamine is given in doses necessary for a central depressant effect (0.6 mg and above) (Ref. 11). Side effects which can be seen with scopolamine hydrobromide in oral doses of 0.6 mg and above are dryness of the mouth, blurred vision, photophobia, and cardia irregularities. Occasionally, constipation, urinary retention, hypersensitivity reactions, acute glaucoma, excessive restlessness and toxic psychosis can be seen. Infants, young children, and old people are especially susceptible to higher doses of the drug (Refs. 3 and 4).

Doses of 2.0 mg orally in man often produce psychotomimetic effects (Ref. 24). On the basis of this toxicity, the Commissioner concludes that doses high enough to be effective as an OTC nighttime sleep-aid would not be safe.

(2) *Scopolamine aminoxide hydrobromide.* There are products presently on the OTC market promoted for sleep which contain 0.125 to 0.5 mg of scopolamine aminoxide hydrobromide per unit dose as part of a combination of ingredients. The Commissioner concludes that this ingredient is not effective as an OTC nighttime sleep-aid in doses presently marketed, and that at higher, possible more effective doses it would not be safe.

While the Commissioner is aware of some animal studies relating to the safety of scopolamine aminoxide hydrobromide, the literature on this ingredient is not voluminous and, in fact, no documented evidence for the safety of this ingredient in humans was located. Even though the Commissioner is aware that scopolamine compounds have been marketed for over 50 years and that the OTC drug review procedures relating to safety (21 CFR 330.10(a)(4)(i)) provide for consideration of marketing experience, the Commissioner finds that such information is insufficient to support safe use of scopolamine at levels that would be effective as OTC nighttime sleep-aids.

The therapeutic value of scopolamine aminoxide hydrobromide is due to its metabolism in the body to scopolamine. The claimed reduction in toxicity compared to that of scopolamine hydrobromide may be due to the slow conversion of scopolamine aminoxide hydrobromide to the parent base, so that a sustained action is seen with few toxic effects (Ref. 10). Since there are no clinical studies in the literature on the scopolamine base substance alone, the usual way to discuss scopolamine aminoxide hydrobromide has been to compare it with scopolamine hydrobromide, for which there are experiments reported in the literature. Therefore, all of the previous discussion on scopolamine hydrobromide (pharmacology, toxicity, side effects, etc.) would be applicable here.

Reports of controlled clinical studies on the effectiveness of scopolamine aminoxide hydrobromide alone as a nighttime sleep-aid in the recommended doses of 0.125 to 0.5 mg could not be located. An old (1927) French thesis by Lados, cited by Scharf (Ref. 10), reported on the effects of scopolamine aminoxide hydrobromide in 16 cases of postencephalitic parkinsonism. Lados claimed that scopolamine aminoxide hydrobromide, in earlier experiments with dogs, was 1/200 as toxic as scopolamine, and proceeded to use doses of 4.0 mg of scopolamine aminoxide hydrobromide per day with no toxic symptoms in patients with parkinsonism. Scharf himself (Ref. 10) used scopolamine aminoxide hydrobromide in doses of 2.0 mg/day to treat patients with parkinsonism, with no toxic effects. On the other hand, doses of 2.0 mg 3 times a day of scopolamine aminoxide hydrobromide do produce a significant number of side effects (nightmares, blurred vision, dry mouth and tinnitus or ringing in the ears) when given for seasickness (Ref. 25). These

authors noted that 2.0 mg of scopolamine aminoxide hydrobromide "produced far more severe reactions than had 0.75 mg of scopolamine hydrobromide." They stated that in these doses the toxicity and duration of action of scopolamine aminoxide hydrobromide were at least as great as those of scopolamine hydrobromide. A more recent paper, in which antimotion sickness drugs were reviewed (Ref. 26), indicates that scopolamine aminoxide hydrobromide 2.0 mg and scopolamine hydrobromide 0.6 to 1.0 mg have similar actions, toxicities, and durations of action.

Another old paper (1945) by Co Tui and Debruille (Ref. 27) states that scopolamine aminoxide hydrobromide is one-third as potent and one-sixth as toxic as scopolamine hydrobromide, and that in equipotent doses the effect of scopolamine aminoxide hydrobromide seems to last only one-third as long as that of the nonaminoxide compound. However, these conclusions were drawn on the basis of lethal dose studies in mice and abolition of the acetylcholine depressor effect on the blood pressure of the cat, and are difficult to extrapolate to man. Most importantly, the literature regarding the toxicity and effectiveness of scopolamine aminoxide hydrobromide appears to be too sparse and inconsistent to substantiate the routine use of this derivative in an OTC product.

If it is assumed from these animal studies that scopolamine aminoxide hydrobromide is one-sixth as toxic and one-third as effective as scopolamine hydrobromide, then in equipotent doses scopolamine aminoxide hydrobromide becomes only one-half as toxic as scopolamine hydrobromide; therefore, the safety is still questionable. Furthermore, clinical studies have not confirmed this reduced toxicity of scopolamine aminoxide hydrobromide.

Although these early uncontrolled studies in animals suggested that scopolamine aminoxide hydrobromide is less toxic than other scopolamine salts, most newer reports conclude that scopolamine aminoxide hydrobromide and scopolamine hydrobromide have similar actions, toxicities, and durations of action in doses of about 2:1, aminoxide hydrobromide to hydrobromide (Ref. 28). On the basis of the toxicity associated with scopolamine aminoxide hydrobromide, the Commissioner concludes that doses high enough to be possibly effective as nighttime sleep-aids would have toxicity similar to that of scopolamine hydrobromide, and that these doses would not be safe.

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d. *Miscellaneous compounds*—(1) *Acetaminophen, aspirin, salicylamide.* The Commissioner has no evidence that these ingredients are effective OTC nighttime sleep-aids. The drugs were deferred to the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products for an opinion on their analgesic effects. That Panel's recommendations were published in the FEDERAL REGISTER of July 8, 1977 (42 FR 35346).

(2) *Passion flower extract, thiamine hydrochloride.* The Commissioner has not been presented with any valid scientific data to support the use of these ingredients as OTC nighttime sleep-aids. The Commissioner is unable to identify a role for either passion flower extract or thiamine hydrochloride in the central nervous system in inducing sedation. Therefore, these ingredients are classified by the Commissioner as Category II for use in OTC nighttime sleep-aid products.

Category II Labeling

The Commissioner concludes that the following labeling claims are classified as Category II and shall be removed from OTC nighttime sleep-aid labeling because they are seriously misleading or ambiguous: "natural sleep", "normal sleep", "sound sleep", "non-habit-forming", "guaranteed (fast acting)", "refreshing sleep", "helps you relax so you can fall asleep".

"Natural sleep" is ambiguous since "natural is not a well-defined term and

could have referred to a natural feeling state in the morning or to normal appearing sleep by any number of physiological criteria. The term is misleading when these drugs are taken, since the drug is an exogenous nonnaturally occurring agent introduced into the body. Hence, the body is obviously not entirely in its "natural" state during drug-induced sleep.

"Normal sleep" is ambiguous and is misleading for the same reasons given under natural sleep. "Sound sleep" is similarily ambiguous. The term "nonhabit-forming" is misleading, undesirable and probably false because it is very hard to prove that any product with psychotropic activity can be nonhabit-forming; but more importantly, there is an insinuation that other OTC sleep-aid products obviously are habit-forming.

"Guaranteed" is misleading and a false promise if used in a general way such as "guaranteed fast-acting". No drug helps 100 percent of the time. The Commissioner concludes that the word "guarantee" should be prohibited in regard to medical claims. The Commissioner will not comment on the use of the term in labeling when it refers to promotional consideration such as "Guarantee: Your money will be refunded without question if you are in any way dissatisfied with this product".

"Refreshing sleep" is misleading and ambiguous since the term "refreshing" is difficult to define.

As discussed in comment 44, the claim "Helps you relax so you can fall asleep" is confusing since the term "relax" has calmative connotations that do not properly relate to the OTC use of nighttime sleep-aids.

The Commissioner concludes that approval of an active ingredient or combination of active ingredients for a particular indication should not be interpreted as unique to the active ingredient or to the combination. Labeling, package insert, or advertising shall not refer to such approval either directly or by inference as a unique or an exclusive endorsement of such an ingredient or combination of ingredients.

3. *Category III conditions under which the available data are insufficient to permit final classification at this time.*

CATEGORY III ACTIVE INGREDIENTS

The Commissioner concludes that the available data are insufficient to permit final classification of the claimed OTC nighttime sleep-aid ingredients listed below. The Commissioner believes it reasonable to provide 3 years for the development and review of such data. Marketing need not cease during this time for those products currently being marketed as OTC nighttime sleep-aids if adequate testing is undertaken. If adequate effectiveness and/or safety data are not obtained within 3 years, however, the ingredients listed in this Category shall no longer be marketed as OTC nighttime sleep-aids.

ANTIHISTAMINES

Diphenhydramine hydrochloride.[1]
Doxylamine succinate.[1]
Phenyltoloxamine dihydrogen citrate.[1]
Pyrilamine maleate.

a. *General discussion.* The Advisory Review Panel on OTC Nighttime Sleep-aid, Daytime Sedative, and Stimulant Drug Products proposed (40 FR 57292) a concept known as "Category III with a marketing hold" for doxylamine succinate and phenyltoloxamine dihydrogen citrate, two ingredients never before marketed as OTC nighttime sleep-aids. These ingredients are currently available in OTC drug products for other indications at dosages lower than those recommended for these ingredients as nighttime sleep-aids.

The Panel also recommended that the ingredient diphenhydramine hydrochloride, a prescription drug which has never been legally marketed for any indication for OTC use, be classified as Category III as a nighttime sleep-aid, and suggested marketing be permitted while final testing is carried out.

The Commissioner determined that the procedures promulgated in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), establishing the OTC Drug Review, did not provide for a "marketing hold" for Category III conditions and that such a concept is equivalent to classifying an ingredient in Category II. In addition, the Commissioner determined that the classification of a prescription ingredient, like diphenhydramine hydrochloride, in Category III represented no more than an opinion that the ingredient may be shown at some future time to be generally recognized as safe and effective for OTC use with adequate studies.

The Commissioner concluded that doxylamine succinate, phenyltoloxamine dihydrogen citrate and diphenhydramine hydrochloride as nighttime sleep-aids were new drugs within the meaning of section 201(p) of the act implemented by § 310.3(g) and (h)(5) (21 CFR 310.3(g) and (h)(5)).

Subsequently, the Commissioner issued final regulations (21 CFR 330.13) to clarify the interim marketing status of prescription ingredients or OTC ingredients in higher dosages than those available OTC and reviewed and classified by the Panel in Category I, II, or III. Those regulations were published in the FEDERAL REGISTER of August 4, 1976 (41 FR 32580), and became effective on September 3, 1976. The regulations provide, among other things, that an OTC advisory review panel may place in Category III an active ingredient, limited on or after May 11, 1972, to prescription use for the indication under consideration by the panel, or an active ingredient recommended for use at a dosage level higher than that available in any OTC drug product on December 4, 1975. However, these ingredients may not be lawfully marketed until the ingredient is determined by the Commissioner to be generally recognized as safe and effective, or until a new drug application for the product has been approved.

The Commissioner concludes, based on the available data, that doxylamine succinate, phenyltoloxamine dihydrogen citrate and diphenhydramine hydrochloride shall be Category III as OTC nighttime sleep-aids. However, marketing of these ingredients for the sleep-aid indication cannot take place unless and until they are classified in Category I in the final monograph, or until the required testing is completed pursuant to the Category III Testing Guidelines published in the FEDERAL REGISTER of April 12, 1977 (42 FR 19137), and described below and the Commissioner determines the ingredients to be generally recognized as safe and effective for such use pursuant to a petition to amend the monograph, or a new drug application is approved for such use.

b. *Antihistamines.* Histamine is a chemical substance normally concerned with inflammatory responses to irritants or injury. In sensitized individuals, it is released in one or more target organs (especially skin and mucous membranes) causing allergic reactions such as itching, swelling, hay fever, asthma, etc. (Ref. 1).

The antihistamines, as their name implies, are a class of drugs useful in antagonizing these actions of histamine. They can also exert side actions, including both drowsiness and then stimulation, depending upon the dose (Ref. 2). The sedative action, commonly seen in allergic patients, may be the major effect observed with their use in nonallergic individuals. This has led to the introduction of the application of this sedative action as the primary effect of some antihistamines in OTC sleep-aids marketed for a target population whose chief complaint is sleeplessness.

The mechanism by which antihistamines accomplish the blockage or antagonism is apparently a competitive

[1] These ingredients have not been marketed previously as OTC nighttime sleep-aids. Therefore, according to 21 CFR 330.13 (41 FR 32850, August 4, 1976), marketing of these ingredients as OTC nighttime sleep-aids is prohibited prior to determination by the Commissioner that they are generally recognized as safe and effective, or a new drug application for the product has been approved.

inhibition of already released histamine, rather than an interference with the release itself (Ref. 3). Thus, the skin manifestations of histamine release, i.e., itch, flare, wheal, capillary permeability and edema, are all decreased by antihistamines, although the dosage varies with the relative potency of the compound used. For example, equivalent inhibition of histamine-induced skin wheals is produced in man by 25 mg promethazine and 175 mg of pyrilamine (Ref. 4).

In the respiratory tract, rhinorrhea and bronchospasm are both decreased by antihistamines. Paradoxically, antihistamines themselves can cause bronochoconstriction in man, and they have been shown to cause contraction of isolated strips of guinea pig tracheal smooth muscle at concentrations in the usual antihistaminic therapeutic range (Refs. 5 and 6).

Apart from their specific antogonism to the actions of histamine, the antihistaminic drugs may also exert other effects, some useful, some undesirable. Stimulation of the central nervous system has been observed in some patients with focal cortical lesions, in whom small doses of antihistamines may cause electroencephalographic (EEG) activation and even frank seizures (Ref. 7). Excessive doses in any patient may cause restlessness, excitation, delirium, tremors and even convulsions (Ref. 2). Depression of the central nervous system is also frequently observed with the use of antihistaminic drugs. When these drugs are used to block histamine, drowsiness is common with antihistaminic therapeutic doses, a characteristic which makes the use of these drugs possible as OTC nighttime sleep-aids.

Sedation is perhaps the most frequently reported side effect associated with the use of antihistaminic agents (Ref. 1). Its manifestations may vary from inability to concentrate, dizziness and incoordination, to deep sleep. The sedative effect can be hazardous in ambulatory patients whose daytime activities require mental alertness and motor coordination (e.g., driving an automobile). The sedative effect, of course, would become the primary indication when these drugs are marketed for use as OTC nighttime sleep-aids.

Antihistamines not only have the two primary indications discussed above, but also exhibit a number of other side effects and toxicities, many related to anticholinergic activity (Ref. 8).

Central and peripheral nervous system manifestations of toxicity from the use of antihistaminic drugs may include dizziness, tinnitus (ringing in the ears), lassitude, incoordination, fatigue, blurred vision, double vision, euphoria, nervousness, irritability, insomnia, anxiety, disorientation, vertigo, confusion, deliruim, hyperreflexia, tremors, muscle spasm, convulsions (especially in children) and coma (Ref. 9). Fatal or near fatal overdoses cause fixed, dilated pupils, muscular twitchings followed by convulsions, coma, circulatory collapse and respiratory failure. Convulsions may persist for 24 hours, coma for 2 days, but death rarely occurs later than 24 hours after ingestion, unless due to infection associated with agranulocytosis (Ref. 10).

Gastrointestinal manifestations may include loss of appetite, nausea, vomiting, epigastric distress, constipation or diarrhea.

Cardiovascular symptoms may include palpitations (i.e., irregularities of heart rate and/or rhythm), hypotension, headache or tightness of the chest. In the genitourinary system, increased urinary frequency and/or difficulty in urination may be encountered. Skin rashes and photo-sensitivity may occur. Hematologic complications, fortunately rare, include leucopenia, thrombocytopenia, hemolytic anemia and agranulocytosis. Depending upon dose response relationships, some antihistamines may actually liberate histamine or serotonin, thus possibly contributing to adverse reactions such as bronchospasm.

Most antihistamines have some anticholinergic (artopine-like, belladonna-like) activity (Ref. 8). The action is not usually intense enough to be of therapeutic significance, but this activity may account for dryness of the month seen in some patients and, more rarely, for other dysfunctions such as difficulty in urination and impotence (Ref. 1). Tingling, heaviness, and weakness of the hands may also be observed. Overdoses may cause mammary gland enlargement in both sexes, with secretion of milk. This effect has been attributed to depression of the hypothalamus with release of lactogenic hormone (Ref. 10).

The Commissioner is aware that the differences in chemical structure of the various antihistamine groups will have a significant effect on the sleep-aid indication. The groups may be classified as follows (Ref. 11):

Ethanolamines (examples: Diphenhydramine, doxylamine and phenyltoloxamine). The drugs in this group are potent and effective histamine antagonists that possess significant atropine-like activity and have a pronounced tendency to induce sedation. With conventional antihistamine treatment doses, about half of the individuals who are treated with these drugs experience drowsiness. The incidence of gastrointestinal side effects, however, is low in this group.

Ethylenediamines (examples: Methapyrilene and pyrilamine). These, too, are highly effective histamine antagonists. These agents do not have a strong central nervous system action and may not produce a therapeutic somnolence even though a fair number of patients will exhibit drowsiness. Gastrointestinal side effects are quite common. This group contains some of the oldest and best-known antihistamines.

Alkylamines (example: Chlorpheniramine). Antihistamines in this group are among the most active histamine antagonists and are generally effective in relatively low doses. These agents are not so prone to produce drowsiness and may be among the more suitable agents for daytime use; but again, a significant proportion of patients do experience this effect. Side effects involving central nervous system stimulation are more common in this than in other groups.

Piperazine (example: Chlorcyclizine). The oldest member of this group, chlorcyclizine, is a valuable histamine antagonist with prolonged action and comparatively low incidence of drowsiness. The others are used primarily to counter motion sickness. The incidence of untoward effects, both central nervous system depressant and atropine-like, seems to compare favorably with that of other antihistamines. The possibility of some dulling of mental alertness should be borne in mind when the subject may be called upon to perform exacting and potentially hazardous tasks, such as driving a car.

Phenothiazines (example: promethazine). Most drugs of this class are histamine antagonists. The prototype, promethazine, was introduced in 1946 for the management of allergic conditions. The prominent sedative effects of this compound and its value in motion sickness were early recognized. Promethazine and its many congeners are now used primarily for their central depressant properties.

The problem for all the antihistamines when used as OTC nighttime sleep-aids, is to ensure that the dosage recommended is adequate for the intended sedative effect desired, yet not so large that toxic effects result. The Commission is concerned that in currently available antihistamine OTC products promoted for sleep, dosages may have been reduced by the manufacturer to borderline or ineffective levels to avoid toxicity. The Commissioner concludes that higher doses as recommended below should be studied for some antihistamines to be used as nighttime sleep-aids.

Except for methapyrilene and pyrilamine, the Commission is unaware of any products containing antihistamines promoted for sleep on the OTC market. Pyrilamine is currently used as an OTC sleep-aid at very low doses and therefore, information to make a final determination that this ingredient should be generally recognized as

safe and effective is insufficient. Until such time as these data are available to the FDA, the Commissioner concludes that pyrilamine be placed in Category III, with an additional period of 3 years for testing. As discussed above in this document, methapyrilamine has been reclassified as Category II due to its possible carcinogenic potential.

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(1) *Diphenhydramine hydrochloride.* The Commissioner concludes that clinical experience with diphenhydramine hydrochloride as a prescription drug for use as an antihistamine agent strongly suggests that in an appropriate dosage (50 mg to a maximum 100 mg single dose at bedtime) it may be effective as an OTC nighttime sleep-aid.

Physicians have used diphenhydramine hydrochloride as a sleep-aid for many years because of its sedative side effects. However, since only a few studies exist for the sleep indication, the Commissioner has determined that further testing is required to establish the safety of diphenhydramine hydrochloride as an OTC nighttime sleep-aid.

Diphenhydramine hydrochloride is not currently available as a single active ingredient for OTC use, but because of well-established and documented safe clinical use for many years as a prescription drug for various indications the Commissioner concludes that this ingredient is classified as Category III for the sleep-aid indication. However, since diphenhydramine hydrochloride has never been legally marketed OTC for any indication, regulations governing the marketing status of ingredients recommended for OTC use (21 CFR 330.13), prohibit marketing of diphenhydramine hydrochloride as an OTC nighttime sleep-aid until the Commissioner determines that it is generally recognized as safe and effective or a new drug application for this indication has been approved.

Available evidence suggests that doses of 25 mg are ineffective (Refs. 1, 2, and 3). However, EEG studies with 25 and 30 mg doses indicate sedation, especially with the larger dose (Ref. 4). Doses of 50 mg or more have been reported to be as effective as doses of 100 mg or more of secobarbital or pentobarbital (Refs. 5 through 9). An additional well-controlled study is required to determine whether diphenhydramine in doses of 50 mg is both effective and sufficiently safe to permit its use as an OTC nighttime sleep-aid. This will not require but may include EEG studies.

Diphenhydramine was the first antihistamine produced in this country (Ref. 10). It is described (Ref. 11) as a potent antihistamine with a high incidence of sedation, mild antitussive effects and antiemetic effectiveness equal to dimenhydrinate, and is the antihistamine of choice for parenteral use in treatment of anaphylactic reactions.

Based on a review of this drug by the National Academy of Sciences/National Research Council (NAS/NRC), it was classified as "probably" effective for the sedation indication as follows: "For intractable insomnia and insomnia predominant in certain medical disorders." That group recommended that final classification required further investigation (Ref. 12).

The sedative properties of diphenhydramine have been employed by anesthesiologists as a useful adjunct to preoperative medication (Refs. 13 and 14). The sedative action of diphenhydramine has been utilized in obstetric patients during labor (Ref. 15) and in the preoperative preparation of surgical patients (Ref. 13). Sedation determined by EEG examination was reported ih one laboratory study (Ref. 4), while effectiveness in producing sleep was verified in two other EEG laboratories (Refs. 5 and 21) and also in a comprehensive drug surveillance program (Refs. 6 and 9).

Curiously, although antihistaminic drugs commonly produce drowsiness in patients, this effect is not observed in animals receiving comparable doses (Ref. 16). Therefore, a suitable animal model to test the sedative effect of new antihistaminic compounds in man does not exist. However, Winter (Ref. 16) postulated that it is possible to demonstrate a sedative action of an antihistaminic drug in animals by giving the test drug in connection with administration of a drug of know sedative action. This was accomplished with diphenhydramine and other antihistaminics administered in doses of 10 mg/kg injected subcutaneously into mice, followed in ½ hour by intraperitoneal administration of hexobarbital 100 mg/kg. The mean (average) sleeping time was prolonged about 40 percent by diphenhydramine, from 39.2±1.4 minutes to 56.4±1.9 minutes. Similarly, diphenhydramine 10 mg/kg prolonged mean sleep time obtained with pentobarbital 50 mg/kg in mice from 36.0±0.86 minutes to 53.8±0.86 minutes. Comparable results were obtained using guinea pigs receiving diphenhydramine 10 mg/kg and hexobarbital 35 mg/kg. Sleep time was prolonged from 50 to 73 minutes.

Other investigators (Refs. 17 and 18) have confirmed prolongation of barbiturate sleep as a valid method for demonstrating the sedative action of antihistaminic drugs in animals. It should be noted that the studies above demonstrate only prolongation of sleep and not a true potentiation of the sediative effect of the barbiturate used. For example, a subhypnotic dose of pentobarbital (25 mg/kg intraperitoneally) in mice was not converted to a sleep dose by the addition of diphenhydramine in doses of 12.5 to 100 mg/kg orally (Ref. 3).

The sedative effect of diphenhydramine, alone or in combination, has been evaluated in a variety of ways. Sachs (Ref. 19) found it the major side effect in a series of 1,210 patients receiving diphenhydramine.

Friedlander (Ref. 5) examined sleep EEG's of 48 patients receiving secobarbital 200 mg or diphenhydraime 100 mg by mouth (the first sleep was with secobarbital in 21 patients). Both drugs were equally effective in induction and maintenance of sleep. Minor differences in the amount of abnormal brain activity of various types led Friedlander to the conclusion that, in the dosage given, diphenhydramine might be "a little better drug" than secobarbital for obtaining sleep EEG's.

In a study by Goldstein et al. (Ref. 4), EEG frequency analysis in 42 human volunteers receiving diphenhydramine in doses of 25 or 50 mg revealed predominantly increased low amplitude activity (i.e., "low energy sedation"). Not surprisingly, the effect was more marked with the larger dose.

Noell et al. (Ref. 8) used more than 3,000 male volunteers in a carefully controlled daytime EEG study of 33

antihistamines, secobarbital and placebo. Diphenhydramine 50 mg ranked second among the antihistamines, after dimenhydrinate, in time to "end of wakefulness" and thirteenth in time to "onset of sleep". It was significantly superior to placebo in both of these effects.

Jaattela et al. (Ref. 20) compared the effects of oral daytime administration of the tranquilizer diazepam 10 mg, diphenhydramine 50 mg and placebo (sodium lactate) on mood and psychomotor function in 270 healthy medical students 20 to 23 years of age, divided into three groups (65 men, 25 women). Both drugs decreased activity in men and women and caused some euphoria in men. Diphenhydramine had a slightly greater depressant effect than diazepam on mental functions (as determined by standard tests, e.g., Nowlis adjective check list, digit symbol test and ability to repeat numbers in series).

An abstract by Bjerver and Goldberg (Ref. 2) refers to the central depressant action of as number of antihistamine compounds, including diphenhydramine, without providing details.

Three studies were designed to evaluate the sedative-hypnotic effects of the ingredients methaqualone 250 mg and diphenhydramine 25 mg separately and together in combination. The combination was derived from the demonstrated potentiation of methaqualone by diphenhydramine in the laboratory (Ref. 21). The first study was conducted by Beaubien et al. (Ref. 1) on psychiatric in-patients who received unidentified capsules containing either the combination, methaqualone 250 mg or diphenhydramine 25 mg. The capsules were distributed at random to 18 patients in double-blind fashion for a total of 200 sleeps. Nurses and patients each rated induction and duration of sleep and presence or absence of morning drowsiness and sluggishness on a 4-point scale.

There was some indication that the combination is superior to either methaqualone or diphenhydramine alone in regard to sleep induction, while the combination and methaqualone alone are equal and both superior to diphenhydramine 25 mg in maintaining sleep.

In the second study, Bordeleau et al. (Ref. 22) compared the sleep produced during 5 consecutive nights by the combination (methaqualone 250 mg and diphenhydramine 25 mg), methaqualone 250 mg, diphenhydramine 25 mg, secobarbital 200 mg and placebo in 101 female psychiatric patients averaging 37.1 years (range 17 to 62 years.). Results were evaluated with a questionnaire concerning duration and quality of falling asleep, duration and quality of sleep itself and subjective state on awakening and during the morning. The two single hypnotics (methaqualone and secobarbital) and the combination were found significantly superior to diphenhydramine and the placebo in quality and duration of both falling asleep and sleep itself. It was impossible to differentiate diphenhydramine 25 mg from the placebo in any of the five parameters of sleep studied.

In a third study, by Norris and Telfer (Ref. 14), the sedative effectiveness of diphenhydramine 25 mg appeared more favorably. This again was a comparison of the sedative effects of methaqualone 250 mg and diphenhydramine 25 mg in fixed combination, the individual ingredients and placebo in 200 otherwise healthy female patients undergoing minor gynecologic operations. The patients were divided into groups of 50, handled in double-blind fashion. Although both the mean sedation score and the number of patients showing good sedation were higher after the combination than after diphenhydramine 25 mg, the differences were not statistically significant. Changes in heart rate and blood pressure were minimal after each of the drugs, and postoperative nausea and vomiting were rare.

Cappe and Pollin (Ref. 15), aware of the sedative side effects of antihistamine drugs, explored the extent of hypnosis and analgesia with diphenhydramine and chlorprophenpyridamine in obstetric patients during labor and delivery. Each drug was administered to 30 patients in fractional doses intravenously. Moderate analgesia was achieved in 35 to 40 percent of patients receiving diphenhydramine (30 to 120 mg) or chlorprophenpyridamine. Untoward effects included nausea, vomiting and drop in blood pressure, but not respiratory depression in the newborn.

In another study, Lear et al. (Ref. 13) compared the sedative effectiveness of preoperative medication with various tranquilizers in 1,159 surgical patients. They administered chlorpromazine 12.5 to 50 mg intramuscularly to 350 patients, mepazine 200 to 400 mg orally to 434, promethazine 25 to 50 mg intramuscularly to 193 and diphenhydramine 50 to 100 mg intramuscularly to 132, using as controls a mixed series of 262 patients who received either morphine or meperidine and a belladonna derivative with or without a barbiturate. All of the tranquilizers diminished undesirable reflex activity while causing less overall depression than with the narcotics and barbiturates. The incidence of post-operative nausea and vomiting was reduced, especially with chlorpromazine. Among the 182 patients receiving diphenhydramine, sedation was rated as nil in 15 percent, slight in 34 percent, moderate in 46 percent and marked in 5 percent. The authors noted that diphenhydramine has been used clinically at bedtime for sedation, either alone or in combination with barbiturates, for the apprehensive patient. Occasionally it has replaced the barbiturates for sedation, even in the allergic patient. The authors further noted that diphenhydramine combined with meperidine is useful preoperatively for brief procedures requiring early ambulation such as vein ligations and for other forms of minor surgery such as dilatation and curettage, removal of simple breast tumors, and incision and drainage.

Two pertinent papers have emerged from a group headed by Jick and Slone, who have established a comprehensive drug surveillance program in three Boston hospitals. The first of these (Ref. 6) concerns a double-blind comparison in adult medical patients of three hypnotic drugs: Chloral betaine 750 mg (equivalent to chloral hydrate 500 mg), diphenhydramine 50 mg, pentobarbital 100 mg and a placebo. Fifty bottles of each of the drugs and 100 of placebo were numbered randomly and assigned in numerical order to patients requiring hypnotics. Of the original 250 patients entered into the trial, 195 (86 males, 109 females) received one or more of the prepared capsules. The average age and weight of patients receiving one of the hypnotic drugs were 56.3 years and 70.8 kg, respectively, and of those receiving placebo were 53.7 years and 68.5 kg, respectively. Hypnotic effectiveness was rated by the physician as "good," "fair," "poor," or "don't know." Because 59 patients received a "don't know" rating, analysis of effectiveness was confined to the remaining 136 patients. Statistically, no differences were evident ($P=0.50$) among the hypnotic drugs but all were superior to placebo: Ratings were "good" or "fair" in 17 of 24 patients receiving chloral betaine, 23 of 28 with diphenhydramine, 20 of 24 with pentobarbital and 28 of 60 with placebo.

The second report from this drug surveillance program (Ref. 9) concerns the clinical effects of four hypnotic drugs (chloral hydrate, diphenhydramine, secobarbital and pentobarbital) in 2,045 patients, each receiving one or more of the four drugs in the treatment of insomnia. All four drugs were reasonably effective but, unfortunately, no placebo was used. In the case of diphenhydramine, it is of interest to note that doses were 100 mg in 46 patients (9 percent) and 25 mg in 24 patients (5 percent). Adverse effects were reported in nine patients (1.8 percent) receiving diphenhydramine; of these, seven received 50 mg and two received 100 mg. Vomiting occurred in one case and central nervous system depression in eight, in one of which depression was deemed "major." All of the patients recovered promptly when the drug was discontinued, and there were no complications.

Another study, by Teutsch et al. (Ref. 23), evaulated sleep following pentobarbital 100 mg, diphenhydramine 50 mg, methapyrilene 50 mg or placebo in 159 patients in two Veterans Administration Hospitals. They found that both pentobarbital and diphenhydramine, but not methapyrilene, were significantly better than the placebo when evaluated by the subjective question "How long did you sleep?" In one of the two hospitals, methapyrilene was superior to the placebo, while in the other hospital, it was not. The authors further state that these findings confirm the results of another comparison between pentobarbital and diphenhydramine which they conducted earlier in 110 patients.

Vogel et al. (Ref. 24) conducted a double-blind EEG study of the effect of diphenhydramine 50 mg on the sleep of six healthy adult volunteers with both subjective and objective insomnia. Placebo controls were not used.

Significant changes were observed by Vogel. They included a decrease in sleep latency and an increase in total sleep time, the latter being mainly accomplished by a significant increase in stage 2 sleep. The drug had no effect on delta or deep sleep. There was a small but statistically significant rapid eye movement (REM) deprivation (significant reduction in duration of REM sleep and increase in REM latency, with an almost significant REM rebound). There were no significant changes in subjective sleep variables, nor were important side effects encountered. Slightly more than base line drowsiness was reported by four of the six subjects the next morning, by two subjects on three and six mornings, respectively, following drug administration and by one subject one evening. It was concluded that diphenhydramine 50 mg significantly decreased EEG latency and increased duration of EEG sleep without significant side or toxic effects.

Diphenhydramine has been classed as a potent antihistamine with a high incidence of sedation (Ref. 11). The data in the present reports are confirmatory and suggest that a useful sedative-hypnotic effect may be obtained with diphenhydramine in doses of 50 to 100 mg. Diphenhydramine hydrochloride 25 mg, the amount contained in a combination preparation previously described (Ref. 14), is much less effective than the other constituent, methaqualone 250 mg.

With reference to safety, available data (Ref. 25) indicate a definite but low order of toxicity, unless dosage exceeds 100 mg. Instances of poisoning, accidental and suicidal, have been reported with diphenhydramine. Toxic psychoses from overdose of the drug have been observed (Ref. 26). Possibly the earliest suicide was that reported by Duerfeldt in 1947 (Ref. 27). Wyngaarden and Seevers (Ref. 28) listed a 6-month-old child who died in convulsions and a group of adults, ranging from 18 to 72 years in age, who sustained nonfatal convulsions, excitation, toxic psychosis, coma, petit mal or somnolence. These are typical examples rather than a complete compilation.

Also of interest are observations that diphenhydramine is an enzyme inducer, i.e., it stimulates the activity of microsomal enzymes in the liver which metabolize a variety of drugs (Refs. 29 through 32). Examples of drugs whose metabolism in the body is so accelerated are zoxazolamine (Ref. 29), aminopyrine (Ref. 31) carisoprodol (Ref. 30), some oral anticoagulants, barbiturates, corticosteroids, diphenylhydantoin, griseofulvin and diphenhydramine itself (Ref. 27). Since enzyme induction requires repeated use of the inducing drug, this problem would ordinarily not occur with OTC preparations intended for occasional use.

The Commissioner concludes that evidence already at hand strongly suggests that diphenhydramine in an appropriate dosage (50 mg single dose at bedtime) could prove effective as an OTC nighttime sleep-aid.

However, only a few studies exist for the sleep indication, and, therefore, the Commissioner concludes that a minimum of two well-controlled clinical studies following the principles established in § 314.111(a)(5)(ii) are required to establish the safety and effectiveness of diphenhydramine hydrochloride as an OTC nighttime sleep-aid. The Commissioner believes that reported observations of anticholinergic and other side effects cannot be overlooked and need to be evaluated. Both the 50 mg and 100 mg dosage levels should be studied with a careful comparison of side effects at both dosage levels. In view of the extensive EEG data already available, additional EEG studies will not be required to demonstrate effectiveness. While this ingredient is classified in Category III, regulations on the marketing status of ingredients recommended for OTC use (21 CFR 330.13) prohibit lawful marketing of diphenhydramine hydrochloride as an OTC nighttime sleep-aid until the Commissioner determines that it is generally recognized as safe and effective or a new drug application for the product has been approved.

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(2) *Doxylamine succinate.* This drug is presently marketed as an antihistamine available by prescription in doses of 12.5 to 25 mg 3 to 4 times daily for adults, or 6.25 mg 2 to 4 times daily for children under 12 years and is also available OTC as an antihistamine in doses of 3.75 to 7.50 mg 3 to 4 times a day for adults or 3.75 mg 4 times a day for children under 12 years.

The Commissioner concludes that in an appropriate dosage (25 to a maximum 50 mg single dose at bedtime), doxylamine succinate may be both safe and effective as an OTC nighttime sleep-aid, but further evidence of safety and effectiveness is needed and therefore, places this ingredient in Category III.

However, final regulations on the marketing status of OTC ingredients (21 CFR 330.13) state that an active ingredient at a dosage level higher than that available in any OTC drug product on December 4, 1975, and classified in Category III, may not be lawfully marketed until the ingredient is determined by the Commissioner to be generally recognized as safe and effective or a new drug application for the product has been approved.

In antihistaminic sedative potency, doxylamine succinate resembles other antihistamines in the ethanolamine class. One paper (Ref. 1) indicates that doxylamine succinate is a potent antihistamine which shows a high incidence of sedation with average therapeutic doses. Feinberg (Ref. 2) grades the sedation of 12.5 mg of doxylamine succinate the same as that of 25 mg of methapyrilene hydrochloride, while other researchers contend that the sleep-inducing effect of doxylamine is significantly greater than that of methapyrilene (Ref. 3).

The exact mechanism of central nervous system depression by doxylamine is unknown and there is nothing in the literature on the absorption and fate of doxylamine in humans. In male rats, 7 to 21 percent of a single intravenous or oral dose of the succinate is excreted in the urine within 24 hours of administration, while in female rats the amount excreted is 17 to 30 percent (Ref. 14). Dogs receiving daily oral doses of doxylamine succinate for prolonged periods consistently eliminate about 20 percent of the daily dose in the urine. Snyder and co-workers (Ref. 4) concluded, on the basis of tissue determinations of the drug and urinalysis of excreted products, that the bulk of the administered drug is metabolized in the body.

Brown and Werner (Ref. 1) found the intravenous LD_{50} (defined as a dose that is lethal for 50 percent of the test animals) for doxylamine succinate to be 49 and 62 mg/kg for rabbits and mice, respectively. Subcutaneously in mice and rats or orally in mice, the compound was about ⅛ as toxic as when given intravenously. It was about ⅕ as toxic orally in rabbits. In mice and rats, acute toxicity was similar for both sexes. They also found a favorable ratio of effectiveness to toxicity for guinea pigs.

Acute toxicity studies in dogs showed that oral doses of 7.5 mg/kg of doxylamine succinate produced no evidence of toxicity (Ref. 5). Repeated administration of 15 mg/kg 3 times a day caused some loss of appetite and weight, mydriasis, apprehension, and muscular tremors in three out of four dogs. Similar effects occurred in one of two monkeys at dose levels of 16 to 20 mg/kg 3 times daily. Lower doses produced no such toxic effects.

In the same studies, the administration of doses of doxylamine succinate as high as 45 mg/kg twice daily for a period of 38 days had no significant effect in rats, as judged by gross signs of toxicity, hematologic determinations, and histopathology. Repeated administration of increasing doses from 50 to 150 mg/kg also had no gross effects. However, an increase to 200 mg/kg resulted in a decreased rate of growth in some animals, and an increase up to 400 mg/kg caused anorexia and death in one case. Thus repeated doses resulted in toxicity only when the doses approached acutely lethal ones.

In a test for teratogenic effects of a combination of doxylamine and dicyclomine (a product used for treating nausea of pregnancy), doxylamine succinate was given orally to rabbits, in doses of 10 to 100 mg/kg/day (Ref. 6). Neither doxylamine, dicyclomine nor the combination had any deleterious effects on pregnancy maintenance, litter size or fetal weight in the rabbit, except when maternal toxicity was produced. In rats, the same doses produce no alteration in breeding, conception, pregnancy maintenance, litter size or fetal weight, although a dose-related decrease in body weight gain did occur in rat pups from doxylamine and dicyclomine-treated mothers.

Feinberg and Bernstein (Ref. 7) found that in 118 patients being treated for allergy with doses of 12.5 to 25 mg of doxylamine succinate, side effects were observed in 39 of them. Sedation or sleepiness was seen in 36 of the 39 patients. Nervousness was noted in four patients, and vertigo in four others. No serious toxic effects were noted after use of the drug for 6 months.

Keeney (Ref. 8) states that the use of doxylamine succinate as an antihistamine is infrequently followed by side effects, but McQuiddy (Ref. 9) says that such side effects are "quite frequent" with the 50 mg dose of doxylamine succinate although with the 25 mg dose the number of reactions decreases "materially" while clinical results remain satisfactory. McQuiddy concludes that doxylamine succinate is a safe and effective medication, having seen no reactions of any severity during his clinical study, with principally drowsiness and occasionally nausea being the main side effects.

Sheldon et al. (Ref. 10) gave allergic patients 12.5 to 200 mg of doxylamine succinate and found that 57 percent complained of drowsiness. However, the authors noted no apparent correlation between the dosage of the drug and drowsiness. Palpitations, irritability, and diarrhea were noted in three separate instances. There was no evidence of any hepatic, renal or vascular changes.

Finally, Ferguson (Ref. 11) gave schizophrenic patients up to 1,600 mg of doxylamine succinate daily by mouth for up to 6 months and found few side effects. He even remarked about the lack of sedation or drowsiness with high doses, noting that a combination of 900 mg doxylamine and 270 mg of phenobarbital daily produced no sedation, whereas 270 mg of phenobarbital alone produced an all-day sleep, therefore suggesting even

an antagonism of phenobarbital's hypnotic effects by doxylamine. There were no changes in pulse, respiration, temperature or blood pressure with the high doses used in Ferguson's study, and blood chemistry and organ function tests remained normal, yet the doses were encouragingly effective in treating schizophrenic patients. In addition, after giving doxylamine to schizophrenics, Ferguson found "there has been no habituation to doxylamine, but a mild degree of tolerance has been noted." He indicated that during a 6-month period the dose had to be increased in some patients from 300 to 900 mg daily to maintain satisfactory results. Partially confirming these data was the work of Selzer and Waldman (Ref. 12), who gave chronic psychotic patients doses of doxylamine (unspecified salt) up to 900 mg/day for 3 months. Side effects were also virtually nonexistent in this study.

There were only a few citations found in the literature for tolerance buildup to the sedative effects of antihistamines, and all of these are unsubstantiated.

Thompson and Werner (Ref. 5), for example, state in their toxicity experiments that repeated administration of doxylamine succinate to rats in large doses for a comparatively long period did not lead to tolerance or accumulation. However, Feinberg (Ref. 2) states that there is a definite tendency for the rapid development of tolerance to the sedative effects of (all) antihistamines.

It has been reported that the depressant actions of antihistamines are additive with the effects of alcohol and other central nervous system depressants (Refs. 13 and 14). Brown (Ref. 14) says that such combinations produce deepened and prolonged sleep.

It appears from some studies that 50 mg and above of doxylamine succinate produce the side effect of sedation when the drug is used as an antihistamine (Ref. 7 and 14). However, as stated above, Ferguson (Ref. 11) and Selzer and Waldman (Ref. 12), gave doses up to 900 mg daily in three divided doses with little evidence of drowsiness in schizophrenic patients. Such apparently contradictory results need to be explained.

No literature was found concerning poisoning or doses which cause death in humans.

Acute toxicity studies in animals which have been reported make no mention of the behavior of the animals before death, except that they died in convulsions. Chronic toxicity studies (Ref. 5) mention that dogs appear "apprehensive" after 15 mg/kg of doxylamine succinate 3 times daily, and that a monkey given 20 mg/kg 3 times daily yawned frequently, was apprehensive, and upon handling exhibited convulsive tremors.

The drowsiness effect of doxylamine in humans, as with other antihistamines, is well documented (Ref. 2). As mentioned earlier, doxylamine is a potent antihistamine with a high degree, compared with other antihistamines, of central nervous system depression as well. It may be stimulatory at higher doses, as suggested by the chronic toxicity studies in dogs and monkeys.

Only two clinical reports on the effectiveness of doxylamine as a sleep-aid have been found. The first study, by Noell et al. (Ref. 15), was performed on more than 3,000 men for the purpose of evaluating the sedative effects of over 20 antihistamines by EEG methods and comparing these effects with those of baribiturate and nonbarbiturate hypnotics. Doxylamine succinate 25 mg was one of the three most sedating antihistamines, producing a significantly reduced latency to end of wakefulness and comparing favorably with established hypnotic drugs such as secobarbital and pentobarbital in sedation activity. It was chosen as the antihistamine, based on dosage, causing the earliest onset of sleep.

The second study, by Sjoqvist and Lasagna (Ref. 3), compared the effectiveness of 25 and 50 mg of doxylamine succinate as a nighttime hypnotic with that of placebo and two doses of secobarbital. Both drugs were shown to be significantly better than placebo, and both doses of doxylamine scored better than 100 mg of secobarbital but not as well as 200 mg of secobarbital. There were few side effects, other than hangover, with both drugs. Two weaknesses of the study were (1) the high placebo effect (50 percent of the patients slept as well on placebo as on their previous hypnotic medication) and (2) the lack of a dose-related difference in effectiveness between the two doses of doxylamine used.

Both of the above mentioned studies suggest that doxylamine may have nighttime sleep-aid potential.

In summary, the Commissioner notes that the potential effectiveness of doxylamine succinate as an OTC nighttime sleep-aid is shown by the fact that there were 33 percent side effects (primarily sedation or sleepiness) in one study where individual doses of up to 50 mg were used for the treatment of allergy (Ref. 7). No serious side effects were noted after use of the drug for 6 months. The Commissioner notes that studies in which high doses (up to 1,600 mg/day) of doxylamine succinate were given to schizophrenic patients (Ref. 11) suggest that the drug is relatively safe. However, it is possible that psychotic patients do not respond to high doses of centrally active drugs in the same manner as non-psychotic individuals.

The Commissioner concludes that two well-controlled clinical studies following the principles established in § 314.111(a)(5)(ii) plus one EEG study are required to determine the safety and effectiveness of doxylamine succinate as an OTC nighttime sleep-aid. The appropriate dosage for testing should be limited to 25 mg to a maximum 50 mg single dose at bedtime. While this ingredient is classified as Category III as an OTC nighttime sleep-aid, regulations on the marketing status of ingredients recommended for OTC use (21 CFR 330.13) prohibit OTC marketing until the Commissioner determines it to be generally recognized as safe and effective or a new drug application for the product has been approved.

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(4) *Phenyltoloxamine dihydrogen citrate.* The Commissioner concludes that in an appropriate dosage (100 to a maximum 200 mg single dose at bedtime) phenyltoloxamine dihydrogen citrate may be both safe and effective as an OTC nighttime sleep-aid, but further evidence of safety and effectiveness is needed.

Phenyltoloxamine (also called phenoxadrine), one of the ethanolamine group of antihistamines, is available on an OTC basis in a dose of 30 mg as an ingredient in a combination analgesic-calmative preparation. It is also marketed in OTC combination products (22-89 mg of the dihydrogen citrate salt) for the treatment of bronchial asthma, allergic coryza, allergic cough, headache and other pain, and gastric hyperacidity due to nervous tension.

The Commissioner concludes that this ingredient is Category III as an OTC nighttime sleep-aid, but since the recommended dose is higher than that available in any OTC product on December 4, 1975, regulations on the marketing status of OTC drugs (21 CFR 330.13), prohibit marketing of this ingredient as an OTC nighttime sleep-aid until the Commissioner determines the ingredient to be generally recognized as safe and effective or a new drug application for the product has been approved.

Phenyltoloxamine is a potent histamine antagonist, and the early literature on this drug stresses its apparently low acute and chronic toxicity. Extensive clinical studies have provided evidence that the drug is effective in relieving vasomotor rhinitis, hay fever, pruritis, eczema, urticaria, asthma, and certain allergic drug reactions (Ref. 1). Like other antihistamines, the drug has distinct local anesthetic properties and some antispasmodic activity. In addition, LaVerne (Ref. 2) lists the following properties without documentation: autonomic suppressant, adrenergic stimulant, sedative, mild hypnotic effect, and no adverse effect on mental acuity. After the 1957 report by Sainz (Ref. 3) on the effects of the drug on psychotic patients, phenyltoloxamine achieved the reputation of being a "phrenotropic" or tranquilizing drug. A number of reports then appeared on its therapeutic usefulness as a sedative (Refs. 4, 5, and 6).

The side effects of phenyltoloxamine are apparently mild in therapeutic doses, and soporific (sleep-inducing) effects are low and occur in less than 7 percent of patients (Ref. 7).

In general, the mechanism of central nervous system depression by phenyltoloxamine is unknown, although a report by DeSalva and Oester (Ref. 8) suggests that phenyltoloxamine acts similarly to mephenesin and morphine sulfate in depressing polysynaptic reflexes in cats. Such a test has traditionally been used for studying central muscle relaxant activity, which may be indicative of sedative or tranquilizing potential.

The only study found concerning the absorption and fate of phenyltoloxamine was performed by Hoekstra et al. in 1953 (Ref. 9). Extrapolating from experiments performed in dogs, rats and mice for other purposes, it was concluded that phenyltoloxamine is readily absorbed from the gastrointestinal tract and peritoneal cavity and distributed rapidly throughout the body. Very little is known of its destruction, conjugation, or excretion, since attempts to isolate unchanged phenyltoloxamine or certain possible breakdown products from the urine of dogs were not successful. Hoekstra et al. (Ref. 9) also did acute toxicity studies in mice which compared the LD_{50}'s of phenyltoloxamine hydrochloride, phenyltoloxamine dihydrogen citrate, diphenhydramine hydrochloride and tripelennamine. Phenyltoloxamine hydrochloride was one-fifth as toxic intraperitoneally and one-twelfth as toxic orally as when given intravenously. It was one-half as toxic as tripelennamine and two-thirds as toxic as diphenhydramine hydrochloride when intraperitoneal LD_{50}'s were compared.

Acute toxicity studies of various doses of phenyltoloxamine in a few rats showed that oral doses greater than 680 mg/kg caused death preceded by hyperactivity, excitement, convulsions and respiratory depression. In dogs, intravenous doses above 20 mg/kg caused death, while lower doses produced ataxia, excitement followed by depression, and slight narcosis (Ref. 9).

Finally, limited chronic studies showed that dogs tolerate phenyltoloxamine dihydrogen citrate in daily oral doses of 20 and 40 mg/kg (calculated in terms of active moiety) with no untoward effects. There were no indications of blood dyscrasia at any time during the experiments.

In general, clinical studies in man in which phenyltoloxamine has been evaluated as an antihistamine consistently show few side effects with doses of 25 to 50 mg of the dihydrogen citrate salt. Sainz (Ref. 3) performed a preclinical study in 48 patients to determine side effects and toxicity and found that mild drowsiness appeared at oral doses above 200 mg 4 times a day, or with single doses of 400 mg. Ataxia or abnormal reflexes were not noted at oral doses of 400 mg 4 times a day; there were no extrapyramidal symptoms; the EEG was not affected; and a slight blood pressure increase was seen. Doses higher than 200 mg 4 times a day produced adrenergic stimulation (increased salivation, gastritis, and diarrhea). Heartburn was found in 14 percent of patients taking the drug, and occasionally nausea was seen. No changes were noted in metabolic, nutritional, endocrine, hematologic, urologic or liver function studies. Sainz concluded that the drug is not only safe but remarkably free from undesirable reactions at oral doses of 100 mg 4 times daily.

Cronk and Naumann (Ref. 10) gave 2,380 allergic patients with non-specific upper respiratory infections 100 to 600 mg of phenyltoloxamine dihydrogen citrate daily and reported only three cases of side effects caused by the drug. These were manifested as a mild soporific state after administration of 200, 300 and 600 mg of the salt, and in no case was the side effect severe enough to warrant discontinuation of the drug. Although this study suggests that the incidence of drowsiness with phenyltoloxamine is low, a later study by Fleischmajer et al. (Ref. 4) found a much higher incidence of central nervous system depression. Fifty patients received the drug (unidentified salt) for treating allergic cutaneous disorders in doses of 100 mg 3 times a day (after meals) and 200 mg at bedtime. In 39 patients (78 percent) there was excellent relaxation, lessening of inner tension, and improvement in the ability to sleep. Most of these patients noted a pleasant calmness within 30 to 60 minutes after taking the drug. The other side effects noted were blurred vision, vomiting, tachycardia, dry mouth, and marked hypnosis, but only 3 patients discontinued therapy because of the severity of these effects.

Finally, in a study designed to test the usefulness of phenyltoloxamine in chronic schizophrenics, Barsa and Saunders (Ref. 11) gave 60 female patients gradually increasing doses of phenyltoloxamine (unidentified salt) with the highest dose reached being 800 mg 4 times a day. The patients received the drug for 3 to 5 months. It was seen that when the dose was below 1,600 mg per day, most of the patients were stimulated, becoming more alert but also more restless and irritable. As the daily dose went above 1,600 mg, the excessive stimulation disappeared and the psychosis appeared to improve. However, most of the patients could not tolerate the high dose. Forty patients (67 percent) complained of nausea or loss of appetite; 10 of these also experienced vomiting. Fifty patients showed an average weight loss of almost 5 kg (11 lb). Other patients complained of generalized weakness, fainting, ataxia, parkinson-like symptoms, and generalized tremulousness. All of these side effects disappeared when the dosage was reduced. Hematological tests, liver function tests, and urinary studies showed no significant changes in any of the patients.

Few reports on tolerance to phenyltoloxamine were found in the literature. Cronk and Naumann (Ref. 10) mentioned in passing that at the end of their experiments considerable adaptation had apparently developed in that the sedation effect had become subjectively less severe after 200 to 600 mg of dihydrogen citrate salt per day for 3 days.

Although there are no reports in the literature on interactions of phenyltoloxamine with other drugs, the Commissioner expects that, like other antihistamines, phenyltoloxamine could interact with central nervous system depressants.

The average oral antihistamine dose of the dihydrogen citrate salt for adults is 50

mg 3 to 4 times daily. This may be increased if the desired therapeutic response is not obtained or in side effects do not become pronounced (Ref. 7). In one study such doses produced a rather low incidence of drowsiness (approximately 7 percent) (Ref. 7), but another sutdy (Ref. 4) suggests a much higher incidence of central depression (78 percent) with higher doses (100 mg 3 times a day, unspecified salt). Single doses of 400 mg (unspecified salt) produced sedation and moderate hypnotic effect in 100 percent of healthy volunteers in one study (Ref. 12).

Doses higher than 1,600 mg per day (unspecified salt in 4 divided doses) in humans apparently can be considered to be the upper limit of usage of the drug, since above this amount generalized toxicity is observed in schizophrenic patients (Ref. 11). Below this dose, however, signs of central nervous system stimulation were apparent in the same patients.

No literature was found concerning poisoning or doses which cause death in humans.

Two uncontrolled and three controlled studies were found concerning the effectiveness of phenyltoloxamine as a sedative. In an apparently uncontrolled study (Ref. 3), phenyltoloxamine (dihydrogen citrate salt) was used to treat 227 cases of psychotic behavior, using oral doses of 100 to 500 mg 4 times a day. Sainz concluded that the drug has a powerful affective and behavioral effect, although it does not produce euphoria, exhilaration, mental cloudiness, or confusion. Addiction and withdrawal reactions were not noted after 6 months of continued high dosage in certain patients. For certain anxieties, the calming effect produced by the drug is, in Sainz' opinion, slightly more pronounced than that produced by phenobarbital and the meprobamates and, because of the absence of immediate or eventual reactions, much safer and preferable to either.

The other uncontrolled study was by Fleischmajer et al. (Ref. 4), who gave 500 mg per day (unspecified salt) by mouth to 50 patients with a variety of dermatoses in whom a tension factor was believed to be associated with the disorder. They found that in 39 of the patients there was excellent relaxation, lessening of inner tension, and an improvement in the ability to sleep. They evaluated various dosage schedules and recommended 200 mg for nighttime sedation, with the comment that the ideal individual dose should be determined for each person.

The first controlled study by Noell et al. (Ref. 5) was performed on over 3,000 men for the purpose of both evaluating the sedative effects of more than 20 antihistamines by EEG methods and comparing these effects with those of barbiturate and nonbarbiturate hypnotics. Phenyltoloxamine (dihydrogen citrate salt) 50 mg was significantly better than placebo and ranked better than 50 mg of methapyrilene hydrochloride in the experiment on determination of onset of sleep. The dihydrogen citrate salt ranked better than diphenydramine hydrochloride 50 mg, considered by the authors one of the three most sedating antihistamines.

The second controlled study (Ref. 12) was a comparative double-blind study with reserpine and placebo on 15 volunteers who received single oral doses of 400 mg of phenyltoloxamine (unspecified salt), 5 mg of reserpine, or placebo. Physiological measurements and a battery of psychological performance and learning tests were used to determine drug effects on behavior and function of the individuals. The results showed that 400 mg of phenyltoloxamine produced sedation and a moderate hypnotic effect, reaching a peak in 4 to 5 hours. Although latency and duration of sleep itself were not measured in this study, at the peak action of the drug there was drowsiness and a slowing of psychomotor and mental performance, followed by a state of relaxation, increased learning, and improved performance.

The third controlled study (Ref. 6) evaluated the effectiveness of phenyltoloxamine (unspecified salt, 50, 100, and 200 mg orally) as a daytime sedative, comparing it with 2 doses of phenobarbital and a placebo. One hundred and thirty-one ambulatory patients, all of whom required a sedative for control of an anxiety state, were used. The workers concluded that phenyltoloxamine 3 to 4 times daily for several weeks of continuous therapy is safe. Although they did not make any comparisons with phenobarbital in their discussion, it appears that 100 mg of phenyltoloxamine was equivalent to 15 mg of phenobarbital in a "combined sedation and hypnotic effect" measure that they presented.

In summary, the Commissioner concludes that the available data on the safety and effectiveness of phenyltoloxamine dihydrogen citrate in the dose range of 100 to 200 mg are not adequate to permit its use as an OTC nighttime sleep-aid. There is some evidence that the drug may have effectiveness as an OTC nighttime sleep-aid. For example, in one study (Ref. 5) the drug ranked better than methapyrilene hydrochloride when measuring "end of wakefulness" and better than diphenhydramine hydrochloride on determination of "onset of sleep."

The Commissioner concludes that a minimum of three additional well-controlled studies are necessary to establish the safety and effectiveness of phenyltoloxamine dihydrogen citrate as an OTC nighttime sleep-aid. At least one EEG study and at least two clinical studies are necessary. The Commissioner has determined that an appropriate dosage for testing should be limited to a single dose of 100 mg to 200 mg at bedtime. However, as stated previously, phenyltoloxamine dihydrogen citrate cannot be lawfully marketed as an OTC nighttime sleep-aid until it is determined by the commissioner to be generally recognized as safe and effective, or a new drug application for the product is approved.

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(4) *Pyrilamine maleate.* The Commissioner concludes that there is insufficient information on the safety and effectiveness of pyrilamine maleate as an OTC nighttime sleep-aid and has therefore placed the ingredient in Category III. Described as an effective antihistamine with low incidence of sedation (Ref. 1), it appears ancillary to methapyrilene as an ingredient in three currently marketed OTC products promoted for sleep. The usual single OTC dose for an adult is 25 to 50 mg. The Commissioner has determined that further testing in well-controlled studies is required to assure the safety and effectiveness of a suggested dosage of 25 to a maxi-

mum 50 mg single dose at bedtime. (See part II. paragaraph D. below—Data Required for OTC Nighttime Sleep-Aid Ingredient Evaluation.)

Pyrilamine is chemically related to methapyrilene. To date there is no evidence that pyrilamine has any carcinogenic, cocarcinogenic, or carcinogen-synergistic effects. In the event that any data demonstrating such effects are developed, the Commissioner will carefully review such studies. However, in the absence of any current evidence suggesting a potential for carcinogenicity, the Commissioner considers any regulatory action to be inappropriate and premature at this time.

Pyrilamine was discovered in France (Ref. 2) 2 years after the introduction of Antergan, the first antihistamine used clinically (Ref. 3). Pyrilamine effectively inhibits experimental production of skin wheals by histamine and can prevent the increase in capillary permeability ordinarily produced by histamine (Ref. 5). In addition to its effectiveness as an antihistamine, pyrilamine also possesses local anesthetic activity (Refs. 6 and 7) and even exerts a mild analgesic action (Ref. 8).

In doses of 25 to 50 mg, anorexia, nausea, and vomiting are commonly encountered but can be minimized by the simple precaution of taking this ingredient at mealtimes. However, the Commissioner believes that this is difficult when pyrilamine is used as an OTC nighttime sleep-aid. The Panel located only one study pertaining to the hypnotic potential of pyrilamine used alone (Ref. 9). This study provides some evidence that pyrilamine maleate 50 mg is superior to placebo in reducing the time to "end of wakefulness" by EEG criteria but not in the subjective evaluation of "time to sleep onset." Subjects were military personnel studied under daytime nap conditions.

The Commissioner is aware of instances of accidental poisoning with pyrilamine (Ref. 10). For example, two fatalities of accidental poisoning have been reported in the literature. In one case a 15-month-old infant died 6 hours after ingestion of 1,500 mg of the drug, and in a second case a 23-month-old infant died 6 hours after ingestion of 10 tablets (dose unspecified). Both victims exhibited coma and/or convulsions previous to death. The Commissioner therefore believes that when further testing is conducted, special attention should be given to the minimum dosage level required for effectiveness.

The Commissioner concludes that insufficient data are available on the safety and effectiveness of pyrilamine maleate as an OTC nighttime sleep-aid and has therefore placed the ingredient in Category III. Further testing is necessary in a suggested dosage of 25 to a maximum 50 mg single dose at bedtime. The Commissioner concludes that three additional well-controlled studies are necessary to establish the safety and effectiveness of the ingredient as an OTC nighttime sleep-aid. At least one EEG study and at least two well-controlled clinical studies are necessary to support safety and effectiveness of this drug and permit reclassification from Category III to Category I.

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Category III Labeling

The Commissioner concludes that the following label claims would be acceptable for OTC nighttime sleep-aid products if sufficient data were provided to substantiate their use. Labeling such as "Reduces time to fall asleep in persons with difficulty falling asleep." "Reduces number of awakenings in persons who wake frequently during the night," and "Prolongs sleep," may be valid if proven by well-controlled studies. (See part II, paragraph D, below—Data Required for OTC Nighttime Sleep-aid Ingredient Evaluation.)

D. Data Required for OTC Nighttime Sleep-Aid Ingredient Evaluation

The Commissioner considers these testing guidelines to be final, subject to modification upon request. These guidelines, and future modifications thereto, will be available in the office of the Hearing Clerk, Food and Drug Administration, Room 4–65, 5600 Fishers Lane, Rockville, Md. 20857. No further changes in these guidelines will be published in the Federal Register. However, notification of amendments to the guidelines will appear as a notice in the Federal Register pursuant to § 10.90(b) of the agency's administrative practices and procedures (21 CFR 10.90(b)).

The Commissioner concludes that the following data are required for the evaluation of safety and effectiveness of an agent to be used as an OTC nighttime sleep-aid:

1. *Minimum requirements to determine safety and effectiveness.* The active ingredient must be safe in the doses suggested on the labeling for OTC use. Regarding effectiveness, a number of important variables must be considered: (1) Sleep latency (time required to fall asleep), (2) number of awakenings, (3) total time spent awake, (4) sleep duration, (5) sleep quality, as estimated by the sleeper, (6) sleep stages and cycles evaluated by EEG and polygraphic criteria (may or may not be necessary as stated in individual ingredient discussions), and (7) side effects. Typically, an OTC medication might be tested to determine whether it reduces sleep latency (or possibly increases sleep duration) without detrimental effects on the other variables.

A target population must be identified so that wherever possible in studies of effectiveness subjects tested are similar to those who will eventually take the drug. For OTC nighttime sleep-aids, the population would consist of individuals with symptoms of mild or occasional sleep disturbance.

It is important to provide both subjective and objective assessment of sleep. Certain important aspects, such as the subject's estimate of the quality of sleep and feeling state in the morning, can only be assesed subjectively. On the other hand, objective sleep laboratory studies have obvious advantages to assess objectively and exactly continuous measures of sleep, thus providing exact measures of sleep latency, sleep duration, number of awakenings, and other variables of interest. Other clinical aspects can also be assessed both subjectively and objectively.

Any claimed ingredient(s) or labeling claim(s) classified by the Commissioner as Category III should be evaluated using the concepts and methodology described below in the suggested guidelines.

2. *Sleep laboratory studies.* A small number of appropriate subjects (e.g., 6 to 12 per study) should be studied intensively in a sleep laboratory. Sleep

laboratory studies should involve the use of both placebo and active medication in a properly controlled design. The exact design would depend on individual drug factors, such as time required for washout, necessity in some cases for studies of continuous administration, etc. This would allow precise determination of sleep latency, sleep duration, number and length of awakenings, and time spent in the various sleep stages. Such a study can help determine effectiveness and can also be used as a safety or toxicity study since disturbances of sleep and mood can be studied during and after drug administration. Such laboratory studies would ideally include investigation of the drug when taken on multiple consecutive nights and after discontinuation, since withdrawal effects after continuous administration can be of importance. However, since the drug is an OTC preparation to be taken as a single dose for occasional insomnia, such long-term studies are not absolutely essential, though still advisable.

3. *Clinical studies in a suitable target population.* A large number of appropriate subjects should be studied for subjective effects on sleep. Subjects should be mild insomniacs falling directly within the target population expected to take the drug. Such a study should preferably use separate large groups, perhaps 40 to 80 subjects per group, since intergroup comparisons have statistical advantages. A well planned crossover study, however, might also be acceptable. If several doses of a drug are to be studied, or if a combination of several ingredients is being studied, a larger number of groups is required. For instance, if a combination containing two ingredients (A+B) is studied, a design should include four separate groups: One taking placebo, one taking A, one taking B and one taking A+B. Subjects are to be assinged by systematized randomization with packaging and coding of the drug on an individual patient basis rather than on a treatment group basis. The integrity of the study should be maintained and subjects should not be able to determine drug from placebo, since the findings are heavily dependent on subjective parameters. Each dose unit (drug or placebo) should be singly identified by code and administered singly (e.g., in envelopes) in a predetermined sequence.

The variables to be investigated include the subject's estimate of quality of sleep, sleep latency, number of awakenings, sleep duration, how well he feels in the morning, and a report of any side effects.

In certain cases other designs may be reasonable; for instance, a design in which the subject indicates a preference between two treatments (drug versus placebo) may be used but would not be considered a pivotal study.

4. *Clinical studies for OTC nighttime sleep-aids*—a. *Objectives.* The overall objectives are: (1) To determine the efects of the drug on sleep in individuals in the target population with symptoms of mild insomnia likely to use such an OTC drug, (2) to determine the subjects' estimate of quality of sleep (an estimate of how well they feel in the morning) and (3) to determine any preferences the subjects may have between 2 ingredients (drug versus placebo).

These studies, if results are clinically significant, will provide an extension of comparative controlled studies to confirm fully in a target population the drug's basic nighttime sleep-aid activity and to provide more specific information about symptoms and subject types in which the drug is especially effective. The studies will also establish an optimal dosage for the target population for which it is intended under conditions which more closely resemble these of actual OTC use.

b. *Sample considerations.* Subjects should be mild insomniacs falling directly within the target population expected to use the drug. Subjects with severe or chronic insomnia are not candidates for self-medication since they should be under the supervision of a physician.

A greater variety of populations differing as to age, sex, diagnostic categories, social class, treatment setting, previous treatment, etc., may be studied. Within each study, groups of subjects should be selected so as to be as homogeneous as possible regarding the variables above. In any case, full reporting of subjects' characteristics is necessary to allow for adequate interpretation of results. Exclusions should be stated.

Females of childbearing age may be included. However, the Commissioner believes that new drugs not intended for lifesaving use should not be used in women known to be pregnant or who are nursing a baby.

c. *Sample size.* The studies should use separate large groups containing 40 to 80 subjects per group. In a study comparing separate groups, a minimum of two groups (drug and placebo) are necessary. A large number of groups are required if several doses of a drug are studied or if a combination of several ingredients is evaluated, since each ingredient should be compared to the combination and a placebo.

d. *Setting.* Varying environmental influences should be decreased as much as possible in each study. Different treatment environments may be used which should be similar to those likely to be found among users (consumers) of such OTC products. Since these drugs are indicated for nighttime use, their action should not persist into the daytime hours or beyond the intended period of sleep.

e. *Investigators.* As discussed in comment 67, the commissioner is deleting the Panel's recommendation concerning investigators.

f. *Design.* Of primary importance are well-controlled studies designed to confirm fully the effectiveness of the drug as a nighttime sleep-aid. Special consideration should be given to controls, duration of study, dosage, and design which do not interfere with validity (biostatistical consultation is recommended), to accommodate greater variation in settings and subjects.

g. *Duration.* The duration of studies may vary from 1 to 2 weeks. The normal length of time for OTC nighttime sleep-aids use is not to exceed 2 weeks. It is therefore reasonable to require that testing be done within that same basic length of time. The Commissioner realizes, however, that there may be protocols developed which would require slight deviation from this guideline. Such deviation will be permitted, on an individual basis, if there is sufficient justification. In most cases the drug will be taken as a single dose for occasional insomnia, and therefore long-term studies are not absolutely essential. However, the Commissioner believes that such studies are advisable.

h. *Assessment.* Activity as an OTC nighttime sleep-aid should be determined by accepted methods. Determination of clinical effectiveness should include subjective reports from patients or subjects and EEG, and inpatient studies should also include objective measures.

5. *General concepts for conducting clinical drug evaluation of OTC nighttime sleep-aids.* The Commissioner concurs with the current regulations for conducting clinical trials evaluating efficaty as defined in 21 CFR 314.111(a)(5)(ii). The desired studies shall include a systematic assessment of possible adverse side effects as discussed above under clinical studies for nighttime sleep-aids and shall include contined surveillance for adverse side effects after marketing.

6. *Minimum data required for classification as a Category I ingredient.* In summary, the commissioner concludes that similar methodology should be used in the evaluation of an OTC nighttime sleep-aid as in the evaluation of a prescription hypnotic with two major exceptions:

a. Only those who are occasionally insomnic are included.

b. A larger patient sample than is customary in the evaluation of prescription drugs is necessary for a parallel design study (for example, 80 and not 40 patients per drug group may be needed), since relatively smaller clinical effects may be encountered.

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E. COMBINATIONS OF ACTIVE INGREDIENTS

1. *General statements.* The Commissioner notes the current regulation (21 CFR 330.10(a)(4)(iv)) which states:

An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Commissioner concludes that, in general, the fewer the ingredients, the safer and more rational the therapy. The Commissioner believes that the interests of the consumer are best served by exposing the user of OTC drugs to the fewest ingredients possible at the lowest possible dosage regimen consistent with a satisfactory level of effectiveness. The Commissioner further concludes that OTC drugs should contain only such inactive ingredients as are known to be safe and are necessary for pharmaceutical formulation.

2. *Requirement of significant contribution.* The Commissioner concludes that each claimed active ingredient in a combination must make a significant contribution to the claimed effect or effects.

The Commissioner is unable to establish the percent of contribution that an active ingredient must make to the effectiveness of the product for that contribution to be considered "significant." The Commissioner concludes that where a combination product is permitted, as discussed below, it is sufficient to demonstrate in well-controlled clinical trials that each of the ingredients makes a statistically significant contribution to the claimed effect. (See part II. paragraph D. above—Data Required for Nighttime sleep-Aid Ingredient Evaluation.) As long as "statistical significance" is shown in meaningful sample sizes, the Commissioner concludes that the contribution toward OTC nighttime sleep-aid activity will also have been shown to be clinically "significant."

3. *Single active ingredients.* The Commissioner concludes that the most desirable product for the consumer is one that contains the least number of ingredients. A product containing a safe and effective single ingredient is preferred to one having multiple active ingredients because of the reduced risks of toxic effects, allergic and/or idiosyncratic reactions, and possibly unrecognized and undesirable drug interaction(s). Because of these increased risks, the Commissioner further concludes that the use of two active ingredients of the same pharmacological class in the same preparation is not rational.

The Commissioner applies this view to all ingredient combinations that the Panel has reviewed. Even the antihistaminic drugs cause non-dose-related adverse reactions, such as drug allergy. In other words, even the presence of two antihistamines may increase the risk that a subject will have an allergic response to the OTC preparation. A person may not be allergic to one of the two active ingredients whereas he might respond with an allergic reaction to the other. Paradoxically, such hypersensitivity reactions do occur to the antihistamines, drugs which are themselves often used to treat allergic responses.

Certain problems peculiar to the formulation of combination products should be stated explicitly before dealing with specific cases. First of all, there are situations where the use of a combination is appropriate and clearly rational. Such an example is the case of the "triple sulfas" described below.

The misconception about the safety of using more than a single member of a pharmacologic class of drugs seems to be based upon a very special case. When the sulfonamides were introduced to clinical medicine, it became apparent that their low solubilities (particularly in the large doses needed to treat certain bacterial infections of the urinary tract) could result in precipitation of crystalline drug in the kidney. This problem was solved by using combinations of sulfonamide drugs, e.g., "triple sulfas," such that each of the three sulfonamides was present in an amount too small to crystallize out in the kidney but such that the combined three sulfonamides provided an effective therapeutic concentration. The basis for this effect is the fact that the solubility of each member of the series is independently determined. No such problem of dosage scheduling that approaches saturation leading to crystallization has been noted in the review of the antihistamine drugs submitted.

The Commissioner is aware of other cases where multidrug therapy is rational. Two different antibiotics may be given together for an organism known to be sensitive to the combination. Perhaps one of the best known combinations is the use of multivitamin preparations for the treatment of nutritional deficiencies. In these last two cases, the combination is used to achieve a certain convenience where the individual active ingredients are known to be effective separately. The Commissioner recognizes, that, in vitamin and in certain antibiotic therapy, a large dose of drug usually, but not always, carries no more risk than a smaller dose. This is an unusual situation in medicine.

If an OTC nighttime sleep-aid is indicated, it may very well be that a consumer will need one or two doses to get the intended effect. An occasional subject may need half of the suggested dose. If an analgesic is also needed, the consumer through experience will be able to judge whether he needs one, two, or one-half of the usually recommended OTC analgesic dose. If a consumer needs an OTC nighttime sleep-aid alone or an OTC analgesic alone, it would be an irrational act to take a combination product.

The Commissioner questions the advantage the combination confers. If the consumer cannot fall asleep readily, he may wish to take an OTC nighttime sleep-aid for this condition. He may also have some discomfort due to an injury, infection, burn or other ailment and may wish to take an OTC analgesic. The Commissioner concludes that the likelihood that a combination drug will contain the optimal dose is less than if the consumer is permitted to make this decision, that is, to take individually an analgesic and/or nighttime sleep-aid.

In light of present knowledge, it is not wise to give two or more different active ingredients in fixed combinations to different individuals. In addition, it does not make sense unless there is information that the effective dose of each active ingredient is known for the individual taking such a combination.

A very simple exercise will demonstrate the decreasing benefit to be expected when two or more active ingredients are combined in a single preparation. Suppose that 60 percent of the population requires one unit of drug A for relief of pain. Now, combine A with ingredient B, a drug that promotes sleep. Assume that, by good fortune, a dose of B is found that will have a favorable effect on 60 percent of the population. The chances that the 60 percent who need one unit of A will also need one unit of B is 0.60x0.60, or 36 percent. Thus, by combining we have reduced the chance of a successful outcome for both indications from these preparations. The number of people who need half of A and half of B or two of A and two of B are vanishingly small and may be ignored for present purposes. One could add yet a third active ingredient (certainly not unheard of) and find that the appropriate population for this preparation would be 0.60x0.60x0.60, or 22 percent of consumers.

Thus the Commissioner concludes that even if the addition of another active ingredient represents addition of a potential benefit to an existing product, the chances that the consumer will benefit from a fixed combination is in fact less likely than if that individual has the option to use active ingredients separately.

The Commissioner notes that individuals metabolize different active in-

gredients at vastly different rates and may eliminate them at different rates.

These biochemical difference are the basis for different dosage requirements on the part of individual human subjects. Ordinarily, in a relatively small group of persons there may be as much as a 10-fold difference in the rate of metabolism of a drug. The effect of these differences becomes apparent in the case of drugs used chronically. For OTC drugs used only occasionally and for nonfatal illnesses, it is not necessary to ensure that the dosage provided will be effective for 90 or 100 percent of the population. A 2- to 4-fold variation in the dose needed may be expected to achieve a desired effect in a significant proportion of the population. It has been pointed out above by simple calculations, using the probability of independent events, that combinations may reduce the likelihood of achieving the most effective dosage regimen because of differences between individuals with respect to drug metabolism. The implications of this knowledge for dosage requirements cast some doubt upon the comination of nighttime sleep-aids and analgesics.

In spite of the considerations above, the Commissioner recognizes the argument that there may be convenience in putting more than one active ingredient into the same product. The Commissioner concludes that, if a combination contains an analgesic and a nighttime sleep-aid both of which are safe and effective when used alone, it is convenient to combine the ingredients in a combination for the treatment of concurrent symptoms. The Commissioner would recognize the combination as safe and effective (effective as both a nighttime sleep-aid and as an analgesic in a significiant proportion of the population having both sleeplessness and pain at the same time). The Commissioner concludes that permission to market such a combination should be granted. However, it will be necessary to demonstrate that there exists a well-defined target population that requires both an OTC nighttime sleep-aid and an analgesic. Several studies are necessary using a factorial design demonstrating that the combination is safe and effective for a significant proportion of the target population requiring relief from both symptoms of pain and sleeplessness. For these reasons, a combination containing a nighttime sleep-aid and an analgesic is placed in Category III. If the target population is not demonstrated or if the combination is not found to be effective in a significant portion of the target population within the 3-year testing period, these products will be withdrawn from the market.

The labeling of a combination product of the type described above should reflect its limited applicability to persons with both symptoms, pain and sleeplessness, who respond favorably to the unit dose of each active ingredient in the combination. The labeling should indicate that only that portion of the target population having both indications at the same time may be expected to derive effective and safe responses to the fixed combination.

It is an established medical principle to give only those medications, preferably as single entities, necessary for the safe and effective treatment of the patient. This principle applies equally to self-medication. To add needlessly to the patient's medication increases the risk of adverse reactions. Therefore, only single ingredients of each pharmacologic class should be permitted in Category I combinations. Combinations containing more than one active nighttime sleep-aid ingredient of the same pharmacological class are classified as Category II products.

4. *Active ingredients not reviewed by the Panel.* The Commissioner concludes that each claimed active ingredient must be an ingredient that was reviewed by the Panel. If a product contains an active ingredient that was not reviewed by the Panel and consequently not found in their report, such ingredient is automatically classified as a Category II ingredient, i.e., it is not generally recognized as safe and/or effective. Appropriate animal and human testing and prior approval by the Food and Drug Administration are required before a product containing such an ingredient may be marketed.

5. *Review of submitted combination products.* The Commissioner is considering only those combination products submitted pursuant to the notice published in the FEDERAL REGISTER of August 22, 1972 (37 FR 16885). The Commissioner recognizes that other combination products may be in the market place, but he has either no knowledge of such products or insufficient data with respect to such products to make a reasonable judgment of safety and/or effectiveness.

Accordingly, the Commissioner concludes that any new combination, or any presently marketed combination not submitted, be evaluated through the new drug procedures or be the subject of an appropriate petition to the Commissioner for review and amendment of the OTC nighttime sleep-aid monograph.

6. *Combinations containing irrational ingredients.* The Commissioner is aware of the available data of those nighttime sleep-aid ingredients which are in combination with such nonnighttime sleep-aid ingredients as vitamins and passion flower extract. The Commissioner considers such combinations to be irrational.

For example, generally a healthy individual ingesting a well-balanced diet will receive adequate daily vitamin intake. The safety, effectiveness and labeled claims for vitamins have been deferred to the Advisory Review Panel on OTC Vitamin, Mineral and Hematinic Drug Products. However, the Commissioner recognizes that most clinicians agree that the therapeutic use of vitamins should be restricted to the treatment of unequivocal deficiency states or as dietary supplements in certain clinical situations, such as (1) inadequate intake due to poor diet, (2) malabsorption, (3) pregnancy, or (4) hypermetabolic states producing increased tissue requirements.

The proper functioning of all cells requires an adequate intake of all vitamins (water-soluble and fat-soluble). It is misleading to assume or propose that individuals consuming certain OTC nighttime sleep-aids, tranquilizers and sedatives have selected deficiencies of just those water-soluble vitamins discussed in this document. Vitamin deficiencies are generally manifold and not restricted to one or two vitamins. If treatment of vitamin deficieneies is indicated, high doses are used and ordinarily several vitamins are given, particularly in the case of water-soluble vitamins. Also, there is virtually nothing in the current medical or pharmaceutical literature to support the inclusion of selected water-soluble vitamins in the OTC nighttime sleep-aids, daytime sedatives, or stimulants. The water-soluble vitamins discussed in this document appear to be of no use in conditions unassociated with vitamin deficiency or impending deficiency. In addition to the irrationality, there is a danger in the possibility that administration of one or two vitamins in small amounts may delay proper diagnosis and treatment in occasional cases of true deficiency. The vague suggestion in the labeling of such products is that "nerves" may be the reason for wakefulness, anxiety or agitation and that B-vitamins are good for the nerves. This claim, whether explicit or implicit in the labeling, is not supported by objective and conclusive clinical data.

7. *Criteria for determining Category I combinations.* Although the Commissioner has not placed any products containing combinations of active ingredients in Category I, appropriate guidelines are necessary. Accordingly, to qualify as a Category I combination, i.e., one that is generally recognized as safe and effective, each of the following conditions must be met:

a. The combination should include only one Category I active nighttime sleep-aid ingredient from a given pharmacological class when such ingredient(s) is identified.

b. Each ingredient in the subject combination will have to be present within the dosage range for a Category I active nighttime sleep-aid ingredient when each such ingredient is identified.

8. *Criteria for Category II combination products.* A combination is classified by the Commissioner as a Category II product, i.e., one that is not generally recognized as safe and/or not generally recognized as effective, if any of the following apply:

a. The combination contains two or more drugs from the same pharmacologic class as nighttime sleep-aids.

b. The combination contains any ingredient that is listed elsewhere in this document as a Category II ingredient.

c. The combination contains any active nighttime sleep-aid ingredient that has not been reviewed by the Panel and accordingly is not listed in this document.

d. The combination contains a nighttime sleep-aid ingredient combined with a non-nighttime sleep-aid ingredient which the Commissioner has found to be an irrational ingredient.

e. The following combinations have been classified by the Commissioner as Category II: (1) *Combinations containing two or more antihistamines.* The Commissioner concludes that there is no rationale for combining two or more drugs of the same pharmacologic class to achieve a desired effect. There are no data to support claims of safety and effectiveness for such combinations.

(2) *Combinations containing bromides (ammonium, potassium and sodium).* The Commissioner concludes that combinations containing ammonium bromide, potassium bromide or sodium bromide are not safe for OTC use.

(3) *Combinations containing scopolamine compounds (scopolamine aminoxide hydrobromide and scopolamine hydrobromide).* The Commissioner concludes that combinations containing scopolamine aminoxide hydrobromide or scopolamine hydrobromide are not safe at dosage levels possibly effective as OTC nighttime sleep-aids.

(4) *Combinations containing passion flower.* The Commissioner concludes that there is no rationale for adding passion flower to a nighttime sleep-aid. The relationship between the ingredient and sedation has not been demonstrated.

(5) *Combinations containing vitamins [all vitamins, including thiamin (vitamin B_1), niacin (nicotinic acid), and niacinamide].* The Commissioner concludes that there is no rationale for adding vitamins to a nighttime sleep-aid. The relationship between vitamins and sedation has not been demonstrated.

9. *Criteria for Category III combination products.* A combination is classified as a Category III combination if the nighttime sleep-aid active ingredient is classified as Category III elsewhere in the document. The following combinations have been classified by the Commissioner as Category III:

a. *Combinations containing antihistamines and certain analgesics (acetaminophen, aspirin, and salicylamide).* These combinations are placed in Category III for two reasons: (1) The sleep-aid component has been categorized as Category III by the Commissioner; and (2) the Commissioner has insufficient information to identify a significant target population. Additional studies are required to show that there is a target population of significant size requiring ingredients for both pain and sleep. Experimental design for such studies should include double-blind investigations using a factorial design testing the combination against each ingredient and placebo. If evidence is not forthcoming within 3 years that each ingredient (e.g., the claimed nighttime sleep-aid and the analgesic) makes a meanginful contribution to the claimed effect, these products shall be withdrawn from the market.

The Commissioner concludes that combinations containing a nighttime sleep-aid and an analgesic are not rational therapy for patients suffering from sleeplessness or pain alone.

In a combination drug containing a nighttime sleep-aid ingredient and one or more analgesic compounds such as acetaminophen, aspirin or salicylamide, these latter ingredients are considered only as analgesics. If the analgesic component is judged effective by the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products, if the sedative component can be proved to be a safe and effective OTC nighttime sleep-aid, and if well-controlled studies can identify a significant and meaningful target population for use of such a combination, then the combination may prove to be rational for concurrent use, i.e., for sleeplessness when accompanied by pain. For example, in a currently marketed sleep-aid combination product containing an antihistamine and analgesics, the manufacturer recommends "For best results, adults take two tablets at bedtime to help relieve pain and aid sleep." Thus, according to the manufacturer's claim, this particular combination is recommended for nighttime use in patients sufering from a combination of pain and insomnia or from "insomnia expectation." The analgesic combination, when taken as recommended, namely, two tablets, seems to be a fairly appropriate mild analgesic, although the final decision regarding this effect has been deferred to the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products.

Whether the combination of an analgesic and a nighttime sleep-aid enhances the effectiveness of either type of agent cannot be answered from the data reviewed. Only a factorial design (Ref. 1) comparing the combination with a placebo would provide the answer. One may well postulate that, once pain is relieved by the analgesic component, the patient will sleep even without a nighttime sleep-aid. On the other hand, the OTC nighttime sleep-aid may indeed provide additional benefits. The studies submitted do not provide an answer to these uncertainties.

In any studies designed to evaluate such a combination, subjects selected should be individuals with pain as well as sleep problems. A more elaborate design could include a group of subjects with both pain and sleep problems, a group of subjects with only sleep problems, and a group of subjects with only pain, but the first factorial design is considered sufficient.

The data presented to the Commissioner do not establish whether patients use the combination primarily for pain or primarily for sleep induction. The combination seems to be proposed primarily as a pain reliever implying that, if one does not have pain, one will sleep well. The combination is not suggested for the general insomniac.

The manufacturer produced seven well-designed, well-controlled studies in support of its claim. Four of these studies were "analgesic-sedative studies" conducted in patients suffering primarily from pain, possibly associated with secondary sleep disturbances (Refs. 2 through 5); one was a study of chronic insomniacs in an outpatient population (Ref. 6); one was a study conducted in a nursing home (Ref. 7); and one was an experimental study conducted in normal subjects who were loaded with water to produce wakefulness (Ref. 8).

All seven studies were generally well done, some involving an acute type of experiment with each patient receiving one medication; a few studies involved giving medication to geriatric patients and other outpatients over a longer period of time. The most clear-cut and best designed experiments are some of the acute experiments (Ref. 3). They indicate clearly that the combination is more effective than placebo in inducing sleep, creating a better quality of sleep, and reducing pain. The problem with all of these investigations is that they were designed to show effectiveness of the combination. They were not designed to find out whether both the analgesic and antihistamine medications are needed or whether all patients with pain and pain related insomnia, or even only expected insomnia, would have been improved just as well with only the analgesic medication. Therefore, these seven well-designed studies do not define the relative effectiveness of the hynoptic and analgesic ingredients in the combination.

In an analgesic nighttime sleep-aid combination such as that discussed

above, the Commissioner concludes as follows:

The general regulations for the OTC drug review required the Panel to address drug active ingredients and claims, rather than finished total products. In this case, the Panel was required to determine which ingredient in the combination product has activity as an OTC nighttime sleep-aid and which ingredients have activity as analgesics. The Panel could not, as was suggested in one submission, set aside this requirement and merely determine that the whole product is safe and effective.

Pain may indeed prevent sleep, as might acid indigestion, coughing or sunburn. If the Commissioner were to follow the rationale that pain discomfort prevents sleep and that something which affords relief from pain discomfort can therefore be considered a nighttime sleep-aid, it would be necessary to permit the use of a similar nighttime sleep-aid claim for any ingredient used to treat any condition that might interfere with sleep. Such ingredients might be antacids, cough remedies, or sunburn lotions. It is obvious that such drugs are not intended to induce sleep per se. If evidence is not forthcoming to support the presence of Category III antihistamines as active OTC nighttime sleep-aid ingredients in combination with analgesics, nighttime sleep-aid labeling claims made on the basis of analgesics alone would be misleading.

The Commissioner is aware that there may well be a significant number of people suffering from both pain and sleeplessness caused by factors other than pain. An analgesic nighttime sleep-aid combination could be rational for such a group. Its target population, however, would include only those individuals suffering from both symptoms simultaneously. Labeling for such a combination would have to state clearly that it is for use only when both symptoms occur together, not only that one or the other is anticipated.

For combinations containing both antihistamines and analgesics, additional studies are required to show that there is a significantly large target population requiring ingredients concurrently for both pain and sleep. Experimental design for such studies should include double-blind investigations using a factorial design testing the combination against each ingredient and placebo. If evidence is not forthcoming within 3 years that each ingredient (e.g., the sleep-aid and the analgesic) makes a meaningful contribution to the desired effect, the product should be withdrawn from the market.

10. *Inactive ingredients.* The Panel recommended that OTC drugs should contain only such inactive ingredients as are necessary for pharmaceutical formulation and are known to be safe and they also expressed concern about the presence of talc containing asbestos in OTC products. As discussed in comment 12, the Commissioner concluded that inactive ingredients, including talc, will be governed by the Commissioner's proposed regulation on inactive ingredients published in the FEDERAL REGISTER of April 12, 1977 (42 FR 19156). Therefore, the Commissioner has deleted any further discussion of inactive ingredients from this document.

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III. THE COMMISSIONER'S CONCLUSIONS ON DAYTIME SEDATIVES

A. GENERAL DISCUSSION

The Commissioner concludes that the term "tranquilizer" is not an apt description of the drugs promoted as daytime sedatives or calmatives, because it promises a qualitatively different effect from that which an OTC drug can provide. Therefore, the Commissioner has used the term "OTC daytime sedative" within this document to describe an OTC drug claiming mood modification.

The Panel voted to place OTC daytime sedatives in Category III to offer maximum opportunity for those wishing to develop evidence that suitable target population existed and that these ingredients were effective in reducing nervous tension. The Commissioner has reviewed the available data and concludes that he is unable to permit the marketing of these ingredients during the 4 to 6 years necessary to complete testing. The labeling claims for these ingredients suggest that they are useful for occasional "simple nervous tension," "nervous irritability," and "simple nervousness due to common everyday overwork and fatigue." The Commissioner has determined that these claims do not refer to any definable symptom requiring medication, but that they are descriptions of normal transient variations in mood which are inappropriate for OTC drug therapy. Thus these ingredients offer no benefit to the user.

The major class of drugs reviewed for use as OTC daytime sedatives was the antihistamine group, products that the Commissioner recognizes as probably effective at appropriate doses in producing drowsiness and sleep. The Commissioner has reviewed that available data and has determined that there is no evidence of any anti-anxiety or calmative effect apart from the sleep-inducing properties of antihistamine daytime sedatives. (See comment 68.) This sedative effect would be hazardous in persons whose daytime activities require alertness and coordination.

Based on the scientific data available for marketed products and on the Panel's review of the literature, the Commissioner has concluded that there are no demonstrable conditions for which OTC daytime sedatives are useful, and hence no target population who could benefit by their use. These issues are more fully discussed in comments 68, 73, and 76.

The Commissioner concludes that he will accept the minority position of the Panel with respect to OTC antihistamine daytime sedatives and that these products shall be classified as Category II, and shall be removed from the market. Scopolamine and the bromides were classified by the Panel as Category II on grounds of safety and effectiveness, and the Commissioner concurs with these findings.

B. SAFETY AND EFFECTIVENESS

Currently marketed products which have been classified as OTC daytime sedatives generally contain antihistamines, scopolamines or bromides either singly or in combinations. Scopolamines and bromides have been determined by the Commissioner to be unsafe for OTC use and will be further discussed below. Antihistamines, as stated previously in the discussion pertaining to OTC nighttime sleep-aids, may, in addition to their antihistaminic action, induce drowsiness when used in the treatment of allergies. (See part II. paragraph C.3.a. above—Antihistamines.)

Furthermore, with respect to the profile of pharmacological activities of the antihistamines, the Commissioner concludes that there is little or no evidence that such drugs possess anti-anxiety psychotropic properties comparable to those demonstrated in clini-

cal studies with the prescription tranquilizers. Some antihistamines may, however, produce a sedative effect that would have no value as a mood modifier or anti-anxiety drug. Any anti-anxiety psychotropic activity, if it exists, most likely would be related to the "drowsiness" effect of the antihistamines.

Therefore, the Commissioner is concerned with a possible danger in "treating" simple and transient variations in normal mood and behavior with OTC products containing antihistamines or any similar sedating agent. The Commissioner believes that such drugs affecting mind and mood have much broader implications than other OTC classes of drugs (e.g., antacids, laxatives) in that alterations in an individual's mood indirectly affect other individuals. There is also possible danger that because of the excessive sedation, individuals with normal anxiety-like symptons will involuntarily, and unwittingly suffer reduced alertness, ability to concentrate and motor coordination. The Commissioner concludes that such use will restrict the individual's ability to cope with his environment. In the case of antihistamines, depressant effects appear at low concentrations and excitatory effects at high concentrations (Ref. 1); however, this varies from person to person. In some cases the excitatory effect is dominant even at low concentrations, and in other cases antihistamines produce depression throughout the normal dosage range so that therapeutic effects lack predictability.

In the general population, many people experience tension and most people have learned how to deal with it. Where tension becomes disabling, some individuals need medical assistance (e.g., counseling) and/or psychotropic medication. In such cases, effective psychotropic drugs do exist but are available only on prescription. The Commissioner concludes that it is highly unlikely that the submitted OTC ingredients could be shown to be effective because normal tension or anxiety is difficult to measure in a target population by current medical standards. In any case, the Commissioner concludes that there are insufficient data (or, more accurately, there is a sufficient dearth of data supporting effectiveness) to determine that the ingredients are not generally recognized as safe and effective for treating that condition, and accordingly cannot appropriately be classified in Category III. If they are effective, this can be demonstrated in a new drug application.

A suggestion was made in one submission (Ref. 2) to replace alcohol use (or abuse) with OTC daytime sedatives when individuals, emotionally upset or unable to cope with particular life stresses, would normally turn to alcohol. The Commissioner is aware that there is massive alcohol abuse in the U.S. and that there are also thousands of people who misuse and abuse drugs in this country.

Since the primary function of OTC products is to relieve symptoms of self-limiting diseases not requiring medical intervention, the Commissioner has concluded that OTC daytime sedative self-medication is not safe and not effective in the treatment of serious emotional and behavioral problems, including chronic alcohol and/or drug abuse. A substitution of OTC daytime sedatives for alcohol will certainly not exert any constructive effects on the individual's basic psychological or environmental problems. Where individual subjects are using alcohol to resolve serious personal life stress problems, they most likely would require medical and often psychiatric intervention. Use of an OTC daytime sedative as a substitute for alcohol in relieving life stress is particularly contraindicated since it delays proper medical treatment.

The Commissioner also takes note of the fact that there is a very high frequency of cases of poisoning involving simultaneous use of sedative drugs and alcohol; the additive effects of these agents can lead to serious toxicity. The Commissioner is not aware of any data to support the contention that nonuse of daytime sedatives marketed for "occasional simple nervous tension," or the like, leads to abuse of alcohol or alcoholism. The epidemiology of alcohol abuse is an extremely complex subject that allows very few "causative" statements to be made. It is conceivable that there may be situations where drugs should be substituted for alcohol abuse but that is more properly the province of the physician with a great deal of experience in dealing with alcohol abuse and certainly is far beyond the scope of the OTC Drug Review.

The Commissioner concludes, based upon the current available data and the lack of well-defined indications for safe OTC use, that if there is to be pharmacological intervention in cases of anxiety-like symptomatology, the drugs of choice are tranquilizers, available by prescription, which have been extensively studies and evaluated as psychotropic drugs. The Commissioner recognizes that several antihistamines (methapyrilene, pyrilamine and phenyltoloxamine) have been marketed for OTC daytime sedative activity, but concludes that there is no meaningful data which demonstrate that these ingredients have psychotropic activity. Therefore, the Commissioner has placed antihistamines in Category II since the available data do not show that they are safe or effective as daytime sedatives, and also because of their unacceptably low benefit to risk ratio and lack of an appropriate target population. The following is a review of the available published and unpublished material relating to the effectiveness of products marketed as OTC daytime sedatives.

Only one controlled clinical trial evaluating the role of OTC daytime sedatives in mild to moderately anxious patients exists in the literature (Ref. 3). In this study, a claimed OTC daytime sedative containing methapyrilene, pyrilamine maleate and scopolamine is compared with aspirin, chlordiazepoxide and placebo in a 2-week clinical trial. The results indicate chlordiazepoxide produces significantly more improvement than the other three agents which did not differ significantly from each other. In fact, the OTC product was no different from placebo in effectiveness.

Besides the published study mentioned above, there are only two unpublished reports in the submissions (Refs. 4 and 5).

The first unpublished report (Ref. 4) does not provide enough details to evaluate it fully. This study uses only 25 subjects and a design which identifies drug and placebo simply as A and B, permitting users to determine which drug they are ingesting, thus destroying the double-blind design. The study suggests mild sedative activity of the daytime drug, but it does not conclusively support the effectiveness of the drug reviewed.

The stateistical results in the second unpublished report (Ref. 5) at first sight are more impressive, since the significance obtained is acceptable for clinical studies. However, the fact that patients with headaches had to be omitted from such significance to occur is unfortunate. It is well known that tension and headache are often concommitant symptoms (60 percent of the patients in this study had headache), and breaking any link in the tension-headache-tension cycle by drug treatment is usually sufficient to allay both the tension and the pain.

One other problem concerns the choice of subjects. These were patients who were seen for "other complaints which did not interfere with the evaluation of the sedative." It was not clear how the investigators were sure of that fact. Almost any complaint considered serious enough for the patient to consult his physician could be associated with some degree of stress, which might conceivably interfere with a tension-sedative treatment program.

The possibility mentioned by the authors that some patients took aspirin during the study period is unfortunate because aspirin could significantly alter the tension state by reducing a headache or other body pains which contributed to the tension state. Since the authors did not indicate the

number of patients who took aspirin, it is difficult to evaluate its effect on the results obtained.

Finally, in the first part of the study, in a sample group of 87 patients, drug and placebo responses were practically identical. Drug-placebo differences were only obtained in the crossover portion of the study and no differences were observed comparing the OTC sedative (N=40 patients) and placebo (N=47 patients) when given first (Ref. 6).

This report is the only available to date which may possibly be considered as providing some support for the effectiveness of on OTC daytime sedative. However, the separation between tense individuals who have and who do not have headache, both for the purpose of producing statistical significance in the study and for identifying potential users of the OTC drug in practice, does not seem to be a realistic approach in light of the frequent occurrence of headaches in tense individuals. In addition, the OTC drug was often used only once daily, and without having data as to the time of day the drug was taken. One cannot exclude the possibility that the OTC drug was primarily used in the evening, as a mild sleep inducer and not as a daytime sedative, since it might tend to slant the results toward greater effectiveness.

In summary, the Commissioner is aware of only one published controlled study (Ref. 3). This study established clearly the methodology for clinical studies of OTC daytime sedatives and the ineffectiveness of the OTC sedative combination in relieving mild anxiety tension. The only claims of effectiveness of OTC daytime sedatives have been offered by two submissions to the Panel (Refs. 5 through 8). Of the data submitted, only one study (Ref. 5) presents data on the effectiveness of OTC daytime sedatives and that study has deficiencies discussed earlier in this document.

The Commissioner concludes that evidence presently available does not support the use of OTC daytime sedatives since a suitable target population has not been identified and the sedation accompanying these ingredients produces an unacceptalby low benefit to risk ratio. Therefore the Commissioner concludes that daytime sedatives shall be classified as Category II.

LABELING

The Panel discussed several warnings to be included on daytime sedative products. The Commissioner has concluded that all daytime sedatives are Category II and concludes also that all labeling for these products is Category II. Therefore a general discussion on labeling is not warranted.

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C. CATEGORIZATION OF DATA

1. *Category I conditions under which daytime sedatives are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredients

The Commissioner concludes that none of the submitted active ingredients can be generally recognized as safe and effective and not misbranded as daytime sedatives.

Category I Labeling

The Commissioner concludes that since all daytime sedatives are Category II no labeling can be generally recognized as safe and effective and not misbranded. Therefore, a discussion of Category I labeling is unnecessary.

2. *Category II conditions under which daytime sedatives are not generally recognized as safe and effective or are misbranded.*

Category II Active Ingredients

The Commissioner concludes that the following daytime sedative active ingredients cannot be generally recognized as safe and effective or are misbranded:

Antihistamines:
- Diphenhydramine hydrochloride
- Doxylamine succinate
- Methapyrilene (methapyrilene hydrochloride, methapyrilene fumarate)
- Phenyltoloxamine dihydrogen citrate
- Pyrilamine maleate

Bromides:
- Ammonium bromide
- Potassium bromide
- Sodium bromide

Scopolamine compounds:
- Scopolamine aminoxide hydrobromide
- Scopolamine hydrobromide

Miscellaneous compounds:
- Acetaminophen
- Aspirin
- Salicylamide
- Niacinamide
- Thiamine hydrochloride

The Commissioner discusses above the reasons why agents that produce drowsiness are not properly classified in Categories I or III for use as daytime sedative or calmative drugs. Below, he discusses particular aspects of individual ingredients considered by the panel for this indication.

a. *Antihistamines.* The Commissioner concludes that while the pharmacological effects of the antihistamines may be of value as nighttime sleep-aids as discussed earlier in this document, there are no meaningful data to determine that the antihistamines are safe or effective for OTC use as daytime sedatives.

(1) *Diphenhydramine hydrochloride.* The Commissioner concludes that diphenhydramine hydrochloride cannot be generally recognized as safe or effective because there are no data to support clinical effectiveness as a daytime sedative product and because although the drug may be safe in terms of toxicity, the drowsiness effect could be hazardous in daytime use. The Commissioner notes that no submission was received for this ingredient as an OTC daytime sedative and that it has no claim and has never been marketed for this activity. In addition, unlike the extensive clinical use of diphenhydramine as a nighttime sleep-aid, there are no reports of clinical experience with this ingredient as a daytime sedative.

The discussion above relating to diphenhydramine hydrochloride for use as an OTC nighttime sleep-aid carefully sets forth the action as well as side effects of this ingredient. From that discussion, the Commissioner is unable to determine how this ingredient should be employed in OTC daytime sedatives. All of the discussion in the OTC nighttime sleep-aid area tends to show diphenhydramine hydrochloride as an ingredient which will produce excessive drowsiness at therapeutic levels resulting either in sleep or decreased motor function (e.g., inability to function properly when driving or operating machinery).

(2) *Doxylamine succinate.* The Commissioner concludes that doxylamine succinate cannot be generaly recognized as either safe or effective because there are no data to support clinical effectiveness as a daytime sedative product and because, although the drug may be safe in terms of toxicity, the drowiness effect could be hazardous in daytime use. The Commissioner notes that no submission was received for this ingredient as an OTC daytime sedative and that it has never been claimed or marketed for this use.

In the discussion above relating to doxylamine succinate for use as an OTC nighttime sleep-aid, the action as well as side effects of this ingredient

have been carefully set forth. From this discussion the Commissioner is unable to determine how this ingredient should be employed in OTC daytime sedatives. All of the discussion in the OTC nighttime sleep-aid area tends to show doxylamine succinate as an agent which will cause drowsiness, although only two clinical reports on the effectiveness of doxylamine as a nighttime sleep-aid have been found. No reports have been found on the use of this ingredient as a daytime sedative.

(3) *Methapyrilene hydrochloride, methapyrilene fumarate, pyrilamine maleate.* The methapyrilenes appear in a number of marketed OTC products with daytime sedative claims. Pyrilamine appears in one marketed OTC combination product submitted to the Panel but there are no data on the single ingredient.

The Commissioner concludes that there is no evidence of effectiveness for methapyrilene hydrochloride, methapyrilene fumarate and pyrilamine maleate to be used in a daytime sedative product. The Commissioner concludes that, while these antihistamines may be safe in terms of toxicity, the drowsiness that occurs with both methapyrilene and pyrilamine could be hazardous in daytime use. For these reasons the Commissioner has placed these ingredients for use as daytime sedatives in Category II. In addition, as previously discussed, the Commissioner has placed methapyrilene in Category II due to its possible carcinogenic potential.

In the discussion above relating to the methapyrilenes and pyrilamine for use as OTC nighttime sleep-aids, the Commissioner has carefully set forth the actions as well as side effects of these ingredients. From these discussions, the Commissioner is unable to determine how these ingredients should be employed in OTC daytime sedatives.

(4) *Phenyltoloxamine dihydrogen citrate.* The Commissioner concludes that there is no evidence of effectiveness for phenyltoloxamine dihydrogen citrate to be used in a daytime sedative product. While this product may be safe in terms of toxicity, the drowsiness effect could be hazardous in daytime use. The drug is currently promoted as a "calmative" in an OTC combination drug product.

In the discussion above relating to phenyltoloxamine dihydrogen citrate for use as an OTC nighttime sleep-aid, the Commissioner has carefully set forth the actions as well as side effects of this ingredient. From these discussions, the Commissioner is unable to determine how this ingredient should be employed in OTC daytime sedatives and has classified this ingredient as Category II.

b. *Bromides (ammonium, potassium, sodium).* Based on the discussion above relating to bromides for use as OTC nighttime sleep-aids, the Commissioner concludes that they are unsafe as daytime sedatives. If taken over the period of time needed to reach therapeutic levels, severe toxic symptoms frequently occur. This is because bromides and chlorides are cleared from the kidney, but bromide clearance is slightly less efficient, so that the bromide level tends to build up.

The only submitted product suggests a dosage level of not less than 600 mg and not more than 1,800 mg per day of a combination of all three bromide salts. This product, which claims "calmative" action, sets no limit on the length of use of bromides. Yet, to use the bromides chronically without monitoring the patient's chloride balance and serum bromide is not safe medical practice since small changes in chloride intake or small changes in renal function can lead to severe poisoning.

The Commissioner concludes that ammonium bromide, potassium bromide and sodium bromide, which act by displacement of body chloride, if taken in dosage levels presently recommended, do not act as daytime sedatives in a single dose. If taken over the period of time needed to reach therapeutic levels, severe toxic symptoms frequently occur. In addition, bromides readily cross the placental barrier, which might result in teratogenic effects such as mental retardation of the offspring.

The discussion of bromides in the nighttime sleep-aids section above shows not only that the bromides are agents which, once they finally reach therapeutic levels, can cause excessive drowsiness, but also shows them to possess sufficient toxic characteristics to render them unsuitable for use as OTC daytime sedatives.

c. *Scopolamine compounds (scopolamine hydrobromide, scopolamine aminoxide hydrobromide).* The Commissioner concludes that these compounds are unsafe because of their extensive toxicity and are ineffective in presently marketed dosages.

In the discussion above relating to scopolamine for use as an OTC nighttime sleep-aid, the Commissioner has carefully set forth the action as well as toxic effects of this ingredient. From this discussion the Commissioner is unable to determine how this ingredient should be employed in OTC daytime sedatives. All of the discussion in the OTC nighttime sleep-aid area tends to show scopolamine compounds as agents which may result in extensive toxicity without any data to support their clinical effectiveness as daytime sedatives.

d. *Miscellaneous compounds (acetaminophen, aspirin, salicylamide, niacinamide, thiamine hydrochloride).* The Commissioner concludes that these compounds are irrational for use either singly or in combination as daytime sedatives.

The Commissioner is unaware of any data for analgesics (acetaminophen, aspirin, salicylamide) or vitamins (niacinamide, thiamine hydrochloride) which support their use as daytime sedatives.

Category II Labeling

The following claims were submitted for the daytime sedative products: "occasional simple nervous tension", "nervous irritability", "nervous tension headache", "simple nervousness due to common everyday overwork and fatigue", "a relaxed feeling", "calming down and relaxing", "gently soothe away the tension", "calmative", and "resolving that irritability that ruins your day". The Commissioner has concluded that there appear to be no clear cut indications for the use of OTC daytime sedatives, and that the area of normal or relatively normal variations in mood is not an appropriate one for pharmacological intervention. Also, an indication has not been clearly identified. For these reasons the Commissioner has determined that daytime sedatives are Category II. Since the entire class of daytime sedatives are Category II the Commissioner concludes that all labeling for such products is also Category II.

3. *Category III conditions under which the available data are insufficient to permit final classification at this time.* The Commissioner has determined above that all daytime sedatives and labeling are Category II. Therefore, any discussion of Category III conditions will be deleted from this document.

D. DATA REQUIRED FOR OTC DAYTIME SEDATIVE INGREDIENT EVALUATION

The Commissioner is unable to determine a class of drugs that are safe and effective in the relief of anxiety-like symptoms for daytime use. The Commissioner has determined that all OTC daytime sedatives are Category II. The Commissioner concludes that any further testing for safety and effectiveness would be fruitless and therefore deletes any discussion of testing guidelines from this document.

E. COMBINATIONS OF ACTIVE INGREDIENTS

The Commissioner has not identified an indication or appropriate active ingredient for use in OTC daytime sedatives and has placed all daytime sedatives in Category II. Therefore, any product containing a Category II daytime sedative would also be Category II. There was one combination containing the antihistamine phenyltoloxamine dihydrogen citrate, an analgesic and caffeine in a submitted prod-

uct which claimed both calmative action and enhanced pain relief. This particular combination divided its analgesic and calmative claims and attributed the calmative action only to phenyltoloxamine dihydrogen citrate. The Commissioner places this combination in Category II for the calmative claim. As to the claimed enhancement of the analgesic effect which results when the analgesic is combined with the antihistamine, the Commissioner deferred to the OTC Internal Analgesics Panel for such a determination. That Panel's recommendations were published in the FEDERAL REGISTER of July 8, 1977 (42 FR 35346).

IV. THE COMMISSIONER'S CONCLUSIONS ON STIMULANTS

A. GENERAL DISCUSSION

The Commissioner is aware of the use of either prescription drugs (e.g., amphetamines, desoxyephedrine) or OTC drugs (e.g., caffeine) by many individuals to promote wakefulness and to decrease the sense of fatigue and boredom in performing tedious work over rather long periods of time. Such drugs are referred to as stimulants and are used to increase mental alertness. For example, caffeine is commonly used as an aid to automobile driving, especially for the relief of the phenomenon "highway hypnosis" encountered during extensive periods of continuous driving. Currently marketed OTC products are promoted with such claims as "keep alert," "restore mental alertness," and "for fast pick-up."

The Commissioner believes that a suitable adult target population exists which can benefit from the occasional use of safe and effective OTC stimulant drugs. In cases where mental alertness or motor performance is necessary, such drugs can modify fatigue states to allow successful completion of a required task. The Commissioner concludes that use of such OTC products by individuals under 12 years of age should only be under the advice and supervision of a physician.

The Commissioner concludes that an ideal OTC stimulant preparation must be able to produce enhanced motor performance when such performance is reduced because of fatigue or drowsiness. The therapeutic effect should be of sufficient duration to be useful in accomplishing a particular task. For example, the drug should permit an automobile driver to maintain normal performance in completing a reasonably short journey to a stopping place. Hence, such products are for occasional use only and never for more than 1 to 2 weeks except under the advice and supervision of a physician.

B. SAFETY AND EFFECTIVENESS

The Commissioner concludes that the ideal OTC stimulant preparation should produce stimulation without untoward physiological effects on the central nervous system or the cardiovascular system or other acute toxic signs. Such undesirable effects would include an appreciable number of abnormalities of rate and/or rhythm of the heart or of respiration, or excitment or other undue disturbances of central nervous system function. In general, side effects that follow use of the drug should not be of such a degree or quality as to offset the beneficial effects of the drug. For example, excessive nervous system stimulation to an extent that would exceed the effect required to reduce fatigue could reduce the efficiency of a motor vehicle operator. The drug should produce enhanced performance without leading to a dangerous and unanticipated letdown after the therapeutic effect is achieved. There should be no distressful effect upon peripheral nervous functions, such as an obvious tremor or incoordination caused by the stimulant. There should be no interference of a significant degree with the normal pattern of sleep, including the quality, distribution in time, and the quantity of REM sleep. REM or D-state is rapid-eye-movement sleep associated with dreaming. When the amount of such sleep is reduced, it may lead to excess restlessness or irritability in the waking state. The drug should be for occasional use of not more than 2 weeks, and there should neither be tolerance nor dependence after such use. There should be a safe margin between the toxic and therapeutic doses of the drug. There should be no interactions of a dangerous or unpleasant nature between the drug and the other commonly employed drugs, foods or beverages when these are taken concomitantly.

C. CATEGORIZATION OF DATA

1. *Category I conditions under which OTC stimulants are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredients

a. *Caffeine.* The Commissioner concludes that caffeine is safe and effective for use as a stimulant when used in the recommended oral dose of 100 to 200 mg not more often than every 3 to 4 hours.

The Commissioner is not aware of any reports of fatal accidents after oral ingestion of caffeine and concludes that the incidence of fatal toxicity is low. The fatal dose for man is probably far greater than recommended doses since ingestion of up to 10 g was followed by complete recovery in 6 hours (Ref. 1). With doses of 1 g, insomnia, anxiety, irritability, muscle twitching, headache and nausea may be experienced. Palpitations, tachycardia and cardiac irregularity may also occur (Ref. 2).

Death was reported after intravenous administration of 3.2 g. In such cases, there may well be other factors. Too rapid injection of almost any drug can cause cardio-respiratory collapse and death. A review of acute and chronic toxicity with regard to caffeine has been prepared by Peters (Ref. 2). Severe poisoning causes cardiovascular collapse, including a fall in blood pressure. Vomiting and convulsions have followed oral doses of 10 g of caffeine with complete recovery in 6 hours.

Chronic ingestion of caffeine in larger than recommended doses can lead to "habituation" which is a mild form of drug addiction. When this occurs, caffeine, usually taken in the form of beverages, is required to feel "normal." Withdrawal symptoms are not severe or life-threatening (Refs. 3, 4, and 5). However, the Commissioner concludes that products containing caffeine should not include claims such as "non-habit forming" in their labeling. Caffeine affects the pattern, but not the total amount of REM sleep (Ref. 6).

The Commissioner notes that coffee (or strong tea) contains about 100 mg caffeine per cup, the same amount as the usual recommended dose of caffeine currently marketed in OTC preparations. The literature contains much information about studies on coffee drinkers vs. noncoffee drinkers.

The stimulating effect of caffeine (100 to 200 mg) on motor performance has been quite consistently reported by many investigators using a variety of experimental designs and tests of performance. The drug is most effective in the presence of fatigue, restoring altertness and the ability to perform tasks requiring muscular coordination with greater facility and less error. Reports of such effects can be explained on the basis of CNS stimulation and do not depend on peripheral effects, such as direct effects on the retina, improvement in "night vision," or the like (Refs. 7 through 10). In large doses, caffeine can stimulate respiration, but drugs are not ordinarily used for this effect in present day clinical medicine (Ref. 11).

Chemically, caffeine is 1,3,7-trimethylxanthine. It is an alkaloid that occurs in plants (coffee, tea, cocoa, cola) widely distributed around the world. Because of its ubiquitous use and availability from nondrug sources, the Panel felt and the Commissioner concurs that assessment of the compound should be based on an "in-depth" review of its pharmacology.

Approximately 7 million kg of caffeine in coffee are consumed each year in the United States (Ref. 12). As mentioned above, 1 cup of coffee contains about 100 to 115 mg of the drug. The major pharmacological effects are on the CNS and the cardiovascular

system. It is also diuretic and stimulates gastric secretion.

Caffeine stimulates the cerebral cortex and medullary centers. In usual doses, it causes wakefulness and alterness. As a beverage form, caffeine in coffee (among others) has been habit-forming in a proportion of the population. This "habituation" is probably a weak form of "addiction" in that differences may be detected between persons who use coffee regularly and those who do not use it at all. Goldstein and colleagues showed that chronic coffee drinkers given decaffeinated coffee showed sleepiness and irritability whereas noncoffee drinkers given caffeine-containing coffee showed upset stomachs and jitteriness due to caffeine. Users of coffee felt increased alertness and "Contentedness" when given caffeine in the "coffee" (Ref. 3). In a related study conducted by questionnaire, it was found that chronic users of coffee did not experience as much wakefulness due to coffee as did nonusers. Moreover, they experienced unpleasant symptoms when morning coffee was omitted (Ref. 4). Additional evidence for an addiction of some degree is the finding that sudden withdrawal of caffeine produced severe headache in a majority of trials among volunteer subjects. The headache produced in these young adults was relieved by aspirin, but more efficiently by caffeine (Ref. 5). Many of the persons studied by these authors were subject to migraine headaches. It is noteworthy that caffeine, generally in large doses, is used in the treatment of migraine.

The stimulatory effect of caffeine on motor performance has been quite consistently reported. The clearly effective CNS caused by caffeine ingestion has been supported by carefully designed studies (Refs. 3, 4, 7, 8, and 13).

In a comprehensive review of the effects of stimulant drugs, Weiss and Laties (Ref. 9) concluded that caffeine can enhance "a wide range of behavior * * * all the way from putting the shot to monitoring a clock face." There is evidence from a variety of studies that nervousness, headache, and irritability, for example, may accompany the use of large doses, 240 mg of caffeine and above. There seems to be no evidence of serious types of addiction, and their conclusion is that the incidence of habituation is quite low.

Studies that measure ability to perform simulated driving tests with adequate lighting and in conditions of reduced lighting were submitted by one of the manufacturers of a drug containing caffeine (Ref. 10). All responses that were favorable may be explained on the basis of enhanced CNS performance and did not seem to involve improvement in vision at the level of the orb itself, that is, cornea to retina. In so far as any may be demonstrated, effects on "night vision" are probably due to enhanced alertness (Ref. 10).

Caffeine has a stimulant action on the heart and can increase cardiac output. Sollman (Ref. 14) states that methylxanthines (which include caffeine) are useful potentially in acute heart failure, but the effects appear to be manifold and unpredictable. Theophylline, another xanthine, is said to be more effective than caffeine in stimulating the output of the failing heart by a direct inotropic effect.

For OTC oral use as a stimulant, citrated caffeine is currently available in 60 and 120 mg oral tablets. Caffeine is also added to headache remedies containing salicylates and acetaminophen, and to ergotamine for the relief of migraine. The Commissioner deferred to the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products the determination of the safety and effectiveness of caffeine for the relief of headache or migraine. The Panel's recommendations were published in the FEDERAL REGISTER of July 8, 1977 (42 FR 35346).

Caffeine and sodium benzoate are given also by physicians in dosages of 0.5 to 1.0 g for subcutaneous or intramuscular use as a central nervous system stimulant. Small doses seem to enhance alertness and ability to perform learned tasks. Large doses can stimulate respiration. Caffeine and other xanthines are often used as acetate, benzoate, or salicylate salts. Forming the salt simply increases solubility; it does not affect action. Addition of sodium benzoate probably assists absorption in the acid ph of the stomach, although the nonionic form would probably be well absorbed from the intestine. In any case, the drug appears to be well absorbed when given by mouth (Ref. 15).

The exact mechanism of action of caffeine in not precisely known.

The problem of mutaginicity of caffeine has been reviewed. There is evidence that concentrations of caffeine many times higher than would ordinarily be found in human or animal tissues cause certain mutations in the bacterium *Escherichia coli*, and in the fungus *Ophiostoma multiannulatum* (Refs. 16 and 17). Caffeine has also been reported to induce chromosome aberrations in onion root tips and in human cells in vitro (Refs. 18 and 19). Very careful studies in mammals have failed to reveal evidence of mutagenicity (Refs. 20 and 21).

Caffeine causes chromosome breakage in the human lymphocyte in tissue culture (Refs. 20, 22, 23, and 24) but no evidence for this action in vivo in man or other mammals has been found (Ref. 20). The mechanism of the chromosome breakage has been studied, but not explained (Ref. 25). Lymphocytes from human volunteers ingesting 800 mg caffeine daily (equivalent to 8 cups of coffee) for 30 days showed no increase in chromosome damage when the cells were placed in culture. In the human volunteers, the peak plasma levels were 29.6 ug/ml of caffeine, over 3-fold greater than any pre-experiment level. There was no increase in chromosome breakage when these cells were cultured.

HeLa cells were exposed to concentrations of caffeine in the medium about 10 times greater than that found in vivo in plasma of human subjects drinking 8 cups of coffee per day (800 mg caffeine). There was no increase in chromatid breaks in cultures studied through 48 generations of the HeLa cells (Ref. 26).

Looking for mutagenic indications, different concentrations of caffeine in vitro were studied for an antimitotic action on cell division of human lymphocytes stimulated to divide by phytohemagglutinin, a plant product. Concentrations of caffeine in the medium that interfered with cell division were about 100-fold greater than would be encountered in human tissues after an intake of a usual dose of caffeine or right after drinking a cup of strong coffee (approximately 100 mg caffeine) (Ref. 27). In one study, the effects of three xanthines, theobromine, theophylline, and caffeine were studied for their effectiveness in blocking mitosis of human lymphocytes in 72-hour culture. High concencentrations of caffeine (10^{-3} to 10^{-4} molar) were needed to demonstrate cytostatic and antimitotic effects. It was concluded that any mutations in man caused by caffeine at concentrations ordinarily achieved would have to occur at a rate too low to be detectable (Ref. 28).

The suspected role of caffeine in mutagenesis and also teratogenesis has led to a scrutiny of this substance, a scrutiny that is almost certainly more intensive and extensive than that conducted for any other commonly ingested food or drug. Teratogenicity of caffeine can be detected in rats if sufficiently high doses are given; these are of the order of 250 mg/kg and would be equivalent to 100 cups of coffee containing 125 mg of caffeine each. Metabolism of caffeine in man is rapid, and it may be that this protects man from teratogenic effects (Ref. 29). A review of the mutagenic effects, in particular dominant lethal tests, shows less evidence for organisis higher than bacteria fungi, and higher plants (Ref. 29).

The Commissioner notes that a comment submitted in response to the Panel's report and proposed monograph suggested a pregnancy warning for caffeine-containing products. The

Commissioner has extensively discussed this issue in comment 102 above and will not repeat that discussion here.

The safety of coffee has been questioned recently by a drug surveillance group (Ref. 30). The findings of the group suggested an increase of serious heart disease among heavy coffee drinkers. However, there was no positive association among tea drinkers. This would appear to exclude implication of caffeine present in both coffee and tea. The report has been criticized by others who indicate further evidence is needed to demonstrate a role of coffee in the genesis of cardiovascular disease (Ref. 31). These other invesigators found no evidence for the role of coffee in any increased risk of death because of cardiovascular disease in a large, well-known (Framingham study) prospective study of factors involved in the genesis of coronary heart disease (Ref. 32). No generally accepted evidence would implicate caffeine as a danger in this regard. Furthermore, another recent publication using large numbers of subjects has not supported the contention about coffee drinking promulgated by the Drug Surveillance Group (Ref. 33). The Commissioner concludes that there is inconclusive evidence linking coffee and/or caffeine to cardiovascular diseases. In another study of paired, control patients, there was a higher incidence of myocardial infarction with very high consumption of coffee. Caffeine was implicated only indirectly, on the basis of elevation of serum lipids evoked by caffeine administration (Ref. 34). In a study of 1,700 men between the ages of 40 and 55 years (Ref. 35), there was said to be an "increasing incidence of angina pectoris and of myocardial infarction with survival" among men consuming 5 or more cups of coffee a day. Curiously, the death rate was highest among those who took no coffee or consumed 5 or more cups of coffee per day. There is no level of significance given and the number of deaths is small.

In contrast to the irritating qualities of many coffee extracts, caffeine itself does not seem to cause irritation of the gastrointestinal tract in the usual doses. This is an advantage when the drug is used for its stimulant properties.

The observations that suggest some central stimulation that leads to, or is associated with, a mild form of addiction to caffeine raise questions about long-term use. This appears to be true for most hypnotics in that we now know that there are, at the least, changes in the amount of REM sleep and that some kind of deficit is built up. This occurs in addition to the separate risk of addiction to the hypnotic itself. In the case of stimulants used to enhance the performance of school children deemed hyperactive, Sroufe and Stewart have suggested that there may be no persistent effect of drug therapy upon these children, but that they become dependent upon the stimulant drugs to maintain a level of performance not much different from pre-drug performance (Ref. 36).

The Commissioner has not been presented with any evidence that would suggest this same conclusion from the long-term use of caffeine.

In summary, the Commissioner concludes that caffeine as an OTC stimulant appears to be safe and effective. It is reasonably nontoxic in that fatal doses for man are estimated to be greater than 10 g by mouth.

Caffeine has the ability to produce a low grade of "addiction" that is commonly referred to as "habituation," and has been most extensively studied in coffee drinkers. The Commissioner concludes that this is not a dangerous problem and does not believe that a warning regarding habituation is necessary. However, the Commissioner concludes that stimulant products containing caffeine should not include in the labeling a suggestion such as "non-habit-forming."

Caffeine has not been shown to be mutagenic to man or mammals, although there are some weak mutagenic effects that can be demonstrated in certain bacterial viruses. The claim that coffee drinkers have more heart disease than noncoffee drinkers is not proven to the satisfaction of the Commissioner and is not relevant because it does not extend to caffeine. The claim relating to heart disease has involved coffee and has "absolved" tea drinkers (who ingest caffeine in their tea). The possibility that extensive daily caffeine intake (tablets, coffee, cola drinks, etc.) may mimic neurotic anxiety reaction has recently been raised (Ref. 37). Labeling will therefore include a warning to this effect.

The addition of substances to caffeine preparations as marketed should be closely scrutinized. Since the addition of proprietary flavors such as menthol and peppermint or sugars or their substitutes encourages ingestion by children, they serve to enhance the possibility of poisoning. The Commissioner concludes that such substances should not be included in stimulant products. The Panel expressed concern over the use of talc in preparations intended for human consumption. The Commissioner has concluded earlier in this document (see comment 12 above), that since talc is an inactive ingredient it will be governed by the proposed inactive ingredient regulations published in the FEDERAL REGISTER of April 12, 1977 (42 FR 19156). The Commissioner, therefore, excludes any further discussion of talc from this document.

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Category I Labeling

The Commissioner concludes that the following labeling for stimulant active ingredients shall be generally recognized as safe and effective and not misbranded:

a. *Indications.* "Helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness".

b. *Warnings and/or cautions.* Labeling shall contain the following warnings:

(1) *"Caution:* Do not exceed recommended dose since side effects may occur which include increased nervousness, anxiety, irritability, difficulty in falling asleep and occasionally disturbances in heart rate and rhythm called palpitations".

(2) "For occasional use only. If fatigue or drowsiness persists continuously for more than 2 weeks, consult a physician".

(3) "Do not give to children under 12 years of age". The Commissioner has determined in comment 99 above that the first sentence of the adults only warning recommended by the Panel is redundant and should be deleted.

(4) "The recommended dose of this product contains about as much caffeine as a cup of coffee. Take this product with caution while taking caffeine-containing beverages such as coffee, tea or cola drinks because large doses of caffeine may cause side effects as cautioned elsewhere on the label". The Commissioner concludes that such a warning is necessary since an average cup of coffee or strong tea contains an amount of caffeine about equal to that in the average dose of OTC products. Certain cola drinks also contain a significant amount of caffeine and should also be included in the warning. The combined amount of caffeine ingested could be large enough to produce side effects in some individuals.

2. *Category II conditions under which stimulant products are not generally recognized as safe and effective or are misbranded.* The Commissioner concludes that no scientific basis or even sound theoretical reasons have been presented for the claimed effectiveness of a number of ingredients used in OTC stimulants. In addition, certain labeling claims are clearly misleading. For example, statements or suggestions that stimulants and stimulant combination products (with nonstimulant ingredients) "increase sensual pleasure" are undocumented claims in the presently available literature and are, therefore, unacceptable to the Commissioner.

The Commissioner concludes that stimulant products containing the following ingredients cannot be generally recognized as safe and effective or are misbranded since there are no data to support their use alone or in combination as a stimulant. The Commissioner has determined that these ingredients have no action as a stimulant nor do they contribute to the claimed effectiveness of a stimulant (e.g., caffeine) as an ingredient in a combination product.

Category II Active Ingredients

Combinations of caffeine and nonstimulant active ingredients

Ammonium chloride
Ginseng
Vitamins

a. *Ammonium chloride.* The Commissioner concludes that a combination product in which caffeine is combined with ammonium chloride is not rational for use as an OTC stimulant preparation. The Commissioner is unaware of any data which demonstrate a role for use of ammonium chloride, either alone or in combination with caffeine, as a stimulant.

The Commissioner is aware that products containing ammonium chloride and caffeine are promoted for premenstrual tension with the claim "helps relieve premenstrual symptoms: swelling, weight gain and fatigue."

The Commissioner has not found acceptable evidence that the use of ammonium chloride and caffeine is rational for the purpose of reducing fatigue. Caffeine alone may be expected to increase rather than decrease associated nervousness. The use of ammonium chloride for other claims has been deferred by the Commissioner to the Advisory Review Panel on OTC Miscellaneous Internal Drug Products for review as to the safety and effectiveness of this ingredient.

b. *Ginseng.* The Commissioner concludes that there is no rationale for adding ginseng to a stimulant drug.

The Commissioner concludes that no data have been presented to suggest a stimulant action for ginseng or for potentiation or enhancement of the stimulant effect of caffeine. After an extensive review of the available scientific literature, the Commissioner found no reasonable studies or supporting documentation to suggest ginseng in combination with caffeine to affect or enhance sexual drives or awareness.

c. *Vitamins.* The Commissioner concludes that there is no acceptable medical rationale for combining vitamins (especially Vitamin E) with caffeine. The Commissioner further makes reference to the discussion of vitamins in the section on nighttime sleep-aids. (See part II. paragraph E.6. above—Combinations containing irrational ingredients.) The Commissioner has found no acceptable rationale to explain the combination of caffeine and vitamins.

The Commissioner defers to the Advisory Review Panel on OTC Vitamin, Mineral, and Hematinic Drug Products on the safety, effectiveness and labeled claims for vitamins. The Commissioner notes that the proper functioning of all cells requires an adequate intake of all vitamins (water-soluble and fat-soluble). The Commissioner concludes that it is misleading to assume or propose that individuals consuming stimulant drugs have certain vitamin deficiencies and that there is virtually nothing in the cur-

rent medical or pharmacological literature to support the inclusion of selected vitamins in OTC stimulants. In addition, the small amounts of water-soluble vitamins contained in OTC stimulants are virtually homeopathic due to the fact that vitamins are rapidly excreted in the urine. This provides no rationale to support the inclusion of these ingredients in products designed to provide CNS stimulation.

The Commissioner supports the Panel's statement that polypharmacy and a "shotgun" approach to treatment of symptoms with fixed-dose combinations have no rational, therapeutic basis.

The value of the placebo effect in the management of psychosomatic illness and minor neuroses is obvious. It is extremely doubtful, however, that the inclusion of vitamins in a self-prescribed stimulant enhances any placebo effect these products may confer.

Category II Labeling

In one submission, a combination product containing caffeine and ginseng is claimed to "increase sensual awareness and pleasure". Although not stated explicitly, it is apparent to the Commissioner that the intent of this labeling is to equate sensual awareness and pleasure with increased sexual capability and pleasure. The utility of ginseng has been discussed previously where it was stated that no evidence of enhanced sexual experience or potency has been found. In the case of caffeine, the Commissioner is unaware of any studies that clearly show an enhancement of sensual or sexual experience by the ingestion of this drug. Certainly no submissions to the Panel deal with this indication. In the absence of any positive evidence for an effect on sensual or sexual experience, the Commissioner objects to labeling that states or implies "increases sensual pleasure."

In the same submission, caffeine with vitamin E is claimed to "increase sensual (sexual) awareness." The Commissioner concludes that no reasonable supporting documentation has been presented to even suggest that vitamin E in combination with caffeine affects or enhances the sensual (sexual) experience in people. The Commissioner concludes that neither ingredient has been shown to affect sexual experience in men or women and therefore such claims are false and misleading.

The Commissioner also concludes that labeling claim(s) that suggest a product containing caffeine is "non-habit forming" are misleading and should not be allowed. Prolonged ingestion of caffeine especially in larger than recommended doses can lead to habituation.

3. *Category III conditions under which the available data are insufficient to permit final classification at this time.* The Commissioner concludes that adequate and reliable scientific evidence is not available to permit final classification of the claimed labeling listed below:

Category III Labeling

The question of whether a stimulant such as caffeine "enhances performance" in the nonfatigued state cannot be answered definitively at this time. Although there are some suggestions. but not proof, that this may be true, additional evidence in well-controlled trials would be necessary for such an indication to be included in the labeling. If such proof is obtained, it must also be demonstrated, in the same human subject, that no side effects accompany enhanced performance. In the case of caffeine, such side effects would include, among others, tremor, palpitations, and nervousness.

The Commissioner has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Federal Food, Drug and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371) and the Administrative Procedures Act (5 U.S.C. 553, 554, 702, 703, 704) and under authority delegated to him (21 CFR 5.1), the Commissioner proposes that Subchapter D of Title 21 of the Code of Federal Regulations be amended by adding new Parts 338 and 340 to read as follows:

PART 338—NIGHTTIME SLEEP-AID PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
338.1 Scope.
338.3 Definition.

Subpart B—Active Ingredients

338.10 Nighttime sleep-aid active ingredients. [Reserved]

Subpart C—[Reserved]

Subpart D—Labeling

338.50 Labeling of nighttime sleep-aid products.

AUTHORITY: Secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371), (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 338.1 Scope.

An over-the-counter nighttime sleep-aid product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this Part 338 and each of the general conditions established in § 330.1 of this chapter.

§ 338.3 Definition.

As used in this part, "nighttime sleep-aid" is an agent which helps an individual fall asleep or is used for the relief of occasional sleeplessness.

Subpart B—Active Ingredients

§ 338.10 Nighttime sleep-aid active ingredients. [Reserved]

Subpart C—[Reserved]

Subpart D—Labeling

§ 338.50 Labeling of nighttime sleep-aid products.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug, if any, and shall identify the product as a "nighttime sleep-aid".

(b) *Indications.* The labeling of the product shall contain a statement of the indications under the heading *"Indication(s)"* that shall be limited to one or more of the following phrases; "Helps fall asleep", "For relief of occasional sleeplessness", "Helps to reduce difficulty in falling asleep".

(c) *Warnings.* The labeling of the product shall contain the following warnings under the heading "Warnings":

(1) "Do not give to children under 12 years of age".

(2) "If sleeplessness persists continuously for more than 2 weeks, consult your physician. Insomnia may be a symptom of serious underlying medical illness".

(3) For products containing an antihistamine:

(i) "Do not take this product if you have asthma, glaucoma, or enlargement of the prostate gland except under the advice and supervision of a physician". This warning shall be in type at least twice as large as all other warnings on the package.

(ii) "Take this product with caution if alcohol is being consumed".

(d) *Directions.* The labeling of the product shall contain the following statement under the heading "Directions": Dosage is (insert appropriate dosage of individual product) once daily at bedtime, or as directed by a physician".

PART 340—STIMULANT PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredient

Subpart C—[Reserved]

Subpart D—Labeling

AUTHORITY: Secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 340.1 Scope.

An over-the-counter stimulant product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this Part 340 and each of the general conditions established in § 330.1 of this chapter

§ 340.3 Definition.

As used in this part, "stimulant" is an agent which helps restore mental alertness or wakefulness during fatigue or drowsiness.

Subpart B—Active Ingredient

§ 340.10 Stimulant active ingredients.

The active ingredient of the product consists of caffeine when used within the dosage limit established: Adult oral dosage 100 to 200 mg not more often than every 3 to 4 hours.

Subpart C—[Reserved]

Subpart D—Labeling

§ 340.50 Labeling of stimulant products.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug, if any, and shall identify the product as a "stimulant".

(b) *Indications.* The labeling of the product shall contain a statement of the indications under the heading *"Indications"* that shall be limited to the following phrase: "Helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness".

(c) *Warnings.* The labeling of the product shall contain the following warnings under the heading "Warnings":

(1) *"Caution:* Do not exceed recommended dose since side effects may occur which include increased nervousness, anxiety, irritability, difficulty in falling asleep, and occasionally disturbances in heart rate and rhythm called palpitations".

(2) "For occasional use only. If fatigue or drowsiness persist continuously for more than 2 weeks, consult a physician".

(3) "Do not give to children under 12 years of age".

(4) For products containing caffeine: "The recommended dose of this product contains about as much caffeine as a cup of coffee. Take this product with caution while taking caffeine-containing beverages such as coffee, tea, or cola drinks because large doses of caffeine may cause side effects as cautioned elsewhere on the label".

(d) *Directions.* The labeling of the product shall contain the following statement under the heading "Directions": For products containing caffeine: "Adult oral dosage is 100 to 200 mg not more than every 3 to 4 hours".

Interested persons may file written objections and/or request an oral hearing before the Commissioner regarding these tentative final monographs on or before August 14, 1978. Request for an oral hearing must specify points to be covered and time requested.

All objections and requests shall be submitted (preferably in quadruplicate identified with the Hearing Clerk docket number found in brackets in the heading of this document) to the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, Md. 20857, and shall be accompanied by a memorandum or brief in support thereof. Objections and requests may be seen in the above office between 9 a.m. and 4 p.m. Monday through Friday. Any scheduled oral hearing will be announced in the FEDERAL REGISTER.

NOTE.—The Food and Drug Administration has determined that this proposal will not have a major economic impact as defined by Executive Order 11821 (amended by Executive Order 11949) and OMB Circular A-107. A copy of the economic impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Date: May 27, 1978.

DONALD KENNEDY,
Commissioner of Food and Drugs.

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