DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 330

[Docket No. 82N-0050]

Over-the-Counter Human Drugs Which Are Generally Recognized as Safe and Effective and Not Misbranded; Proposed Amendment of General Provisions

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the general provisions for all over-the-counter (OTC) drugs in Part 330 (21 CFR Part 330) to include a warning concerning the use of systematically absorbed OTC drugs by pregnant or nursing women. FDA believes that it is in the interest of the public health to require OTC drugs to bear a warning against use by pregnant or nursing women in the absence of professional advice.

DATES: Written comments by October 7, 1982. The agency proposed that any final rule that may issue based upon this proposal become effective 30 days following publication of the final rule, except that manufacturers will be provided up to one year for label changes. See "Supplementary Information" for a full discussion of the proposed effective date.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, National Center for Drugs and Biologics (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: FDA is proposing to amend the general provisions for OTC drugs to include a requirement that OTC drug labels contain a statement advising pregnant or nursing women to seek professional advice before using any drug. The proposed warning would apply to all OTC drugs that are systemically absorbed and would state, "As with any drug, if you are pregnant or nursing a baby, seek professional advice before using this product." However, where a specific warning concerning possible adverse effects on pregnant or nursing women is established for an ingredient during the OTC drug review, the specific warning listed in an OTC drug final monograph would apply rather than the general warning proposed in this document. The proposed rule also provides for exemption from the general warning requirement, when appropriate, through petitioning the agency.

FDA and the State of California Department of Health Services have corresponded about the need for warnings concerning the use of OTC drugs by pregnant or nursing women. There has been agreement about the importance of informing these women of the need to exercise caution in using OTC drug products, but there have been differences about the best means of accomplishing this goal. FDA has opposed California's requirement of a general pregnancy/nursing warning because of concern that a general warning would not be consistent with specific warnings developed during the OTC drug review.

Recently, the State of California enacted legislation (section 10381 of Title 17 of the California Health and Safety Code) requiring that any OTC drug intended for systemic absorption into the human body that is not specifically exempted under the State's Health and Safety Code must include a pregnancy warning on the label. The warning states: "Caution: If pregnant or nursing a baby, consult your physician or pharmacist before using this product." The new California statute also provides that this specific warning is not required for an OTC drug that is "labeled with information regarding use in pregnancy and nursing which is substantially similar to (this) statement * * *." Any OTC drug manufactured and labeled after November 18, 1982, will be required to comply with the new California labeling. FDA is aware that similar legislation is also under consideration by other States.

FDA believes that it is in the interest of the public health to require OTC drugs to bear a warning against use by pregnant or nursing women in the absence of professional advice. Drugs taken by pregnant women pose the risk that they may affect the growth and developent of the human fetus. Drugs taken by nursing women may be transferred by the mother's milk to the newborn child for whom they are not intended, and at this stage in a child's life its enzyme system is not fully mature and its kidney function not fully developed so that it is easy for toxic levels of drugs to accumulate in its body (Ref. 1). Although only a small number of drugs have been conclusively shown to have adverse effects on the developing human fetus or newborn, information of this type is inadequate to establish safety for most drugs (Refs. 2 through 7). There is evidence, however, that the developing human organism is most susceptible to the effects of teratogenic drugs or other agents from about 2 weeks to 8 weeks after fertilization when the major organ systems are developing (Refs. 3, 5, 7, and 8). Exposure of the fetus to toxic agents after the embryo stage (i.e., after the basic structures of the organ systems have developed), while not likely to cause major anatomical abnormalities, may result in reductions in cell size or number, or alterations in functional capacity (Refs. 3, 5, and 8). The central nervous system appears to be especially susceptible to changes in functional capacity during the last trimester of pregnancy when the rate of brain growth is normally rapid.

In the course of FDA's OTC drug review, the advisory review panels gave particular consideration to evidence of teratogenicity in evaluating the safety of ingredients. For ingredients for which there were data to suggest a potential hazard, the panels recommended specific pregnancy warnings. For example, the panels recommended pregnancy warnings for aspirin use in the last 3 months of pregnancy and for anthelmintics. However, the agency recognizes that even where there are no data to suggest that particular OTC drugs present a potential hazard, there also may be no data demonstrating that such drugs are safe when used by pregnant or nursing women. Because any drug taken during pregnancy or while nursing may pose some risk to the fetus or newborn child, the agency concludes that in order to minimize this risk the labels of systemically absorbed OTC drug products should advise pregnant or nursing women that professional advice should be sought before using OTC drug products.

The agency has reviewed the labeling adopted by the State of California, which advises pregnant and nursing women to "consult your physician or pharmacist before using this product." Although the agency agrees with the concept of encouraging these women to seek professional assistance before using drug products, the agency does not believe that the warning should specify physicians and pharmacists. Many professional groups, such as nurses, nurse practitioners, certified nurse midwives, and physician's assistants, are also sources of sound information on OTC drugs. The woman who is considering taking an OTC drug is in the best position to choose the appropriate health professional to help her assess the risks and benefits of taking the drug for the medical condition for which she seeks relief. Therefore, the agency is

proposing that the warning advise women to "seek professional advice."

The proposed regulation allows a general warning to be superseded by a specific one where information on the extent of the risk is available. FDA considers that the inclusion of a specific warning instead of a general warning will serve to identify those products for which there are data suggesting a particular risk in pregnant or nursing women. The requirement for a general warning is supported by the need to inform pregnant or nursing women of the advisability of minimizing exposure of the fetus or newborn child to drugs, since a drug taken during pregnancy or while nursing may pose some risk. Because this proposed general warning is based on a lack of data demonstrating that OTC drugs are safe for use by pregnant or nursing women, rather than on data demonstrating that the specific product is unsafe, the proposed warning begins with the phrase "as with any drug." This phrase makes it clear that the general warning applies to all drugs and will help to enhance the effect of those specific warnings that represent demonstrated risks of particular drugs.

If the proposed warning is adopted, the agency will continue to review the scientific data concerning the use of OTC drugs by pregnant and nursing women and will give careful consideration to the need for the warning both generally and for specific classes of OTC drugs. Should it appear, based on these data, that the warning is no longer justified, the agency will propose to revoke the requirement.

References

1. Hecht, A., "Advice on Breast-Feeding and Drugs," *FDA Consumer,* 13:21–22, 1979.
2. Heinonen, O. P., D. Slone, and S. Shapiro, "The Teratogenic Role of Drugs in Humans," *in* "Birth Defects and Drugs in Pregnancy," PSG Publishing Company, Littleton, MA, pp. 1–7, 1977.
3. Howard, F. M., and J. M. Hill, "Drugs in Pregnancy," *Obstetrical and Gynecological Survey,* 34:643–653, 1979.
4. Oakley, G. P., Jr., "Drug Influences on Malformations," *Clinics in Perinatology,* 6:403–414, 1979.
5. Shepard, T. H., "Teratogenicity of Therapeutic Agents," *Current Problems in Pediatrics,* 10:1–42, 1979.
6. Hays, D. P., "Teratogenesis: A review of the Basic Principles with a Discussion of Selected Agents: Part I," *Drug Intelligence and Clinical Pharmacy,* 15:562–566, 1981.
7. Hays, D. P., "Teratogenesis: A review of the Basic Principles with a Discussion of Selected Agents: Part II," *Drug Intelligence and Clinical Pharmacy,* 15:542–561, 1981.
8. Goldman, A. S., "Critical Periods of Prenatal Toxic Insults," *in* "Drug and Chemical Risks to the Fetus and Newborn," edited by R. H. Schwarz and S. J. Yaffe, Alan R. Liss, Inc., New York, pp. 9–31, 1980.

The agency invites comments on the preemptive effect the warning required by this proposal have on State OTC drug labeling requirements such as California's and those under consideration by other States. See *Jones* v. *Rath Packing Co.,* 430 U.S. 519 (1977). The Commissioner notes that the warning proposed in this notice is similar to the California warning and, therefore, might fall within the California law's exception for warnings that are "substantially similar." If the warning were determined to be "substantially similar," the question of preemption would not arise; manufacturers who used the warning required by this proposal would also be in compliance with the California law. However, one of the express purposes of the proposed regulation is to establish a national pregnancy/nursing warning requirement with a specified text. Thus, a State labeling requirement that specified wording for an OTC drug pregnancy/nursing warning that was different from the wording proposed here would prevent the accomplishment and execution of the full purpose and objectives of the agency in issuing the regulation. Therefore, in the opinion of FDA, such a State requirement would be preempted. *Jones* v. *Rath Packing Co., supra* at 521.

The present proposal deals only with pregnancy/nursing warning requirements for OTC drugs. Accordingly, the proposal will affect only related or similar State requirements. FDA is aware, however, that there are a number of State requirements, either in force or pending before the State legislatures, relating to other aspects of OTC drug labeling. The agency believes that it has the authority to preempt State-imposed OTC drug labeling requirements regardless of whether it issues specific, conflicting labeling requirements of its own. See *Brookhaven Cable TV, Inc.* v. *Kelly,* 573 F. 2d 765 (2d Cir.), *cert. denied,* 441 U.S. 904 (1978). There is a substantial federal interest in having clear, unambiguous, and consistent information in the labeling of OTC drugs. FDA is concerned that a proliferation of State labeling requirements may weaken FDA's efforts to develop comprehensive national labeling requirements for OTC drugs. While the regulation proposed in this notice relates only to one labeling requirement, FDA in the future may consider whether State requirements should be generally preempted to preserve the integrity of FDA-mandated labeling requirements.

The agency believes that good cause exists for shortening the usual 60-day comment period provided in 21 CFR 10.40(b). The California requirement will take effect on November 18, 1982, unless preempted by FDA regulations. The 30-day comment period will give the agency additional time to analyze comments and to take appropriate action so as to minimize confusion concerning manufacturers' obligations under State and Federal law.

The agency proposes that any final rule that may issue based upon this proposal become effective 30 days following publication of the final rule. This early effective date will preempt any differing State requirements and will allow manufacturers first marketing in States with differing requirements to use only the new FDA labeling. The agency is aware that manufacturers may be revising their labeling in anticipation of the effective date of the California law, or for other reasons. Therefore, although the regulation will become effective 30 days after publication of the final rule, manufacturers will be permitted to defer labeling changes until present supplies of labels are exhausted, or until one year after publication of the final rule, whichever first occurs. Thereafter, covered OTC drugs initially introduced or initially delivered for introduction into interstate commerce would be required to comply with the new labeling requirements. The agency will consider requests for additional time to comply with the requirements based on a showing of good cause.

The agency has examined the regulatory impact and regulatory flexibility implications of the proposed regulation in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96–354). The proposed rule is estimated to generate one-time label modification costs of $3.8 to $5.7 million to marketers of systemically absorbed OTC drugs, and annual costs of $0.7 to $6 million for consultations between pregnant, and nursing women and health professionals. Thus, first year impacts of the label warning are expected to total $4.5 to $11.7 million. The net cost impact attributable to the proposed rule is less than this because, absent federal action, firms would have to comply with State requirements that would also produce both label modification and consultation costs. These costs are well below the thresholds for a major rule in Executive Order 12291.

Similarly, the costs incurred by small businesses are estimated to be insufficient to warrant a regulatory flexibility anlaysis. Label change costs will be dominated by private label (store brand) OTC drugs which FDA believes to be heavily marketed by larger firms.

FDA further believes that small marketers use relatively simple and inexpensive packaging and labeling. Hence, label change costs to small firms are not expected to be substantial. Costs for additional health care consultants will mainly affect small entities, but will be spread over so many of them, e.g., 47,000 drug stores and 24,000 obstetrician/gynecologist practices, that the average burden per entity appears trivial. Therefore, the agency certifies that the proposal, if adopted, would not have a significant economic impact on a substantial number of small entities. A copy of the threshold assessment for this proposed regulation is on file in the Dockets Management Branch (address above).

The agency has determined that under 21 CFR 25.24(d)(13) (proposed in the **Federal Register** of December 11, 1979; 44 FR 71742) this approval is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 330

OTC drugs.

PART 330—OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), under the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), it is proposed that Part 330 be amended by adding a new § 330.2, to read as follows:

§ 330.2 Pregnancy/nursing warning.

(a) The labels for all drugs that are systemically absorbed into the body contains a general warning as follows: "As with any drug, if you are pregnant or nursing a baby, seek professional advice before using this product."

(b) Where a specific warning relating to use during pregnancy or while nursing has been established for an ingredient listed in an OTC drug final monograph, the specific warning shall be used in place of the warning in paragraph (a) of this section.

(c) The food and Drug Administration will grant an exemption from § 330.2(a) where appropriate upon petition under the provisions of § 10.30. Exemption shall be maintained in a permanent file for public review by the Dockets Management Branch, Food and Drug Administration, Room 4–62, Parklawn Building, 5600 Fishers Lane, Rockville, MD 20857.

* * * * *

The agency has determined under § 10.40(d) (21 CFR 10.40(d)) that good cause exists for a comment period of 30 days rather than the usual 60 days. As discussed in this document, the State of California has adopted a labeling requirement and other States have legislative proposals under consideration. Therefore, it is incumbent on the agency to complete promptly this rulemaking to ensure an orderly and uniform labeling requirement, if deemed appropriate as a result of this rulemaking proceeding. Accordingly, a 30-day comment period is justified.

Interested persons may submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, by October 7, 1982. Three copies of all comments shall be submitted, except that individuals may submit single copies of comments. The comments are to be identified withe the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Arthur Hull Hayse, Jr.,

Commissioner of Food and Drugs.

Dated: August 12, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

[FR Doc. 82–24452 Filed 9–3–82; 8:45 am]

BILLING CODE 4160–01–M

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