DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 5, 201, and 330

[Docket No. 82N-0050]

Pregnant or Nursing Women; Delegations of Authority and Organization; Amendment of Labeling Requirements for Over-the-Counter Human Drugs

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the general drug labeling provisions to include a warning concerning the use by pregnant or nursing women of over-the-counter (OTC) drugs intended for systemic absorption. FDA is also redelegating authority to grant or deny petitions seeking exemptions from the general warning. FDA is taking this action after considering public comments on the proposed rule.

DATES: The effective date of §§ 5.31(d), 201.63 and 330.2 is December 3, 1982. Manufacturers of affected drug products will have until December 5, 1983 to comply with the labeling requirement set forth in § 201.63.

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SUPPLEMENTARY INFORMATION: In the Federal Register of September 7, 1982 (47 FR 39470), FDA proposed 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. This warning was to apply to all OTC drugs that are systemically absorbed and stated, "As with any drug, if you are pregnant or nursing a baby, seek professional advice before using this product." The proposal stated that, where a specific warning relating to use during pregnancy or while nursing 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 proposed general warning. The proposal also provided for exemption from the general warning requirement, when appropriate, through petitioning the agency.

Interested persons were invited to file written comments regarding this proposal on or before October 7, 1982. In response to the proposed rule, comments were received from 11 health professional associations, 2 trade associations, 5 women's organizations, 3 State governments, 14 private individuals, 4 consumer associations, 2 drug merchandisers, and 19 drug manufacturers.

The agency also received six petitions requesting an extension of the comment period from 30 days to 60 days and requesting that public hearings be held in Washington, DC, and other key cities. The agency denied these petitions for the following reasons: In developing the proposal, which concerned a single labeling requirement only, FDA carefully considered potential areas of comment and determined that 30 days would be adequate to develop and submit such comments. Immediately following publication of the proposal, the agency forwarded copies of it to key consumer groups and national women's organizations throughout the country, pointing out to these persons that, the comment period was limited to 30 days. The proposal also received extensive media coverage. Further, because the State of California requirement for a pregnancy-nursing warning for OTC drugs was to become effective on November 18, 1982, FDA concluded that a 30-day comment period was necessary to minimize confusion concerning manufacturers' obligations under State and Federal law. Finally, it is unlikely that public hearings would develop information that could not be furnished to the agency through the submission of written comments.

The final rule is similar to that proposed, but clarifies the agency's intent to include only OTC drugs intended for systemic absorption (see comment 5 below) and the agency's conclusion to include the rule under Part 201 (21 CFR Part 201) (see comment 21 below). Therefore, this final rule contains the agency's decision to amend the labeling requirements for OTC drugs in Part 201 to require for OTC drugs intended for systemic absorption, unless exempted, a warning advising pregnant and nursing women to consult a health professional before using such drugs.

A. The Agency's Conclusions on the Comments

1. A number of comments supported the general warning proposed by the agency. For example, a professor of health policy commented that, although the relative risk generated by an individual OTC drug is likely to be modest, the sheer number of OTC drug products and extent of their use suggest the need for a general warning. A comment from the American Medical Association stated that, even though insufficient research has been performed on most OTC drugs to determine conclusively whether the adversely affect fetuses and breast-fed babies, it is appropriate to be cautious and require a warning advising pregnant and nursing women to use such drugs only with professional advice.

2. A number of comments requested that the general warning specify a physician or a pharmacist as the professional from whom a pregnant or nursing woman should seek advice on the use of OTC drugs. Several of the comments requested that the agency adopt the warning developed by the State of California: "Caution: If pregnant or nursing a baby, consult your physician or pharmacist before using this product." Some comments argued that a pharmacist should be specified because a pharmacist is readily available to consumers at the time of most OTC drug purchases and is particularly knowledgeable concerning OTC drug products. Other comments argued that the physician, as the primary provider of medical care for pregnant and nursing women, should be the only professional specified. One comment from a supermarket chain stated that its consumer board had determined that the word "professional" was subject to varying interpretations by consumers. Pointing out that consumers might construe the broad term "professional advice" to include persons who might not be familiar with the objectives of the warning, another comment suggested that the warning specify a "health professional."

As suggested by the comments, the agency concludes that the warning should be changed to advise pregnant or nursing women to contact a "health professional" for advice regarding OTC drug usage. While physicians or pharmacists would probably be the most likely health professionals to be consulted because of their availability and recognized expertise, the agency does not believe that the warning should specify one or both of these professionals only. FDA pointed out in the preamble to the proposed regulation that many professional groups, such as nurses, nurse practitioners, certified nurse midwives, and physician's assistants, are also sources of sound information on OTC drugs (47 FR 39470). The woman who is considering taking an OTC drug is in the best position to choose the health professional to help her assess the risks and benefits of using the drug, and the warning should not limit her sources of information

as drugs the agency has previously stated do not require a warning against use in pregnancy or nursing.

As discussed in comment 5 above, the regulation has been revised to apply only to OTC drug products intended for systemic absorption into the human body. Therefore, a number of the products for which exemptions were requested are not within the scope of the final regulation. Cosmetic products were not covered by the proposal, nor are they included in the final rule. Topically applied products, such as many of those listed in the comments, are not intended for systemic absorption and, therefore, are not covered by the rule. Dentifrices and mouthwashes are also not within the scope of the final regulation. Vitamins labeled solely as dietary supplements are considered foods and, therefore, are not covered by the regulation.

The regulation has also been revised to exempt from the warning requirement drugs intended to benefit the fetus or nursing infant during the period of pregnancy or nursing (§ 201.63(c)(1)). The agency finds this to be a reasonable exemption because such drugs would have been evaluated specifically for their effects on the fetus or infant and demonstrated to be beneficial. Drugs labeled exclusively for pediatric use are also exempted (§ 201.63(c)(2)) because pregnant or nursing women would not be taking such products.

OTC homeopathic drug products intended for systemic absorption are included in the final rule. The agency is aware of no evidence indicating that the potential harm to fetuses or nursing infants from this kind of drug product differs from the potential harm of other kinds of OTC drug products intended for systemic absorption. Individual manufacturers of homeopathic drugs may petition for exemption from the warning requirement if they can present evidence to support an exemption (see comment 7 below). The agency is unaware of any OTC drug products intended to be systemically absorbed that are labeled exclusively for geriatric or postmenstrual use or exclusively for use by men.

FDA does not agree with the comment suggesting that an agency decision not to require a specific warning on certain products (such as pyrantel pamoate as an anthelmintic or certain antiemetics) implies that the general warning also should not be required on such products. The general warning is intended to cover those drugs for which the available evidence shows neither that the product is unsafe for use by pregnant or nursing women *nor* that the product is safe for use by these women.

In addition, the agency is redelegating the authority to grant or deny petitions seeking exemption from the general warning in § 201.63 from the Commissioner of Food and Drugs to the Director, National Center for Drugs and Biologics (NCDB), and the Director and Deputy Director of the Office of Drugs, NCDB. Further redelegation of the authority delegated is not authorized. Section 5.31 (21 CFR 5.31) is revised to include this redelegation.

7. Noting that the proposed regulation included a provision for granting an exemption from the general warning requirement, several comments questioned what the criteria for exemption are. One comment stated that the regulation could be subverted by indiscriminate granting of exemptions unless limitations are stated in the regulation. The comment noted that the State of California regulation has an exemption provision limited to five defined classes of products.

The agency has revised the proposed regulation to clarify the scope of the requirement. As discussed more fully in comment 5, the final regulation will apply only to OTC drugs intended for systemic absorption into the human body. Furthermore, as discussed in comment 6 above, two other categories of OTC drugs are exempted from the regulation: drugs intended to benefit the fetus or nursing infant and drugs labeled exclusively for pediatric use. The clarifications should greatly reduce the number of petitions for exemption to the regulation.

The regulation (§ 201.63(d)) provides for exemptions from the pregnancy-nursing general warning requirement where appropriate upon petition under the provisions of § 10.30 (21 CFR 10.30). For example, manufacturers who believe that available data demonstrate that their products, although intended for systemic absorption, are safe for use by pregnant and nursing women may petition for an exemption from the warning requirement. Consistent with the procedures under § 10.30, the agency will notify the petitioner in writing whether the petition is granted or denied. Exemptions granted will be kept on file for public review in FDA's Dockets Management Branch. Exemptions will not be granted indiscriminately, but only upon adequate demonstration by the petitioner that an exemption is warranted.

8. One comment stated that, for an OTC drug subject to a new drug application (NDA), it should be possible to seek exemption from the general warning requirement through an NDA or a supplemental NDA, as well as through the petition procedures.

Upon request, the agency will consider data included in an NDA or supplemental NDA for an OTC drug subject to an NDA to determine whether the data qualify the drug for exemption from the pregnancy-nursing general warning requirement. Alternatively, the sponsor may follow the petition procedures in § 10.30, as discussed in comment 7 above. For drugs not subject to an NDA, manufacturers should follow the petition procedures in § 10.30.

9. One comment suggested that the phrase "as with any drug" be made optional because labeling space limitations may necessitate its deletion. The comment stated that deletion of this phrase would not alter the meaning of the proposed warning. Another comment endorsed this phrase because it does not single out a particular product labeled with the warning, but rather informs pregnant and nursing women to exercise caution when using it and other OTC drug products. A third comment suggested that this phrase be changed to read "as with any drug used internally" to clarify that the warning does not apply to all OTC drugs.

The agency does not believe the phrase should be optional. As noted in the second comment, the phrase is important because it conveys the message that a product labeled with the warning is one of many drugs that should be used with caution by pregnant or nursing women. The phrase, which makes it clear that this is a general warning, should also help to enhance the effect of those specific pregnancy-nursing warnings that represent demonstrated risks of particular drugs.

FDA agrees with the third comment that this warning requirement does not apply to all OTC drugs. The final regulation has been revised to make it clear that the warning requirement applies only to OTC drugs intended for systemic absorption. The final rule also exempts OTC drugs intended to benefit the fetus or nursing infant and OTC drugs labeled exclusively for pediatric use. However, FDA is not including the phrase "drugs used internally," suggested by the comment, because it does not accurately convey the scope of the regulation. For example, some antacid products are not intended for systemic absorption, although they are taken internally. In addition, it is less confusing to the consumer when the warning is as direct and uncomplicated as possible.

10. One comment proposed that the following language precede the warning:

3. Several comments contended that the phrase "seek professional advice" shifts the burden of establishing the safety of OTC drugs to the consumer and to health professionals. The comments stated that this responsibility properly belongs with the drug manufacturers; one comment stated that it is also FDA's regulatory responsibility.

One comment proposed the following warning, arguing that it would require the manufacturers of OTC drugs to establish the drug's safety and would inform pregnant and nursing women about the inadequacy of scientific testing to establish the safety of OTC drugs for the developing fetus:

> A small number of drugs have been conclusively shown to a degree of scientific certainty to have adverse effects on the developing fetus. However, information of this type is not adequate to establish that this drug is safe for the developing fetus.

Another comment stated that the proposed warning placed full responsibility to discern the possible existence of harmful effects on the woman whose fetus is at risk and suggested the following warning to resolve this problem:

> If pregnant or nursing an infant, do not use this product without consulting a health professional.

The general pregnancy-nursing warning is not intended by the agency to shift responsibility for determining the product's safety to consumers or health professionals. OTC drugs generally are intended for self-treatment to relieve symptoms and to treat conditions that are not serious. Their use is a matter of choice by the individual consumer, and this is no less true if the consumer is a pregnant or nursing woman. A pregnant or nursing woman may, however, need special assistance in determining whether the need to relieve a particular symptom or to treat a particular condition justifies a potential risk to her child. Because of the acknowledged lack of specific information on the effects of most OTC drugs on developing fetuses or on breast-fed infants, the agency believes a woman would be best advised on whether to use a particular OTC drug by a knowledgeable health professional who is either familiar with her medical history or readily available to her and capable of assessing her situation with respect to a particular drug. Comments received from health professional associations indicate that these groups do not perceive that providing such advice would be a burden. Rather, these groups demonstrated a strong desire to provide such advice in the interest of possibly helping to prevent birth defects or harm to nursing infants.

The agency believes the first warning suggested above is not apt to be understood by the average consumer. Further, the message it is intended to convey can be more effectively obtained through consultation with a health professional. The second warning suggested above is similar to the agency's proposed general warning. However, this warning does not convey the message that it is not based on specific information about the particular drug, but applies to most other OTC drugs as well. The agency's warning, which begins with the phrase "as with any drug," makes it clear that this is a general warning (see discussion in comment 9 below). Therefore, the agency is not adopting either of the warnings suggested by the comments.

4. Several comments stated that the general warning should be preceded by the word "Caution" or "Warning" to call attention to it.

The agency agrees with the comments. Labeling directions in those monographs for OTC drugs specify that warning statements should appear under the heading "Warnings." The agency has chosen the word "Warning" as a signal word because it is more likely to attract the attention of consumers than the word "Caution." The language in this final rule has been revised to make it clear that the general warning must appear under the heading "Warning"—or "Warnings" (if it appears with additional warning statements).

5. Several comments stated that the language used by the agency in the proposed rule, which would require the warning for "all drugs that are systemically absorbed into the body," was too broad, ambiguous, and needed clarification. One comment requested that the agency require the warning for OTC drugs that are "orally administered and intended to be swallowed." Several other comments recommended the approach taken by the State of California in requiring a warning only for drugs that are "intended for systemic absorption." Another comment suggested that the regulation be clarified by stating that the term "systemically absorbed" does not apply to those drugs which are not dependent on systemic absorption for their claimed effect.

The agency agrees that the warning should apply only to OTC drug products intended for systemic absorption. Although the proposal stated that the warning would apply to all OTC drugs thar are systemically absorbed, the agency did not intend to include drugs absorbed in amounts sufficiently small as to have no pharmacological or toxicological significance. The final rule has been amended to clarify that drugs that are not intended for systemic absorption need not bear the warning. For example, OTC drugs used topically or mouthwashes regulated as OTC drugs, which due to their method of use are not intended to be systemically absorbed, will not be covered by the regulation. This approach is consistent with that of the California regulation, which applies only to drugs intended for systemic absorption into the human body.

FDA is also amending the regulation to exempt OTC drugs intended to benefit the fetus or nursing infant and OTC drugs labeled exclusively for pediatric use (see comment 6 below).

6. Various comments requested that the following drugs and cosmetics be exempted from the general warning: homeopathic drugs; pediatric oral electrolyte solutions; topical antibiotic, antimicrobial, and antifungal agents; drug products labeled specifically for pregnant or nursing women; drug products with active ingredients known to be safe for pregnant women or recommended for them, e.g., antacid products containing calcium carbonate; topical analgesics for normal or abraded skin or for use in the oral cavity; mouthwashes and dentifrices; anticavity dentifrices; antibacterial mouthwashes; products intended to benefit infants or children; insoluble or nonabsorbed antacids; bulk laxatives; nonabsorbed antidiarrheals; cough lozenges containing menthol and eucalyptol; topically acting nasal sprays; topical skin preparations, including creams, lotions, and shampoos; antimicrobial soap products; shampoos and other topical agents represented to prevent dandruff; suntan products represented to prevent or treat sunburn; antiperspirants; skin moisturizing and protectant products; certain antichapping products; otic drug products; ophthalmic drug products; drug products not intended for women of childbearing years, e.g., geriatric, pediatric, or postmenopausal drug products; or products labeled exclusively for use by men. One comment requested that the warning appear on vitamins, even though these products are dietary supplements, because a pregnant woman is more likely to add a vitamin to her daily intake than any other product. Another comment cited antacids, meclizine hydrochloride and cyclizine hydrochloride used as antiemetics, pyrantel pamoate used as an anthelmintic, and nighttime sleep-aids

accomplishing this goal is through a warning statement. As discussed in comments 5 and 6 above, this warning will not be required for all OTC drug products. Products not intended for systemic absorption need not bear the warning; certain other categories are also exempted. The agency believes that appropriate general warnings, such as this pregnancy-nursing warning, are an important means of educating the public about drug use. Furthermore, when consumers become familiar with the general pregnancy-nursing warning, because of their increased awareness they may more readily understand the significance of specific warnings that describe demonstrated risks of particular drugs to pregnant and nursing women.

15. One comment stated that the agency did not provide any studies to show that the general warning will actually cause women to consult with health professionals before using OTC drugs. The implication was that the warning should not, therefore, be required.

The agency acknowledges that studies of the kind described by the comment have not been provided. The provisions of the Federal Food, Drug, and Cosmetic Act that require labeling to bear adequate directions for use and adequate warnings against unsafe use are designed primarily to enable consumers to use products safely and effectively through reading the labeling. An implicit assumption underlying most OTC drug labeling regulations is that consumers, in pursuing their own best interests, will read labeling that is appropriately designed and worded. The agency does not believe that consumer behavior studies are necessary as a condition to requiring appropriate label warnings. This pregnancy-nursing warning requirement is intended to provide women an opportunity to use OTC drugs safely and effectively in appropriate situations. The agency believes that it is reasonable to expect that most pregnant and nursing women will heed the warning out of concern for themselves and their children.

16. One comment stated that FDA's general pregnancy warning for OTC drugs is inconsistent with the decision of the Bureau of Alcohol, Tobacco, and Firearms of the Treasury Department not to require a warning of this kind for alcoholic beverages. Noting the link between alcohol and the condition known as fetal alcohol syndrome, the comment stated that the fact that FDA is requiring a warning for OTC drugs and the Bureau of Alcohol, Tobacco, and Firearms is not requiring one for alcoholic beverages could provide consumers with the impression that alcohol is safe for use during pregnancy and nursing.

The agency appreciates the comment's concern, but points out that the regulation of the labeling of alcoholic beverages is outside its jurisdiction. FDA does not share the comment's belief that a warning on OTC drugs implies that alcohol is necessarily safe for use by pregnant or nursing women.

17. Several comments pointed out the difficulties posed by the requirement of an additional warning in view of limited labeling space, particularly on small packages. One comment stated, for example, that adding a warning will necessitate reduction of type size on many product labels. Another comment requested use of the word "lactating" for "nursing a baby" in the interest of shortening the warning, and another submitted a letter from the State of California authorizing use of the following shortened warning on small packages as "substantially similar" (Ref. 1): "Caution: if pregnant or nursing, seek professional assistance before using."

One comment requested that the agency permit the warning to be combined with other warnings where possible as a space-saving measure, for example, with the general warnings in § 330.1(g) (21 CFR 330.1(g)) regarding keeping all drugs out of the reach of children and regarding accidental overdose. Another comment suggested combining the warning with other warnings included in the OTC drug monographs and gave the following example, using a warning proposed for many OTC cough-cold drug products: "Persons with high fever or persistent cough, or with high blood pressure, diabetes, heart or thyroid disease, asthma, glaucoma, or difficulty in urination due to enlargement of the prostate gland, or persons pregnant or nursing should not use this preparation unless directed by a physician."

As noted in comment 13 above, the agency will require the full warning as a separate statement to insure that the intended message is conveyed uniformly to all women and to prevent consumer confusion. Alternative language will not be accepted. The word "lactating," suggested as an alternative for "nursing a baby," may not be understood by the average consumer, and in fact does not have precisely the same meaning, but means merely "secreting milk" (Ref. 2). The shortened warning does not include the phrase "As with any drug," which the agency considers important. (See comment 9 above.) Combining the warning with other warnings increases the chance that an essential part of it will be omitted or that the warning may be overlooked. For example "As with any drug" is omitted from the combination with the cough-cold warning above, and a physician is specified instead of a health professional. In addition, in this example of a combined warning, the reference to "persons pregnant or nursing" might all too easily be overlooked because the warning deals primarily with people who have diseases.

The agency recognizes the difficulties posed by limited labeling space. However, FDA concludes that the warning statements required are those that are scientifically documented, clinically significant, and important for the safe and effective use of the products by average consumers. Manufacturers may use various approaches to incorporate all required information, such as the use of package inserts.

18. Several comments argued that, based on the agency's traditional policy, cautionary labeling should be required only when a clearly defined risk supported by scientific data is evident. Noting the extensive nature of the OTC drug review and the immense amounts of data generated by it, the comments argued that the agency should require only specific warnings for particular OTC drugs as supported by the data included in the review. Some of the comments added that if a general warning is required it should be an interim measure, in place only until completion of the OTC drug review, at which time all necessary specific warnings will be included in the OTC drug final regulations. At that time, these comments stated, the general warning should be revoked for those product classes for which there is no demonstrated scientific need.

Over the past 20 to 25 years an increasing body of data has accumulated demonstrating that drugs that are systemically absorbed pass through the placenta to the fetus or reach the milk of a nursing mother. The agency discussed the scientific basis for the warning in the proposal (47 FR 39470). Although there is at present a lack of specific evidence to show that many of these drugs cause harm to the fetus or nursing infant, the agency believes that existing evidence establishing the potential for some OTC drugs to have harmful effects on the fetus or nursing infant warrants warning pregnant and nursing women to exercise caution and seek advice from a health

CAUTION: This drug has not been proven safe for babies before or after birth.

The comment argued that the warning statement proposed by the agency fails to convey the most essential message, i.e., that the risks of taking certain OTC drugs during pregnancy and nursing are either unknown or known to be dangerous. According to the comment, referral to a health professional does not indicate possible danger from use of a drug. The comment added that, for many teenagers and women with low income, consultations with health professionals may be neither feasible nor likely, and it is important to convey in the labeling in a clear and apparent manner dangers that may be associated with an OTC drug. The comment concluded that, in order for its preventive purpose to be fulfilled, any warning on OTC drugs must include a statement that the drug has not been proven safe and that the risks of using it are unknown.

Another comment stated that the proposed warning needed to be strengthened and suggested the following statement to precede the warning:

USAGE IN PREGNANCY: The effect of this drug on the fetus and/or the subsequent development of the exposed offspring is unknown.

The agency believes that additional language as proposed by the comments would not achieve the desired purpose. First of all, if available data show that an OTC drug poses a definite risk in pregnancy or nursing use, and is thus "known to be dangerous," a specific, stronger, warning will be included in the OTC monograph for that drug or required as part of an NDA. As for the general warning, the additional statements proposed by the comments would unnecessarily lengthen the warning by adding a redundant message. The agency does not agree that referral to a health professional does not indicate possible danger. Advising a pregnant or nursing woman to seek the advice of a health professional before using an OTC drug product should convey at once the message that the drug is not known to be unquestionably safe for a fetus or nursing infant. It is a matter of concern that some women are not likely to consult health professionals during pregnancy, but it is unlikely that the statements proposed by the comments would cause such women to seek advice in situations where they otherwise would not.

11. Arguing that the general warning would have no impact on the many women in this country who neither speak nor read English, one comment proposed the following symbol for use in labeling OTC drugs for which the risks to pregnant and nursing women, fetuses, and offspring are unknown:

and the following symbol for OTC drugs that are contraindicated for pregnant and nursing women:

The agency shares the comment's concern for reaching women who are not literate in English. As one means of reaching women who are nonliterate in English, but able to read another language, the regulations at 21 CFR 201.15(c) provide for labeling products in a language in addition to English. The agency believes that properly designed symbols could be used in addition to the written warning in the labeling to attract the attention of women who do not read English. The agency will not require these symbols, but will permit voluntary use of such symbols by manufacturers. Such symbols may not, however, be used as a substitute for the required warning; they may only be used in addition to it. The regulation has been amended accordingly.

12. One comment stated that the agency's proposed warning lacks grammatical preciseness and suggested the following warning:

If you are pregnant or nursing a baby, you should seek professional advice before using this or any other drug product.

The comment's suggested warning may be grammatically more precise than the agency's proposed warning. However, this warning does not convey the same emphasis as the agency's warning; nor does it reflect the decision to specify a health professional as the agency's warning does (see comment 2 above). The agency believes that the addition of the word "health" to the proposed warning, as follows, incorporates this change clearly without losing the emphasis of the original proposed warning:

As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

13. Several comments requested that the agency permit alternative language to that specified in its proposed general warning and noted that the California regulation permits use of "substantially similar" language to that included in the State's warning. One comment stated its intention to propose to manufacturers that they voluntarily add to the warning the words "consult your physician or pharmacist." Another comment requested that FDA allow the California warning as "substantially similar" so that manufacturers who use it for products marketed in California would be spared the expense of relabeling with the agency's warning. The agency believes that a standard warning appearing on OTC drug products covered by the regulation would insure that the intended message is conveyed uniformly to all women and would prevent consumer confusion. Therefore, the final rule will not provide for the use of substantially similar language or for the voluntary addition of words to the warning. As discussed in comment 23 below, manufacturers will be allowed up to 1 year from the date of publication of this final order to incorporate the agency's warning into product labeling. Thus, labels can be changed in the normal course of reordering, keeping expenses to a minimum both for those manufacturers who have incorporated the California warning into their labeling and for other manufacturers.

14. Noting that it has been the agency's consistent and frequently stated policy that warnings must be used judiciously or lose their effectiveness, several comments stated that if the general warning is used when it is not necessary, for example, on all systemically absorbed OTC drugs, it will dilute the impact of important cautionary statements. One comment contended that, if instituted, the general warning will join other phrases that are so ubiquitous they are not read.

The agency acknowledges that warnings must be used judiciously so that they do not lose their effectiveness. However, OTC drugs must be labeled with the information necessary to assure their safe and proper use by consumers. The agency believes that due to the questions that exist concerning the potential effects on fetuses and nursing infants of drugs intended for systemic absorption, it is necessary to alert pregnant and nursing women to the need to consult a health professional before taking such drugs. The agency also believes that the best means of

professional before using OTC drugs that are intended to be systemically absorbed. The agency's decision to require the warning on the labeling of OTC drugs that are "intended for systemic absorption" is discussed in comment 5 above. As set forth in § 201.63(b), the general warning will usually not be required for products labeled with specific warnings against use by pregnant women, such as specific warnings developed in the course of the OTC drug review that will be incorporated into the monographs for the appropriate drug classes. In addition, the general warning will not be required for certain OTC drug product classes. (See comment 6 above.) As the agency stated in the preamble to the proposal for a general warning (47 FR 39471), FDA 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. If it appears, based on these data, that the warning is no longer justified, the agency will propose to revoke the requirement.

19. One comment contended that the general warning undermines the very concept of an OTC drug as one that can be used in the treatment of illnesses and disorders that can be safely diagnosed and treated by the lay person. Another comment stated that to the extent the general warning would encourage physician consultation for every set of symptoms experienced, it could seriously disrupt the delicate balance that now exists in our nation's health care system. The comment cited experts in economics and health care regarding the effect a small shift in the population from self-treatment to physician consultation would have on the health care system in terms of disruption to the system itself and to the economy (Ref. 3).

The agency considers the general warning to be similar in concept to the warnings included in the OTC drug monographs that advise various target populations against using certain OTC drug products without consulting a physician. These warnings are not addressed to all users of OTC drugs, but are intended to prevent indiscriminate use of OTC drugs that might have harmful effects in particular target populations. More specifically, the goal of the general warning is to direct a pregnant or nursing woman to advice that will enable her to make an informed choice with respect to an OTC drug, balancing the benefit it would provide against the potential risk.

In FDA's opinion, the comment concerning potential disruption of the nation's health care system by the general warning is not an accurate assessment of the situation. Because the warning does not cover all categories of drugs, consultation for "every set of symptoms" is not being encouraged. The warning directs pregnant and nursing women to seek advice from a "health professional". While physicians are one of the sources most likely to be contacted, this contact need not be made through an office visit but may be handled by a telephone inquiry. Moreover, most pregnant or nursing women already are consulting with physicians or other health professionals regularly, as part of prenatal or well-baby checkups, so that a consultation on the use of an OTC drug may be an extension of an already established relationship between a patient and a health professional. The American Medical Association, as well as other professional organizations, has supported a warning requirement. The agency has estimated the economic impacts of the warning requirement and has concluded that the increased costs will not be substantial (see 47 FR 39471 and discussion of Executive Order 12291 and Regulatory Flexibility Act below).

20. One comment stated that the general warning would lead the consumer to conclude that products labeled with it have actually been found to be unsafe, resulting in needless avoidance of OTC drugs and pointless suffering of symptoms that might readily and safely be relieved by them. Another comment argued that the language of the proposed labeling is susceptible to misunderstanding by the lay person in that it misleadingly implies that OTC drugs are safe unless otherwise stated when taken under the instructions of a health professional.

The general warning advises the woman who is pregnant or nursing a baby to consult a health professional before using any product on which it appears. The object of the warning is for such a woman to obtain information that will assist her in making an informed decision with respect to the particular drug she is considering, based on a careful assessment of the potential risk involved. The warning neither states nor implies that the drug has actually been found to be unsafe for use by pregnant or nursing women. Nor does the warning imply that the drug has been shown to be safe for use by pregnant or nursing women when taken under the instructions of a health professional.

21. One comment stated that, in order to be immediately applicable to all OTC drugs, the general warning should be incorporated under Part 201 of Title 21 instead of Part 330. The comment added that Part 330 is only applicable to OTC drugs that are generally recognized as safe and effective, and a general warning incorporated in that part would therefore apply only to those drugs that are included in final OTC drug monographs.

The agency agrees with the comment. To ensure that when the general warning requirement becomes effective it will apply to all covered OTC drugs, the agency is placing the warning in Part 201 in new § 201.63 *Pregnancy-nursing warning.* A cross reference will be included in § 330.2 to clarify this location.

22. One comment noted the provision in paragraph (b) of the proposed regulation that a specific pregnancy-nursing warning that is required in a final OTC drug monograph supersedes the general warning, and asserted that it is difficult to interpret this provision without knowing the scope of the specific warning. The comment pointed out that, while a specific warning might indicate that a product should not be used during a defined period of pregnancy or nursing because of some expected or documented adverse reaction, it might be silent about other periods of time during pregnancy and nursing, and the general warning would therefore still be useful. The comment recommended adding to paragraph (b) language indicating that the specific and general warning must both be used as appropriate when required by FDA.

There may be instances in which a specific warning in an OTC drug monograph refers only to use during pregnancy, so that it would be appropriate to require a warning statement regarding use by a nursing woman as well as the specific pregnancy warning in the monograph. The warnings for some OTC drugs will continue to be established through NDA procedures. The agency concludes that the adjustments regarding the appropriate pregnancy-nursing warnings will be best handled in the final OTC drug monographs and in the individual NDA's. Accordingly, § 201.63(b) now states that the specific warning shall be used in place of the general warning, unless otherwise stated in the NDA or in the final OTC drug monograph.

23. Several comments addressed the agency's proposed effective date of the pregnancy-nursing warning regulation. One comment requested that the regulation become effective no sooner

than 18 months following its publication as a final regulation. The comment stated that, because most OTC drugs have a long shelf life, labels are ordered in large quantities, often in excess of 1 year's inventory, and that manufacturers should be permitted to exhaust their supply of old labels. The comment added that, because of the long lead times necessary to print labels, many manufacturers had reprinted their labeling in advance of the publication of the proposed rule, so that compliance with the rule would require a second reprinting. Another comment argued that a reasonable period before the effective date should be allowed for preparation, submission, and evaluation of petitions to exempt ingredients from the requirement. Several comments stated that it should be made clear that products labeled without the warning before the end of the 1-year grace period (or before the exhaustion of current supplies, if earlier) may continue to be distributed after the effective date of the regulation. One comment recommended that the warning be applicable to covered OTC drugs packaged after 1 year after publication of the final rule.

Although this final regulation will become effective upon publication, manufacturers will be permitted to defer labeling changes for a period of up to 1 year. The agency believes that a 12-month period is a reasonable period of time to enable manufacturers to relabel their products with a minimum disruption of the marketplace, thereby reducing economic loss and ensuring that consumers have continued access to safe and effective drug products. Therefore, the final rule will become effective on December 3, 1982; however, manufacturers of affected products may defer labeling changes until December 5, 1983. Twelve months is also a reasonable period of time for the preparation, submission, and evaluation of petitions to exempt products from the requirement. The agency has taken steps to expedite the evaluation process by a redelegation of authority.

After the 12-month period, OTC drug products subject to this regulation that are initially introduced or initially delivered for introduction into interstate commerce must comply with the labeling requirements. Because the warning required by this regulation does not address an immediate public health threat, supplies of drug products already shipped in interstate commerce before December 5, 1983 may continue to be sold without complying with the regulation. The agency encourages manufacturers to relabel their products to include this pregnancy-nursing warning at the earliest opportunity.

24. Several comments that were submitted in response to the agency's invitation for comments on the preemptive effect the FDA warning would have on the California and other similar State OTC drug labeling requirements supported FDA's view that a Federal pregnancy-nursing warning requirement would preempt State pregnancy-nursing warnings. The principal cases cited in the comments were *Jones* v. *Rath Packing Co.*, 430 U.S. 519 (1977), *Brookhaven Cable TV, Inc.* v. *Kelly*, 573 F. 2d 765 (2d Cir.), *cert. denied*, 441 U.S. 904 (1978), which were also cited by FDA in the proposal, and *Cosmetic, Toiletry, & Fragrance Ass'n, Inc.* v. *Minnesota*, 440 F. Supp. 1216 (D. Minn., 1977), *aff'd*, 575 F. 2d 1256 (8th Cir. 1978). Some comments took a more expansive view of the preemptive effects of the proposal, stating that all State OTC drug labeling requirements of any type either already were preempted by virtue of FDA's pervasive regulation of OTC drugs or could be preempted were FDA to issue a statement of its intention to preempt.

A comment submitted by the California Department of Health Services, however, opposed the statements in the proposal on the preemptive effects of the FDA warning on general legal and policy grounds. The California agency reiterated that the California requirement would become operational on November 18, 1982. A separate comment submitted by the same agency stated that FDA's proposed warning was substantially similar to California's requirement and would be acceptable in lieu of California's precise language.

The doctrine of Federal preemption is derived from Article VI of the Constitution, which provides that Federal law is the supreme law of the land, the "Laws of any State to the Contrary notwithstanding." Congress can preempt State laws relating to a particular subject matter, either expressly, by enacting Federal laws that prohibit State regulation of a particular area, or by implication, by enacting Federal laws that conflict with State laws or that reflect an intent to occupy a field of activity to the exclusion of even nonconflicting State law.

The cases cited above discuss the doctrine of implied preemption in a variety of factual situations. These cases and others describe the criteria used to determine whether State and Federal laws are at such odds that the State law must give way, or whether the Federal scheme created by Congress excludes all State regulation. The basic standard that has evolved is whether under the circumstances the State law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress in enacting the Federal law.

The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 et seq.) does not expressly preempt State activity relating to OTC drug labeling. Therefore, in determining whether FDA's pregnancy-nursing warning preempts California's warning, the doctrine of implied preemption must be applied. As stated in the proposed rule, a single national pregnancy-nursing warning with a specified text is necessary to ensure that OTC drugs are used safely and for their intended purposes (47 FR 39471). A single national warning will help ensure that consumers receive clear, unambiguous, and consistent information on the labeling of OTC drugs concerning use by pregnant or nursing women. Differing State requirements could conflict with the Federal warning, cause confusion to consumers, and otherwise weaken the Federal warning. FDA believes that differing State OTC drug pregnancy-nursing warning requirements would prevent accomplishment of the full purpose and objectives of the agency in issuing the regulation and that, under the doctrine of implied preemption, these State requirements are preempted by the regulation as a matter of law.

As noted in the proposal, the California warning allows for the use of pregnancy-nursing warnings that are "substantially similar" to the California requirement. In view of comments made by the California Department of Health Services, the FDA warning would appear to meet the California "substantially similar" exception. Therefore, under these circumstances, the issue appears to be academic: manufacturers who use the FDA warning would also be in compliance with the California requirement.

FDA shares the concerns of the comments that States may elect to regulate aspects of OTC drug labeling other than pregnancy-nursing warnings. The agency is concerned that a proliferation of such State requirements may weaken FDA's efforts to develop comprehensive national labeling and other requirements for OTC drugs. The current regulation, however, is intended to apply only to one aspect of OTC drug labeling: pregnancy-nursing warnings. FDA will monitor future State labeling requirements to determine whether further action is necessary.

The California warning requirement becomes effective on November 18, 1982. FDA regards the California requirement as preempted as of the date of publication of this regulation.

The following information had been placed on display at the Dockets Management Branch (HFA–305), Food and Drug Administration, Room 4–62, 5600 Fishers Lane, Rockville, MD 20857, and may be reviewed by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

References

1. Comment No. C0021, Docket No. 82N–0050, Dockets Management Branch.

2. Webster's Third New International Dictionary, G & C Merriam Co., 1976, s.v. "lactate."

3. Comment No. C00032, Docket No. 82N–0050, Dockets Management Branch.

B. The Agency's Final Conclusions on the Requirement of a General Label Warning Concerning the Use by Pregnant or Nursing Women of OTC Drugs Intended To Be Systemically Absorbed

Based on the available evidence and the comments received by the agency during the comment period, FDA is amending the labeling requirements for OTC drugs to include a warning for all OTC drugs intended for systemic absorption, unless exempted, as follows: "As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product."

FDA has changed the wording of the requirement so that it applies to OTC drug "labeling" rather than "labels' as stated in the proposal. This change reflects what was intended in the proposal and makes the new requirement consistent with other OTC drug warning requirements that have been developed during the OTC drug review.

The effective date of this final rule is December 3, 1982. In view of the November 18 effective date for the California regulation and the need for certainty concerning the labeling requirements that apply to OTC drugs, the agency finds that good cause exists for making this regulation effective immediately upon publication. By this early effective date, the agency intends to preempt any differing State requirements. Manufacturers marketing their products in States with differing requirements will be able to use the new FDA labeling without also being required to use the pregnancy-nursing warning labeling required by any State. Although the regulation will become effective on December 3, 1982, manufacturers of affected products will be permitted to defer labeling changes until December 5, 1983. Thereafter, covered OTC drugs initially introduced or initially delivered for introduction into interstate commerce will 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. Any request for additional time must state the reasons that the drug product's compliance with the labeling requirement cannot be achieved, steps that have been taken to achieve compliance, and when compliance is anticipated. Requests for additional time must be specifically granted by the agency; an extension of time will not be considered granted merely upon submission of a request. Manufacturers are therefore encouraged to submit requests for extensions of time far enough in advance to allow the agency time to act on them.

The agency has examined the regulatory impact and regulatory flexibility implications of the final regulations in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96–354). The proposed rule was estimated to generate one-time label modification costs of $3.8 to $5.7 million to marketers of affected OTC drugs and annual costs of $0.7 to $6 million for consultations between pregnant or nursing women and health professionals. Thus, first year impacts of the label warning were expected to total $4.5 to $11.7 million. These costs were found to be well below the thresholds for a major rule in Executive Order 12291; the exemptions of particular drug categories set forth in this document will further reduce these costs.

Similarly, the costs incurred by small businesses are estimated to be insufficient to warrant a regulatory flexibility analysis. 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, yet will be spread over so many of them, e.g., 47,000 drug stores, 24,000 obstetrician-gynecologist practices, that the average burden per entity appears trivial. Therefore, the agency certifies that the final rule does not have a significant economic impact on a substantial number of small entities.

The agency has determined under 21 CFR 25.24(d)(13) (proposed December 11, 1979; 44 FR 71742) that this action 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

21 CFR Part 5

Authority delegations (Government agencies), Organization and functions (Government agencies).

21 CFR Part 201

Drug labeling.

21 CFR Part 330

OTC drugs.

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, 372)) and 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), Parts 5, 201, and 330 are amended as follows:

PART 5—DELEGATIONS OF AUTHORITY AND ORGANIZATION

1. Part 5 is amended in § 5.31 by adding and reserving paragraph (c) and by adding new paragraph (d), to read as follows:

§ 5.31 Petitions under Part 10.

* * * * *

(c) [Reserved]

(d) The Director, NCDB, and the Director and Deputy Director of the Office of Drugs, NCDB, are authorized to grant or deny citizen petitions submitted under § 10.30 of this chapter requesting exemption from the general pregnancy-nursing warning for over-the-counter (OTC) drugs required under § 201.63 of the chapter.

PART 201—LABELING

2. Part 201 is amended by adding new § 201.63, to read as follows:

§ 201.63 Pregnancy-nursing warning.

(a) The labeling for all over-the-counter (OTC) drugs that are intended for systemic absorption, unless specifically exempted, shall contain a general warning under the heading *Warning* (or *Warnings* if it appears with additional warning statements) as

follows: "As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product." In addition to the written warning, a symbol that conveys the intent of the warning may be used in labeling.

(b) Where a specific warning relating to use during pregnancy or while nursing has been established for a particular drug product in a new drug application (NDA) or for a product covered by an OTC drug final monograph in Part 330 of this chapter, the specific warning shall be used in place of the warning in paragraph (a) of this section, unless otherwise stated in the NDA or in the final OTC drug monograph.

(c) The following OTC drugs are exempt from the provisions of paragraph (a) of this section: (1) Drugs that are intended to benefit the fetus or nursing infant during the period of pregnancy or nursing.

(2) Drugs that are labeled exclusively for pediatric use.

(d) The Food and Drug Administration will grant an exemption from paragraph (a) of this section where appropriate upon petition under the provisions of § 10.30 of this chapter. Decisions with respect to requests for exemptions shall be maintained in a permanent file for public review by the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

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

3. Part 330 is amended by adding new § 330.2, to read as follows:

§ 330.2 Pregnancy-nursing warning.

A pregnancy-nursing warning for OTC drugs is set forth under § 201.63 of this chapter.

Effective date: December 3, 1982.

(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); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).)

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Richard S. Schweiker,

Secretary of Health and Human Services.

Dated: November 18, 1982.

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