Federal Register

Wednesday
January 15, 1997

Part II

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 101, 111, and 310

Iron-Containing Supplements and Drugs: Label Warning Statements and Unit-Dose Packaging Requirements; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 101, 111, and 310

[Docket Nos. 91P–0186 and 93P–0306]

Iron-Containing Supplements and Drugs: Label Warning Statements and Unit-Dose Packaging Requirements

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing regulations to require label warning statements on products taken in solid oral dosage form to supplement the dietary intake of iron or to provide iron for therapeutic purposes, and unit dose packaging for iron-containing products that contain 30 milligrams (mg) or more of iron per dosage unit. FDA is taking these actions because of the large number of acute iron poisonings, including deaths, in children less than 6 years of age attributable to accidental overdoses of iron-containing products. FDA is temporarily exempting one form of elemental iron, carbonyl iron, from the packaging requirements of this final rule. The temporary exemption will automatically expire 1 year from the effective date of this final rule. If, during the temporary exemption period, FDA receives animal data that establish that carbonyl iron is significantly less toxic than at least one commonly used iron salt, FDA will consider permanently exempting carbonyl iron from the packaging requirements of this final rule.

DATES: The regulation is effective July 15, 1997. For compliance dates see §§ 111.50(b)(1) and (b)(2) and 310.518(b)(1) and (b)(2).

FOR FURTHER INFORMATION CONTACT: Linda S. Kahl, Center for Food Safety and Applied Nutrition (HFS–206), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3101.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of October 6, 1994 (59 FR 51030), FDA published a proposed rule (the iron proposal) to require label warning statements for products taken in solid oral dosage form to supplement the dietary intake of iron or to provide iron for therapeutic purposes. The proposal did not cover liquid or powder forms of iron and did not bear in any way on conventional foods containing naturally occurring or added iron. FDA also proposed regulations to require unit-dose packaging[1] for iron-containing products[2] that contain 30 mg or more of iron per dosage unit.[3]

FDA proposed these regulations because of the acute iron poisonings, including deaths, in children less than 6 years of age attributable to accidental overdoses of iron-containing products. The intent of these proposed regulations was to reduce the risk of accidental iron poisonings of young children by utilizing FDA's authority in conjunction with the existing requirements of the U.S. Consumer Product Safety Commission (CPSC) for child-resistant packaging for household substances. Since the publication of the iron proposal, FDA has obtained information from the American Association of Poison Control Centers (AAPCC) that indicates that accidental overdose of iron-containing products continues to be a problem in young children (Refs. 1 and 2). In 1994, at least 3,210 children under 5 years of age were treated in emergency rooms for exposure to iron-containing products, and two children are known to have died following such accidental overdose.

The iron proposal responded to citizen petitions submitted by AAPCC (the AAPCC petition) (Docket No. 91P–0186/CP1) (Ref. 3); the Attorneys General of 34 States, Commonwealths, and Territories (the AG petition) (Docket No. 93P–0306/CP1) (Ref. 4); and the Nonprescription Drug Manufacturers Association (the NDMA petition) (Docket No. 93P–0306/CP2) (Ref. 5). These petitions requested that FDA take action to ensure that products containing iron or iron salts do not pose a health hazard to young children and infants.

In the Federal Register of February 16, 1995 (60 FR 8989), in response to the Dietary Supplement Health and Education Act of 1994 (DSHEA), FDA published a supplemental proposed rule reflecting a shift in the agency's authority to establish regulations for dietary supplements.

[1] For the purposes of this document ''unit-dose packaging'' means a method of packaging a product into a nonreusable container designed to hold a single dosage intended for administration directly from that container, irrespective of whether the recommended dose is one or more than one of these units.

[2] Throughout this document, the term ''iron-containing products'' refers to solid oral dosage forms of both dietary supplement and drug products.

[3] In this document, the term ''dosage unit'' is used to denote the individual physical units of the iron-containing product such as tablets, capsules, caplets, or other physical forms, irrespective of whether one or more than one of these physical units comprises the recommended dose.

The agency received over 100 responses to the iron proposal and the supplemental proposal with one or more comments each from dietary supplement, drug, and packaging trade associations; consumers; Federal and State Government agencies; State attorneys general; poison control centers; the international community; health care providers; and dietary supplement and drug manufacturers and packers. Comments on the proposed requirement for a warning statement on iron-containing products were generally supportive, although many comments disagreed with the specifics of the agency's proposed text and requirements for prominence and placement. Several comments stated that firms already are including a voluntary warning statement on the label of iron-containing products. Comments on the proposed requirement for unit-dose packaging for iron-containing products that contain more than 30 mg of iron per dosage unit were divided on whether the proposed requirement was needed to ensure the safety of these products, and several comments challenged FDA's authority to establish such regulations.

II. Warning Statement for Iron-Containing Products

A. The Proposed Warning Statements

FDA proposed to require label warning statements on iron-containing dietary supplements and drug products. FDA tentatively concluded that the warning statements should incorporate elements from both the AG petition and the NDMA petition, as well as other elements that are designed to ensure that the statements perform their function.

FDA proposed two warning statements—one statement for use on iron-containing products packaged in unit-dose packaging and a slightly different statement for use on iron-containing products packaged in other than unit-dose packaging, e.g., a container with a child-resistant closure (CRC).

The proposed warning statement for use on iron-containing products packaged in unit-dose packaging reads as follows:

WARNING—Keep away from children. Keep in original package until each use. Contains iron, which can harm or cause death to a child. If a child accidentally swallows this product, call a doctor or poison control center immediately.

The proposed warning statement for use on iron-containing products packaged in other than unit-dose packaging reads as follows:

WARNING—Close tightly and keep away from children. Contains iron, which can harm or cause death to a child. If a child accidentally swallows this product, call a doctor or poison control center immediately.

Each of these proposed warning statements included a handling instruction (e.g., ''Close tightly and keep away from children''), an informational statement (''Contains iron, which can harm or cause death to a child''), a provisional statement (''If a child accidentally swallows this product''), and an instructional statement (''Call a doctor or poison control center immediately'').

B. Focus Group Findings

In order to determine the effectiveness of the proposed warning statements in alerting consumers to the danger that an accidental overdose of iron poses to young children, FDA contracted with Macro International, Inc., to test several different potential warning messages for iron-containing products in a total of eight focus groups. A notice of the availability of the focus group report was published in the Federal Register of May 23, 1995 (60 FR 27321). The notice invited the public to comment on this report. This focus group research supported the agency's tentative conclusion, explained in the iron proposal, that many adults are not aware of the danger that an accidental overdose of iron poses to young children.

In the focus groups, all participants were presented with an information piece detailing the danger that an accidental overdose of iron poses to young children. The information piece contained statistics that showed that accidental overdoses of iron-containing products are a leading cause of poisoning deaths in children under the age of 6, that illness can result from the ingestion of as little as 250 mg of iron in a child weighing 10 kilograms (kg) or less (22 pounds (lb) or less) and that ingestion of 600 mg of iron has been reported to be fatal to children weighing 10 kg or less. Half of the eight groups (''pre-evaluation groups'') received the information piece before they evaluated the warning messages, and the other half (''postevaluation groups'') received the information piece after they evaluated the warning messages. Participants in the postevaluation groups initially heard only a brief statement about the need for a standardized warning statement on iron-containing products and heard nothing about the nature of the hazard posed by an accidental overdose of iron-containing products or about the number of children who had died. The postevaluation groups subsequently were given the opportunity to reevaluate the warning messages after hearing the longer, more detailed information piece.

Participants in the postevaluation groups found warning messages such as ''iron can harm or cause death to a child'' to be unnecessarily severe, to the point that they considered the messages to be bizarre and unbelievable. The postevaluation groups tended to like a short generic message that did not identify a specific hazard. In contrast, participants in the pre-evaluation groups were more accepting of stronger statements of the hazard and tended to prefer statements that used the terms ''death'' or ''fatal''—the same statements that the postevaluation groups thought were unacceptably severe. When participants in the postevaluation groups were given information on the nature and magnitude of the hazard subsequent to their evaluation of the various statements, they evaluated the messages in the same way as did the pre-evaluation groups. Finally, when asked for their own suggestions, groups were virtually unanimous in recommending that the general public be better informed about the dangers of iron-containing products to young children.

Most participants in the research expressed the opinion that a good warning statement includes at least three elements: (1) A handling instruction that the product should be kept out of the reach of or away from children; (2) an informational statement that the product contains iron, and that excess or large doses of iron can harm or cause death to a child; and (3) an instructional statement to call a doctor or poison control center immediately in case of overdose. Participants' choices reflected their desire for a concise and unambiguous message with some degree of quantification about the amount of iron that must be ingested to be dangerous. Participants differed over the exact contents and order of the wording for a warning message but agreed that, regardless of what is eventually contained in the message, it should be worded as succinctly and efficiently as possible.

The focus group research also provided information on the language of the handling instruction in the warning statement. The focus group participants did not recognize a strong connection between the informational statement and the specific handling instruction that they were asked to evaluate and were not very positive toward statements such as ''Keep in original container'' and ''Close tightly.'' They were generally confused about how to interpret ''Keep in original package until each use'' with respect to blister-packaged products. Participants did not know whether the statement meant that they should keep the product in its original box or in its blister package. The ''Close tightly'' language was seen as too obvious, intended for products without child-resistant caps or related to product freshness.

The consumer research thus suggests that information about the nature and magnitude of the danger that accidental overdose of iron-containing products poses to young children is essential to the consumer's understanding of the warning statement. It also suggests that the first sentence of a warning statement is likely to influence a consumer's decision as to whether to continue reading the rest of the statement, and that package-specific handling instructions are more likely to confuse consumers than provide a measure of safety. Finally, it evidences that consumers will handle these products appropriately (i.e., by keeping the products in the original package or by keeping a bottle tightly closed) if they are provided with information on the nature and magnitude of the hazard.

C. Comments on the Utility and Scope of the Proposed Warning Statements

Several comments suggested that the warning statement should appear on all iron-containing dietary supplement and drug products rather than only on solid dosage forms. One comment from a State department of health services advised the agency that in September, 1993, a 5-year old child was hospitalized for a serious, though nonfatal, iron poisoning. The iron involved was in the form of a syrup prescribed for the victim. The comment stated that the department of health services did not know how many other children may have suffered injury as the result of ingesting liquid iron supplements.

The agency appreciates receiving the information about the accidental ingestion of a liquid iron-containing product. In the iron proposal, the agency stated that it was not aware of incidents of poisoning being caused by iron-containing products in liquid or powder form, and thus, it did not propose to cover liquid or powder forms of iron-containing products. The agency stated, however, that it would consider what regulatory action is appropriate to take with regard to iron-containing products in liquid or powder form if it becomes aware of information indicating that these products have caused or can cause poisonings in children.

The report of a single case in which a child was hospitalized for a serious, but not fatal, iron poisoning does not justify a change in the agency's tentative view concerning the need for a Federal regulation mandating labeling for liquid forms of iron-containing products. A Federal regulation is appropriate and necessary to protect the public health when safe use of a product cannot be ensured absent such a regulation. No regulation, however, will guarantee zero risk from products regulated by FDA. The existence of a single case report of a serious poisoning does not establish that illness or injury is likely to continue to occur. Rather, this single case report creates some ambiguity. It is not clear based on this report whether poisoning from liquid iron-containing products is an accident of low frequency or one that bears careful monitoring. Therefore, in this final rule, the agency is not including iron-containing products in liquid or powder form within the coverage of the labeling requirement. However, the agency would consider extending the coverage of the labeling and packaging requirements if it receives persuasive information that shows that accidental pediatric ingestion of liquid or powder iron-containing products is a problem, and that a warning statement or some special packaging requirement is necessary to ensure safe use of products that contain either of these forms of iron.

One comment questioned the usefulness of a warning statement because children cannot read. One comment stated that dietary supplement bottles are small, and there is other information competing for attention. Another comment stated that consumers have become accustomed to warning statements, implying that warning statements have become so common that their usefulness is diluted. A comment from a dietary supplement manufacturer stated that a warning statement on all products is not necessary and noted that the firm puts warning statements on products most likely to be attractive to children.

FDA does not agree that a warning statement is not useful because children cannot read. The warning statement is intended to be read by adults so that the adults will understand the nature and magnitude of the problem and the importance of keeping the product out of reach of children. FDA agrees that some dietary supplement and drug bottles are small, and that there is other information competing for attention. Nonetheless, the public health significance of accidental iron overdose compels that manufacturers overcome limitations in package size, if any there be. Therefore, FDA expects that industry will make appropriate revisions to labels on small product containers to provide appropriate space for the warning statement.

FDA does not agree that a warning statement on iron-containing products would be diluted because consumers have become accustomed to such statements. The focus group research shows that consumers want a strong warning on these products, and that consumers will heed the warning if provided with information describing the nature and magnitude of the hazard. FDA disagrees that a warning statement on all products is unnecessary or only useful on products that are attractive to children because the seriousness of the consequences of accidental overdose compel that all products bear the warning. Thus, FDA finds no merit in these comments.

D. Comments on the Text of the Proposed Warning Statement

FDA received a number of comments requesting modification of the wording of the proposed warning statements. The comments objected to the proposed warning statement in three main respects: (1) Failure to include the concept of ''overdose;'' (2) use of the term ''death;'' and (3) use of the phrase ''keep away from children.'' In response to these comments, FDA is revising the text of the wording statement. Table 1 of this document provides a side-by-side comparison of the text of the warning statement in the proposed and final rules.

TABLE 1—COMPARISON OF THE TEXT OF THE WARNING STATEMENT IN THE PROPOSED AND FINAL RULES [1]

Element of the Statement	Text of the Warning Statement in the Proposal	Text of the Warning Statement in the Final Rule
	Warning	Warning
Informational statement	Contains iron, which can harm or cause death to a child.	Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6.
Handling instruction	Keep away from children. Keep in original package until each use.[2].	
	[or]	
	Close tightly and keep away from children.[3]	Keep this product out of reach of children.
Provisional statement	If a child accidentally swallows this product * * *	In case of accidental overdose * * *.
Instructional statement	* * * call a doctor or poison control center immediately	* * * call a doctor or poison control center immediately.

[1] The order of the statements in this table is the order of the statements as they appear in the final regulation.
[2] For use on unit-dose packages.
[3] For use on non-unit packages.

1. Informational Statement

Several comments requested that the wording of the warning statement be changed to refer to ''large doses'' of iron or ''excessive consumption'' of iron. These comments maintained that the proposed wording of the warning statements implies that iron is toxic at any level of intake, even though iron is only dangerous when consumed in excess. Other comments stated that the warning statements as proposed may frighten and discourage appropriate use of iron-containing products. Several comments stated that the essence of the message should be that ''an overdose of iron could be harmful'' because this would be more consistent with FDA's stated objective for the warning statement, which is to ensure that products containing iron or iron salts do not pose a health hazard to young children and infants. Another comment cited § 330.1(g) (21 CFR 330.1(g)) as an example of a regulation that uses the term ''overdose.''

One comment stated that the proposed warning statements appear to be too general and are misleading to the consumer as to the actual danger. This comment stated that it would be sufficient to mention that the products could have the negative effects only in cases of overdose.

FDA has reevaluated the proposed wording of the warning statements in

response to these comments and concludes that the proposed wording implies that iron is inherently toxic and does not inform consumers about the actual nature of the hazard, i.e., an accidental overdose of an iron-containing product. Iron itself is an essential nutrient and is not harmful or fatal unless consumed in large quantities, as may occur in accidental overdoses. Therefore, a statement informing the consumer of the dangers of an accidental overdose is a more appropriate informational statement than those in the proposed warning statements.

The findings of the focus group research support this conclusion. The focus group participants' preferences reflect a desire for some degree of quantification about the amount of iron that must be ingested to be dangerous. The term ''overdose'' conveys a degree of quantification that makes it unlikely that consumers will mistakenly infer that usual or prescribed dosages of iron-containing products are dangerous. For these reasons, the agency is revising the informational statement to clarify that the hazard is from an accidental overdose of an iron-containing product.

Several comments requested that the agency not use the term ''death'' in the warning statement because it is unduly alarming and too harsh and may cause avoidance of iron supplementation by patient populations already at risk for low iron intake. One comment stated that ''death'' may frighten or inflame. Another comment stated that use of the word ''death'' is a departure from most FDA warnings and from warnings recommended in the citizen petitions.

Some comments suggested replacing the term ''death'' with the phrase ''harmful or fatal'' because this phrase conveys the danger of excessive iron while not unduly alarming the general population. A few comments noted that ''fatal'' is the term in the NDMA voluntary warning in use on many product labels. One comment cited the agency's regulations in 21 CFR 101.17(b)(1) (warnings for foods in self-pressurized containers with hydrocarbon and halocarbon propellants), 21 CFR 201.314 (warning statement on over-the-counter (OTC) drugs containing salicylates), and 21 CFR 201.319(b) (warning labels on OTC drugs containing water soluble gums) as precedent for use of the word ''fatal.''

FDA has reevaluated the use of the word ''death'' in this warning statement in light of these comments. FDA sees no reason to maintain the term ''death'' if, as the comments contend, it will unduly alarm consumers, because the term ''fatal'' means ''cause death'' (Webster's New Riverside University Dictionary, 2d ed., 1988). Therefore, FDA is revising the informational statement to remove the term ''death'' and add the term ''fatal.''

As a result of the changes that the agency is making in response to this and the preceding comment, the revised informational statement reads: ''Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6.''

The comments that requested that FDA clarify that the hazard was associated with an accidental overdose of iron-containing products, rather than consumption of iron-containing products under intended conditions of use, made clear that information about the nature and the magnitude of the danger that accidental overdose of iron-containing products poses to young children is essential to consumer understanding of the warning statement. This concept was reiterated by the consumers who participated in FDA's focus group research. Although participants in the consumer research were divided over the order of the elements (informational, handling, provisional, and instructional statements) of the warning statement, the consumer research supported a conclusion that the first sentence of a warning statement is likely to influence a consumer's decision as to whether to continue reading the rest of the statement. Therefore, in this final rule FDA is changing the sequence of the sentences in the warning statement so that the informational statement, which states the nature and magnitude of the danger that accidental overdose of iron-containing products poses to young children, precedes the handling instruction.

2. Handling Statement

FDA proposed two different handling instructions based on whether the iron-containing product was in a unit-dose package or a non-unit-dose package. FDA has reevaluated the need for, and utility of, different warning statements depending on the type of packaging. As already discussed, one of the findings of the focus group research was that package-specific handling instructions are more likely to confuse consumers than provide a measure of safety. Moreover, FDA believes that consumers will handle these products appropriately (i.e., by keeping the product in the original package or by keeping a bottle tightly closed) if they are provided with the information on the nature and magnitude of the hazard. Therefore, in this final rule the agency is removing the proposed package specific element of the handling instruction, which necessitated a different warning statement for products in unit-dose packaging than for products in other than unit-dose packaging. FDA is revising proposed § 101.17(e)(1) and proposed § 310.518(b) (now § 310.518(c)) (21 CFR 310.518(c))) to provide a single required warning statement for all iron-containing supplement and drug products in solid oral dosage form regardless of the type of packaging.

A few comments objected to the phrase ''Keep away from children'' and suggested as an alternative the use of the phrase ''Keep out of reach of children.'' These comments argued that it would be confusing and inappropriate to say ''Keep away * * *'' on iron-containing products intended for children, and that the term ''Keep out of reach * * *'' is a targeted, well understood statement that clearly conveys the message that children should not be given free access to the product.

FDA has reevaluated the proposed language of the handling statement ''Keep away from children'' and agrees that this statement may imply that the product is inherently toxic to children. Thus, the statement would be confusing to consumers when used on a bottle of tablets used by children. The statement ''Keep out of the reach of children'' states the proper handling of the product without implying that the product is inherently toxic under intended conditions of use. Therefore, FDA is revising the proposed text of the handling instruction to read ''Keep this product out of reach of children'' rather than ''Keep away from children.''

Some comments suggested that FDA should require two types of warning statements based on the level of iron in each dosage unit of the product. These comments suggested that products containing higher doses of iron (such as products that contain 30 mg or more of iron) be required to bear a warning statement, such as the industry voluntary warning statement, and that products containing lower doses of iron (such as multivitamin products) be required to bear a more general warning, such as: ''WARNING: Keep out of reach of children. In case of accidental overdose, contact a physician or Poison Control Center immediately.'' The comments asserted that products containing higher levels of iron are associated with a greater risk than multivitamin-mineral products. In contrast, most participants in the agency's consumer research felt that a single warning message should be used on all iron-containing products regardless of the iron dose.

Iron-containing products cause injury, including serious injury and death, when children gain uncontrolled access to them. As discussed in the iron proposal (59 FR 51030 at 51036), children's vitamins were the type of product ingested in the majority (45 of 80 or 56 percent) of the cases of nonfatal pediatric iron ingestion reported to the CPSC from 1986 to 1993. Further, the amount of iron that may produce symptoms of iron poisoning (i.e., 25 mg/kg of iron) for a 10 kg child would be provided by as few as 25 tablets containing 10 mg of iron each or approximately 14 tablets containing 18 mg of iron each (59 FR 50130 at 51041). Ten and eighteen mg of iron are the amounts typically contained in children's and adult multivitamin supplements with iron, respectively.

Ingestion of as little as 650 mg of iron has resulted in death (Ref. 6). This amount of iron would be supplied by 65 tablets containing 10 mg of iron or 37 tablets containing 18 mg of iron.

Based on these data, FDA concludes that the potential for poisoning exists with all iron-containing products in solid oral dosage form, regardless of the iron content, and that label warning statements are necessary on all these products. Therefore, the agency is making no changes in the warning statements in response to these comments.

3. Provisional Statement

As already discussed, several comments maintained that the proposed wording of the warning statements implies that iron is toxic at any level of intake, even though iron is only dangerous when consumed in excess.

The proposed provisional statement: ''If a child accidentally swallows this product, * * *'' implies that iron, rather than an overdose of iron, causes the harm. Therefore, FDA is revising the provisional statement to read: ''In case of accidental overdose, * * *'' to convey that it is an accidental overdose of iron that requires attention, rather than an accidental swallowing of any amount of iron.

4. Instructional Statement

Several comments supported FDA's instructional statement to ''call a doctor or poison control center immediately.'' These comments concurred with FDA that medical personnel are best equipped to determine the significance of the dose a child has ingested, and that, thus, the label should include this instruction.

One comment challenged FDA's proposed instructional statement to ''call a doctor'' and suggested that the instructional statement provided in the voluntary industry warning to ''seek professional assistance'' was more appropriate because it was already understood and accepted when used on OTC products. The comment expressed the opinion that use of the term ''call a doctor'' would limit the assistance options for consumers by suggesting that only a doctor could help them. The comment pointed out that consumers in FDA's focus groups did not express a strong opinion either in favor of, or in opposition to, the substitution of the phrase ''call a doctor'' for the common phrase used on OTC products to ''seek professional assistance.''

FDA realizes that a professional health care provider other than a doctor could provide assistance to a consumer in the event of accidental overdose. FDA disagrees, however, that the word ''professional'' accurately conveys the meaning ''medical.'' The information that the instructional statement must convey is that consumers should seek medical assistance in the event of accidental overdose. FDA sees no reason to replace the phrase ''call a doctor'' with the phrase ''seek medical assistance'' because consumers will understand that ''call a doctor'' implies that they should seek medical assistance, regardless of whether their customary health care provider is a doctor or other medical professional, and because ''call a doctor'' is a more succinct phrase than ''seek medical assistance.'' Therefore, FDA is retaining unchanged the proposed instructional statement that describes the appropriate action to take when a child accidentally consumes multiple tablets (''call a doctor or poison control center immediately'').

5. Comments on the Consumer Research

FDA received only a few comments on the agency's consumer research. These comments maintained that the consumer research showed that the agency's proposed warning statement was ineffective.

FDA agrees that the consumer research showed that the proposed wording of the warning statement was ineffective because the proposed warning statement did not provide adequate information about the nature and magnitude of the hazard and did not provide such information before the handling, provisional, and instructional elements of the warning statement. However, the revised language of the warning statement (see Table 1 and discussion below) adequately responds to all the concerns raised by the comments and the consumer research.

6. Revised Text of the Warning Statement

Based on the findings of the agency's focus group research, the comments on those findings, and the comments on the proposal, FDA is: (1) Revising the proposed warning statement by changing the sequence of the sentences so that the informational statement precedes the handling instruction; (2) modifying the informational statement so that it better describes the nature of the hazard; (3) eliminating the two different handling instructions based on whether the iron-containing product is in a unit-dose package or a non-unit-dose package; (4) modifying the handling instruction informing the consumer that children should not have free access to the product; and (5) including a reference to overdose in the provisional statement regarding the instruction on appropriate action in instances where a child accidentally consumes multiple tablets. FDA is taking this action to provide consumers with clear and appropriate information on the nature and magnitude of the hazard and to clarify that the hazard is not associated with use of iron-containing products under normal conditions. The revised warning statement reads:

WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

7. Other Comments on the Text of the Warning Statement

Several comments suggested that FDA adopt the language of the industry voluntary warning and stated that it is not apparent that FDA's proposed warning statements provide an additional consumer benefit over the voluntary NDMA warning statement. One comment expressed the opinion that FDA's consumer research supported the positions taken by NDMA regarding labeling of products containing iron and did not support the warning statements proposed by FDA. The NDMA voluntary warning statement reads as follows:

WARNING: Close tightly and keep out of reach of children. Contains iron, which can be harmful or fatal to children in large doses. In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately.

FDA has reviewed the language of the suggested NDMA voluntary warning statement in light of the focus group research. FDA agrees that none of the versions of warning statements tested in

the focus groups performed any better than the industry voluntary warning statement. However, none of the messages that were tested, including the industry voluntary warning, performed satisfactorily. The focus groups perceived the industry voluntary warning statement to be a standard kind of warning about product toxicity. Because such warnings are seen frequently on many different kinds of products and provide little new or useful information, they fail to command much consumer attention (Ref. 7). The consumer research did not show that the industry voluntary warning statement effectively conveys to consumers the nature of the hazard to young children presented by careless handling and storage of iron-containing products.

The agency's modified warning statement remedies the deficiencies identified by the consumer research in the tested warning statements, including the NDMA voluntary warning statement, in two ways. First, the agency's modified informational statement stresses the nature and magnitude of the hazard as one of accidental overdose. Second, by placing the informational statement before the handling instruction, the modified informational statement will command consumer attention. In contrast, the key concept of overdose appears at the end of the informational statement of the NDMA voluntary warning statement: ''Contains iron, which can be harmful or fatal to children in large doses,'' which diminishes its impact. In addition, the NDMA voluntary warning statement places the informational statement after the handling instruction: ''Close tightly and keep out of reach of children,'' where it will not command as much consumer attention. FDA therefore is not revising §§ 101.17 and 310.518 to codify the language of the NDMA voluntary warning statement.

Several comments provided variations of the agency's proposed warning statement or the voluntary NDMA warning statement or their own versions of a suitable warning statement. Examples of these proposed variations include:

WARNING: Keep all containers of iron-containing products away from children at all times. Reclose the child resistant cap completely *every time* after use. Keep in original package until each use. Iron-containing products can harm or cause death to a child. Should you suspect a child has accidentally swallowed an iron-containing product call a doctor or Poison Control Center immediately.

WARNING: Keep out of reach of children. Contains iron which can harm or be fatal to a child in large doses. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

FDA is not accepting any of these suggested statements. All of them share one or more fundamental problems with FDA's original proposed statement and the industry warning. Specifically, all of these warning statements begin with a handling instruction rather than an information statement. Some fail to incorporate the concept that it is an overdose of product that is harmful and would therefore lead to the misconception that iron is inherently harmful. Because all of the suggested warnings contain one or more fundamental problems, FDA has rejected these suggested variations.

One comment requested that FDA strengthen the language of the warning so that it is clearly understood that iron may kill.

FDA has considered this comment and determined that the new informational statement that it has developed (i.e., ''Accidental overdose of iron-containing products is a leading cause of fatal poisonings in children under 6.'') clearly articulates and strengthens the wording compared to the wording in the proposal. Therefore, FDA concludes that the concern expressed by this comment is fully addressed.

A comment from 13 State Attorneys General stated that if the term ''warning'' and the treatment-oriented information (i.e., the instructional statement) are included on the label in a prominent manner, then it is not necessary to include a reference to the harm that can come from ingestion of large doses or reference to the specific consequences. Other comments stressed the importance of the term ''WARNING'' and the importance of providing the instructional reference to contact a poison control center.

FDA agrees that the term ''WARNING'' and the instructional statement advising that a doctor or poison control center be contacted are necessary to alert the consumer to the potential consequences of use of the product and the need to take immediate action. The agency disagrees, however, that the informational statement is not necessary when the term ''WARNING'' and the instructional statement are present. An informational statement provides consumers with the information they need to readily understand the serious consequences that may result if the warning is not heeded. Therefore, FDA is taking no action in response to these comments.

One comment raised the concern that the proposed warning statement ignores other potential toxicities, such as that caused by an overdose of vitamin A, and suggested replacing the proposed iron-specific warning statement with a general cautionary statement in bold print. The suggested wording of this general cautionary statement was ''KEEP OUT OF REACH OF CHILDREN. IN CASE OF ACCIDENTAL OVERDOSE, CONTACT A PHYSICIAN OR POISON CONTROL CENTER IMMEDIATELY.''

The agency is not adopting the suggestion to replace the iron-specific warning statement with a general warning statement. The agency has a longstanding policy of limiting the use of warning statements so that such statements do not become so common that they are ignored. The label warning statement required on solid oral dosage forms of iron-containing products is a response to an immediate public health hazard of large proportions, the deaths and injuries of children who accidentally consumed large doses of these products. Therefore, the warning statement is specifically worded to alert consumers to the presence of iron and to the danger that accidental overdose of iron poses to young children.

One comment requested that the label warning statement specifically state that all medicines should be stored in original containers.

As already discussed, FDA has concluded, based on the results of consumer focus groups, that such specific handling instructions are more likely to confuse consumers than to provide an additional measure of safety. Participants in the focus groups were confused about how to interpret ''Keep in original package until use'' with respect to blister-packaged products. They did not know whether the statement meant that they should keep the product in its original box or in its blister package. Therefore, the agency is taking no action in response to this comment.

One comment questioned the need for a specific warning message where general messages already state that supplements and drugs should be kept out of reach of children, or the packaging itself is child-safe. This comment added that, given these facts, a specific warning message would appear to be more trade-restrictive than necessary.

Dietary supplements marketed in the United States are not required to bear a general warning statement on the label. Drug product labels are required to bear warnings that are adequate to protect consumers. As stated in the response to a previous comment, general warning statements fail to describe the nature of the specific and immediate hazard of

accidental iron overdose in young children. Therefore, FDA has determined that the warning statement specified in this final rule responds to the known safety concerns associated with solid dosage form of iron-containing products. The warning statement will apply to both domestically produced and imported iron-containing products.

In the Agreement on Technical Barriers to Trade from the Uruguay Round of the multilateral trade negotiations, ''technical regulation'' is defined as a:

> Document which lays down product characteristics or their related processes and production methods, including the applicable administrative provisions, with which compliance is mandatory. It may also include or deal exclusively with terminology, symbols, packaging, marking or labeling requirements as they apply to a product, process or production method.

Article 2.2 under Technical Regulations and Standards states: ''* * * technical regulations shall not be more trade-restrictive than necessary to fulfil a legitimate objective, taking account of risks non-fulfillment would create. Such legitimate objectives are, inter alia * * * protection of human health or safety.''

The warning statement for iron-containing products is necessary to protect the public health by helping to prevent accidental poisoning of young children. Therefore, the agency concludes that the warning statement is neither trade restrictive nor a trade barrier.

One comment from a physician recommended placing a ''Mr. Yuk'' sticker or emblem on each bottle of iron-containing tablets because this label device is recognized by children as an indication of poison.

FDA disagrees with this comment. The ''Mr. Yuk'' sticker alerts children that the product is not safe to eat. Iron-containing products, when consumed in appropriate quantities, are safe to eat. Placing a ''Mr. Yuk'' emblem on a product such as a bottle of children's vitamins would mean that the label would present an inconsistent message that could confuse children about what is safe to eat and what is not. Therefore, FDA is not taking the action suggested in this comment.

A few comments requested that the warning statement be accompanied by a pictograph to readily depict the hazard and to ensure that it will be readily understood by illiterate or non-English-speaking consumers.

FDA recognizes that a pictograph can be useful to convey some information to consumers. However, no data were submitted to show that the message could not be communicated without a pictograph. Given this fact, FDA finds no basis to require the use of a pictograph. However, FDA would have no objection if manufacturers, in conjunction with the required message, used a pictograph (such as a slash line through a picture of a child with an open mouth reaching for something) in addition to the required warning statement.

One comment requested that FDA reconsider its position and include the physical consequences and symptoms that may result from an iron overdose on the product package or container. This comment stated that adults will readily understand consequences and take effective action to eliminate the risk of an accidental child poisoning based on this information.

In the iron proposal (59 FR 51030 at 51044), FDA stated that it feared that setting out this information could lead parents to conclude erroneously that the child is not in danger because he or she does not exhibit one of the listed symptoms. No information was submitted in this comment that would cause the agency to reach a different conclusion. Listing of symptoms is irrelevant because they may not be exhibited by a child, and the most important information is that an overdose may be fatal. Moreover, as discussed above, FDA has revised the warning statement to include an informational sentence describing the nature of the hazard and providing adults with information to motivate them to eliminate the risk. Therefore, FDA is taking no action in response to this comment.

One comment requested that FDA require that the labeling of all iron-containing products display the exact name of the iron ingredient instead of the equivalent amount of iron present in the product. The comment added that this information is extremely important to the medical professionals and emergency personnel who treat iron poisonings.

No action is necessary in response to this comment because this information is already required on the label of food products containing iron under 21 CFR 101.4(b), which requires that the ''name of an ingredient must be a specific name and not a collective (generic) name.'' For dietary supplements containing iron, the ingredient list must include the source of the iron (e.g., ferrous sulfate). In addition, the amount of iron must also be provided in the nutrition labeling.

For drug products containing iron, section 502(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(e)) and 21 CFR 201.10 require a label statement of a drug's established name and the established name and quantity of the product's active ingredients.

E. Appearance of the Warning Statement on the Label of Iron-Containing Products

FDA proposed in §§ 101.17(e)(2) and 310.518(b)(3) to require that the warning statement:

> * * * appear prominently and conspicuously on the immediate container labeling in such a way that the warning is intact until all of the dosage units to which it applies are used. In cases where the immediate container is not the retail package, the warning statement shall also appear prominently and conspicuously on the principal display panel of the retail package. In addition, the warning statement shall appear on any labeling that contains warnings.

1. Comments on Requiring the Warning Statement to Appear Prominently and Conspicuously on the Immediate Container Labeling

Several comments on the labeling aspects of the proposed rule opposed or questioned the agency's tentative conclusion that the warning statement should be placed on the principal display panel (the PDP) in order to be prominent and conspicuous. Many of these comments noted that warnings on consumer products are generally located together on the side or back panel, and that consumers are accustomed to finding warning information in these places. One comment argued that placing the warning statement on the PDP negates the purpose of the information panel (the IP) because the traditional location for warning statements is the IP, and consumers may overlook a warning statement that is not in the expected location.

One of the comments elaborated upon warning placement by noting that warnings for self-pressurized containers and self-pressurized containers with halocarbons, hydrocarbon propellants, or chlorofluorocarbon propellants are not mandated to appear on the PDP (§ 101.17 (a), (b), and (c)). The regulations for foods containing aspartame also do not require that the warning statement for phenylketonurics appear on the PDP (21 CFR 172.804(e)(2)).

Most of the participants in the focus groups believed that the warning statement should go on the back of the product rather than the front of the product. The participants reasoned that the front of the product was used for marketing purposes, and consumers

were used to looking at the back of the product for warnings. The focus groups also felt that the ''clutter'' on the front of the product label might dilute the warning message. Similarly, several comments pointed out that the placement of the warning statement on the PDP would overcrowd an already space-limited PDP and result in a diluted warning message, especially if a smaller type size was used.

The agency recognizes that the PDP space is often very limited, and that warnings plus other required information could crowd the PDP. Therefore, in deciding how to provide for placement of the warning, the agency reflected on two basic questions: (1) What is the intent of this regulation? and (2) Can the intent be met by placing the warning statement on a panel other than the PDP?

The agency's purpose in this rulemaking is to inform consumers of the dangers to small children from an accidental overdose of a product that contains iron. Because of the serious, life-threatening consequences of such an overdose, FDA tentatively concluded that warning statements are most likely to be read when they are placed on the PDP. This tentative conclusion followed the precedent established in the regulations requiring warning statements on the PDP of protein products (§ 101.17(d)), whose incorrect use can also result in dire health consequences.

However, after evaluating the above comments and the results of the focus groups, the agency agrees that the warning statement does not need to be placed on the PDP to be effective in informing consumers of the hazard associated with overdose. The intent of the regulation can be met by placing the warning statement on the IP. The IP is the traditional location for warning statements. Information on the IP is readily accessible to consumers, particularly when it is presented in accordance with graphical requirements that enhance its prominence (see discussion below). Therefore, in this final rule the agency is revising proposed §§ 101.17(e) and 310.518(b) (now § 310.518(c)) to require that the warning statement be placed on the IP of the immediate container label.

Several of the comments remarked that the proposal did not require that the warning statement be placed on the PDP of the immediate container if the immediate container was not the retail package.

In the iron proposal (proposed §§ 101.17(e)(2) and 310.518(b)(3)), the agency proposed to require that: (1) The warning statement appear on the immediate container labeling; (2) it appear in such a way that the warning is intact until all of the dosage units to which it applies are used; and (3) if the immediate container is not the retail package, the warning statement must appear on the PDP of the retail package. FDA proposed these requirements as a single regulation that would apply to products in unit-dose packaging, in which the immediate container labeling does not have a PDP, as well as products in other than unit-dose packaging, in which the immediate container label does have a PDP. The comments that deduced that the proposed regulation did not require that the warning statement be placed on the PDP of the immediate container label if the immediate container was not the retail package indicate that the language of that single regulation did not clearly articulate the agency's intent, i.e., that the warning statement be on both the PDP of the retail package and the immediate container label, if there is one.

Therefore, FDA is revising §§ 101.17(e) and 310.518(b) (now § 310.518(c)) to clarify where the warning statement must be placed. Specifically, FDA is splitting the applicable provisions into several subparagraphs, which are described below. In addition, the agency has revised the regulations, as already discussed, to require that the warning statement appear on the IP rather than on the PDP.

In this final rule, §§ 101.17(e)(2)(i) and 310.518(c)(2)(i) require that the warning statement for iron-containing dietary supplements and drugs appear ''on the information panel of the immediate container label.'' Sections 101.17(e)(2)(ii) and 310.518(c)(2)(ii) provide that if iron-containing supplements and drugs are packaged in unit-dose packaging, and if the immediate container bears labeling,[4] but not a label, the warning statement must appear ''on the immediate container labeling.'' Sections 101.17(e)(3) and 310.518(c)(3) require that, where the immediate container is not the retail package, the warning statement for all iron-containing dietary supplements and drugs (i.e., regardless of the manner in which the product is packaged) appear ''prominently and conspicuously on the information panel of the retail package label.''

These requirements are necessary to ensure that the warning statement is seen by adults with responsibility for proper storage of the product. The placement of the warning statement on the retail package label will make it likely that the warning statement will be seen at the time the product is purchased to inform the purchaser of the product's potential to cause poisoning and of the need to store the product properly when it is brought into the house. However, under customary conditions of use, the retail container is frequently disposed of, and individuals other than the purchaser may use the product. Therefore, FDA is providing that the immediate container also bear the warning if it bears any labeling at all.

In this final rule, §§ 101.17(e)(4) and 310.518(c)(4) provide that the warning statement shall also appear on any labeling that contains warnings. These requirements are unchanged from the proposal, but they have been moved to a separate subparagraph as part of the overall reorganization of §§ 101.17(e)(2) and 310.518(c)(2).

2. Comments on Prominence Through Graphical Requirements

Several comments discussed the use of graphic requirements to set the warning statement apart from the rest of the label information. One comment pointed out that a warning statement can be made prominent and conspicuous by graphics such as surrounding the warning statement with a box, printing the warning statement in capital letters, printing the warning statement in bold typeface, and using contrasting graphics. Several comments recommended that the agency set requirements for graphics and discussed the need for type size specifications. Another comment suggested that FDA let the manufacturers determine the elements of prominence and conspicuousness needed to call attention to the warning statement. One comment cited the saccharin warning requirements as an example of a warning statement with specific contrasting graphic requirements.

Most of the participants in the focus groups agreed that the warning statement should be in a boxed area to separate it from other information and to call attention to the warning. Many participants also felt that printing the warning statement in a color that contrasts with the predominant color of the packaging was eye-catching. Other graphical options considered by the focus groups included using contrasting

[4] FDA recognizes that the package liner of a unit-dose package that bears no printed material is not labeling and would not need to bear the warning statement. Given the importance of the warning, FDA hopes that this fact will not cause manufacturers to cease putting printed material on the package liner.

print and background, different sizes of print, and bolding of the message.

In the iron proposal, FDA tentatively concluded that graphical requirements were not necessary to ensure that a warning statement placed on the PDP is prominent and conspicuous, because no data were supplied by the petitioners to support the use of graphics in the warning statement, and because the protein products regulation that the agency used as a precedent did not mandate specific graphical requirements. However, as discussed above, in this final rule the agency is moving the location of the warning statement from the PDP to the IP. The agency agrees that use of certain graphical requirements is an effective approach to ensuring that the warning statement is prominent and conspicuous. Moreover, a warning statement that appears on the IP, rather than on the PDP, needs graphical enhancements to ensure that it is prominent and conspicuous because the IP generally is more crowded than the PDP.

Based on the comments and the results of the consumer research, the agency agrees that a box enclosing the warning statement will set the warning statement apart from the rest of the label. FDA has used this mechanism with the nutrition label in response to the directive in the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) that the label be readily observable (Pub. L. 101–535, section 2(b)(1)(A) of the 1990 amendments). Therefore, the agency is requiring, in §§ 101.17(e)(5) and 310.518(c)(5), that the warning statement for iron-containing products be separated from other information by a box. Manufacturers may use other graphics, in addition to the box, if they choose to do so.

Three comments suggested that the cap or the PDP of the product bear a symbol or statement informing consumers that a new warning has been placed on the IP. For example, a prominent flag or a short statement saying ''See Iron Warning'' or ''See New Warning'' could be printed prominently on the PDP.

FDA has decided not to require a flag or statement alerting consumers to the new warning label. The comments and the results of the consumer research have convinced the agency that consumers are already in the habit of looking at the IP for important information such as warnings, and the box around the warning statement will draw attention to it.

3. Comments on the Placement of the Warning Statement on Unit-Dose Packaging.

To reinforce the message of the warning after the product is in the home, FDA proposed (proposed §§ 101.17(e)(2) and 310.518(b)(3) (now § 310.518(c)(3))) to require that the mandatory warning statement appear on the immediate container labeling in such a way that it is intact until all of the dosage units to which it applies are used. This provision would have effectively required that unit-dose packaged products bear the warning either directly on each individual cavity of the unit-dose packaging or on some section of the unit-dose packaging in such a way that separating an individual cavity would not destroy the warning label.

FDA received several comments on this proposed requirement. Comments stated that the proposal was unclear as to whether the warning could appear along the full length of a strip of unit-dose packaging, or whether it must appear in its entirety on each unit dose (e.g., on each tablet in a blister pack). Several comments stated it would be physically impossible to place the entire lengthy warning proposed by FDA on each unit dose and still meet the minimum type size requirements of 21 CFR 101.2(c) or the requirements of 21 CFR 101.15(a)(6) that the labeling be prominent and conspicuous. One comment stated that the label space available for each cavity of a multipack blister type unit-dose package is usually less than 1/2 inch by 1/2 inch and if, as proposed, a firm is required to print the entire warning statement, the print size would be so small that it would require magnification to read.

Several comments suggested that the individual units of a unit-dose package be permitted to bear an abbreviated warning statement that alerts consumers to the hazard and preventive measures, such as: (1) ''WARNING—Contains Iron. Keep Away From Children;'' and (2) ''WARNING: Keep in Original Package Until Each Use. Keep Away from Children.'' One comment also suggested that it would be helpful to manufacturers if FDA specified that the abbreviated warning could be printed on a strip or tab either above or below the individual cavities.

FDA is requiring that the warning must appear on the immediate container of the product because, as discussed in the proposal in this proceeding, reports of 2,000 poisonings in children over approximately 7 years provides strong evidence that many adults are not aware of the potential for serious harm posed by iron-containing products. The agency understands that printing the entire warning statement on each unit dose of an iron-containing product, while necessary to ensure that the warning statement remains intact until all of the individual dosage units to which it applied are used, would present problems in making the warning ''prominent and conspicuous.'' FDA disagrees, however, that placing an abbreviated warning statement on each cavity of a unit-dose package would be effective in alerting consumers to the risk that iron-containing products poses to young children because, as discussed above, FDA has concluded that an informational statement that clearly communicates the nature and magnitude of the hazard is essential for the warning statement to be effective. Therefore, the agency has reconsidered how to achieve the intent of the proposed regulations without requiring that the warning statement remain intact until all of the dosage units to which it applies are used.

FDA notes that, if for example, the full warning statement were placed on any side of a package (i.e., above, below, or on either side of individual cavities) of iron-containing products in unit-dose packaging that contains multiple, individual unit-dose packages that are connected without physical delineations (e.g. perforations) between the individual unit-dose packages, would allow the warning to remain intact until all of the dosage units to which it applies are used. Similarly, for iron-containing products in any unit-dose packaging (i.e., with or without physical delineations between the individual unit-dose packages), multiple copies of the warning statement across the immediate container label would increase the likelihood that at least one complete warning statement will remain intact until most of the individual units have been used. Although this second option could not ensure that the warning statement would remain intact until all of the dosage units to which it applies have been used, it is clear that options such as this can approach, if not fully achieve, the desired outcome of the proposed regulations.

Therefore, in this final rule, FDA is revising § 101.17(e)(2)(ii) to read:

> If a product is packaged in unit-dose packaging, and the immediate container bears labeling, the statements required by paragraph (e)(1) of this section shall appear prominently and conspicuously on the immediate container labeling in a way that maximizes the likelihood that the warning is intact until all of the dosage units to which it applies are used.

FDA also is revising § 310.518(c)(2)(i) to include a parallel requirement. The revised wording of these regulations makes clear that the manufacturer bears the responsibility to show diligence in designing labeling that will meet the agency's goal of informing consumers of the dangers to small children from an accidental overdose of a product that contains iron but provides the manufacturer with flexibility in determining how it will do so.

4. Comments Specific to Prescription Drug Products

One comment suggested that the warning statement on prescription drug products, if placed on a label, should contain a message to the pharmacist not to cover the warning with the prescription label so that the warning remains visible to the consumer.

FDA believes that the comment raises an important point. However, the agency expects that pharmacists will be aware that warnings should not be covered by anything, not by a price tag, a pharmacy label, or anything else. Therefore, FDA is taking no action in response to this comment.

III. Packaging of Iron-Containing Products

FDA also proposed to require unit-dose packaging of iron-containing drugs and dietary supplements with potencies of 30 mg or more of iron per dosage unit. FDA tentatively concluded that unit-dose packaging of such products would contribute in a significant way, over and above the protection provided by warning statements and CRP's, to reduce children's access to potentially fatal doses of iron.

A. FDA's Legal Authority to Establish Packaging Requirements for Iron-Containing Products

Several comments questioned FDA's legal authority to establish regulations requiring packaging of dietary supplements and drugs. The comments argued that Congress never authorized, and never intended, FDA to have such authority under the act. Moreover, these comments contended that even if FDA previously had such authority, Congress transferred this authority from the Secretary of Health, Education, and Welfare (HEW) (now Health and Human Services) to the CPSC under the Poison Prevention Packaging Act (PPPA) (15 U.S.C. 1471 *et seq.*) when that agency was created.

These comments argued that the language of both the PPPA and the act are clear in expressing Congress' intent that FDA was not granted authority over the packaging of foods or drugs to prevent childhood poisonings. These comments contended that through passage of the Consumer Product Safety Act (Pub. L. 92–573) (CPSA), Congress intended that CPSC have exclusive jurisdiction over packaging to limit child access to poisonous substances. These comments noted that in enacting the CPSA, Congress transferred from the Secretary of HEW to CPSC certain functions under the Federal Hazardous Substance Act (HSA) (15 U.S.C. 1261 *et seq.*) and the PPPA. In addition, in enacting the CPSA, Congress transferred the administrative and enforcement functions of the PPPA from the Secretary of HEW to CPSC (15 U.S.C. 2079).

FDA disagrees with the comments' interpretation of the provisions of the laws in question. As discussed in the iron proposal and the supplementary proposal, FDA's authority to require unit-dose packaging of iron-containing dietary supplements and drugs derives directly from sections 402(a)(4) and (g) and 501(a)(2)(A) and (a)(2)(B) of the act (21 U.S.C. 342(a)(4) and (g) and 21 U.S.C. 351(a)(2)(A) and (a)(2)(B)). The existence of other laws to which foods and drugs are subject does not limit FDA's authority to fulfill its responsibility under the act to help ensure that foods, including dietary supplements, and drugs are not injurious to health.

FDA disagrees with the comments that asserted that the agency has no authority over how food is packaged. This claim is belied by the act itself. Section 409 of the act (21 U.S.C. 348), although not applicable to this rulemaking, gives FDA authority to prescribe the conditions under which a food additive may be safely used, including packaging requirements deemed necessary to ensure the safety of such use (section 409(c)(1)(A) of the act). Section 721(b)(3) of the act (21 U.S.C. 379e(b)(3)) provides similar authority for color additives.

More relevant to this rulemaking, sections 402(a)(4) and 501(a)(2)(A) of the act provide that a food or a drug is adulterated if it has been packed under insanitary conditions whereby it may have been rendered injurious to health. Section 402(a)(4) has been read broadly (see *United States* v. *Nova Scotia Food Products, Corp.*, 568 F.2d 240, 247 (2d Cir. 1977)) as a grant of authority to ensure that foods are not packed in a manner, including process, package design, and packaging materials, that creates the possibility that the foods will cause harm under their reasonably foreseeable conditions of use. For example, parts 108, 113, and 114 (21 CFR parts 108, 113, and 114) address the steps necessary to ensure that the packaging of low acid and acidified foods does not permit the outgrowth of botulism, whose presence in the food would render the food injurious to health. Part 110 (21 CFR part 110) defines current good manufacturing practice (CGMP) for food generally, and in § 110.80(b)(13) requires that packaging be done in a manner that protects the food against contamination and that ensures that safe and suitable packaging materials are used (see also § 110.5(a)(2)). These provisions provide authority for the agency to require the use of packaging that is designed to help ensure that dietary supplements that contain 30 mg or more of iron per dosage unit are not rendered injurious to health. FDA is aware of no reason why section 501(a)(2)(A) of the act, which contains virtually the same words as section 402(a)(4) of the act, should not be read equally as broadly.

Section 501(a)(2)(B) of the act provides that a drug is adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to, or are not operated in conformity with, CGMP to ensure that such drug meets the requirements of the act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports or is represented to have. The agency has determined that, under section 501(a)(2)(B) of the act, manufacturers are responsible for preventing certain foreseeable misuse of a drug product. A drug product may be safe and effective as manufactured, but used in an unsafe and ineffective manner. As discussed earlier, data demonstrate that the current manner of holding products that contain 30 mg or more of iron per dosage unit until their use by the intended consumer fails to ensure that the products will be safe (see 59 FR 51030 at 51033). Large numbers of children are ingesting such products and suffering serious injuries and death. Because unit-dose packaging technology is available and can reduce the danger of iron poisoning, CGMP dictates that such packaging be used for products containing more than 30 mg of iron per dosage unit.

FDA concludes that unit-dose packaging will significantly reduce the likelihood of serious injuries to young children. FDA finds that this will be the case because unit-dose packaging will limit the number of unit doses that a child may consume once it gains access to the product, not because unit-dose packaging will make it any more

difficult to open the package.[5] The fewer the number of tablets or capsules the child consumes, the smaller the dose of iron the child will ingest. The smaller the dose, the lower the risk that the child will suffer serious injury. Thus, FDA's unit-dose packaging requirement will significantly limit the likelihood that iron products containing 30 mg or more of iron per dosage unit may be injurious to health because the requirement that the child open each package unit will limit the amount of iron that the child can consume (see 59 FR 51030 at 51049). No comments provided any information to the contrary.

The CPSA, HSA, and PPPA do not prevent FDA from acting. Foods and drugs are neither consumer products (see 15 U.S.C. 2052(a)(1)(H) and (a)(1)(I)) nor hazardous substances (see 15 U.S.C. 1261(f)(2)). Thus, the CPSA and HSA are not relevant to this rulemaking. FDA's action is also not precluded by the PPPA because FDA is not establishing a special packaging performance standard for products that contain 30 mg or more of iron per dosage unit. As explained above, nothing in FDA's regulation is designed to define or modify what constitutes child-resistance for iron-containing products. In this rulemaking, FDA is defining the requirements of CGMP for these products to help ensure that they are not packed under conditions whereby they may be rendered injurious to health (sections 402(a)(4), 402(g)(2), and 501(a)(2) of the act). Such action is fully within FDA's authority under the act. Therefore, FDA finds no merit to these comments.

Several comments argued that section 402(f) of the act makes clear that FDA has the burden of demonstrating that any particular dietary supplement is adulterated or unsafe under the conditions of use recommended or suggested in the labeling, or in the absence of such labeling, under ordinary conditions of use. These comments contended that FDA cannot merely assert that a dietary supplement is no longer safe because of the form of packaging in which it is sold. Moreover, these comments contended that FDA must find, for each product, that under the recommended conditions of use, the product presents a significant or unreasonable risk of illness or injury.

FDA disagrees with these comments. The DSHEA, which added section 402(f) to the act, did not exempt dietary supplements that are foods (that is, e.g., that are not intended to prevent, cure, treat, or mitigate a disease) from the food provisions of the act (see section 201(ff) of the act (21 U.S.C. 321(ff))). Under the act as amended by the DSHEA, a dietary supplement that is a food is adulterated if it is prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health (section 402(a)(4) of the act). This situation is the one that FDA is addressing in this rulemaking. Moreover, section 402(g)(2) of the act specifically authorizes FDA to adopt good manufacturing practice regulations for dietary supplements. FDA is relying on this provision of the act, as well as sections 402(a)(4) and 701(a) of the act (21 U.S.C. 371(a)), in adopting the unit-dose packaging requirement for dietary supplements that are foods that contain 30 mg or more of iron per dosage unit.

The agency received a comment from the CPSC requesting that FDA amend its proposed regulations to clarify that iron-containing products conforming to FDA's regulation are subject to compliance with certain regulations issued by the CPSC.

In light of the desire of both the CPSC and FDA to ensure that manufacturers of iron-containing products comply with both CPSC's regulations for child-resistant special packaging and FDA's CGMP regulations for iron-containing products, in this final rule FDA is revising proposed §§ 111.50 (21 CFR 111.50) and 310.518(a) to make clear that products subject to these regulations are also subject to 16 CFR parts 1700, 1701, and 1702.

B. Effectiveness of Unit-Dose Packaging

The agency received a number of comments bearing on the effectiveness of unit-dose packaging to limit pediatric access to products. The majority of these comments expressed support for FDA's tentative conclusion that unit-dose packaging will effectively limit pediatric access to products. A few comments challenged this tentative conclusion. None of these comments provided data to support their views.

One comment expressed the view that unit-dose packaging would not be effective because such packaging is subject to compromise. Another comment contended that the child-resistant effectiveness of child-resistant unit-dose packaging is not absolute (i.e., because the CPSC specification is based on the number of units that a child is able to access in a period of time) in contrast to the effectiveness of CRC type packaging (i.e., in which the CPSC regulations specify that opening the closure within a period of time constitutes failure of the system).

FDA recognizes that unit-dose packaging, like all packaging, can be compromised, and that packaging in and of itself cannot make a product safe. However, based on information available to the agency (Refs. 8 and 9) and as discussed in the iron proposal (59 FR 51030 at 51049), unit-dose packaging, even conventional unit-dose packaging, limits pediatric access to multiple dosage units of product. Moreover, the effectiveness of unit-dose packaging to limit pediatric access to product is not dependent on proper reclosure of the packaging. In contrast, the effectiveness of closure type packaging to limit pediatric access is dependent on proper reclosure of the container. If the closure is compromised (i.e., opened, improperly reclosed, or damaged), all of the contents of the package are readily available for ingestion. FDA's concern is limiting the possibility that the product will be injurious to health. Unit-dose packaging, even conventional unit-dose packaging, will help to accomplish this end by limiting the amount of iron that a child can consume in a short period of time. Therefore, FDA finds that the comments provide no basis for modifying its approach to the problem of acute iron poisoning in young children.

C. Access to Products by Certain Persons

The agency received several comments bearing on the potential difficulty that some elderly and handicapped persons may have in gaining access to products in unit-dose packaging. For example, one comment noted that unit-dose packaging may limit access to products by persons with rheumatoid arthritis. Two comments expressed their view that unit-dose packaging is inconvenient. Another comment expressed the view that for adults with limited dexterity, conventional unit-dose packaging is not difficult to open. None of these comments provided any data or information to support their views.

A comment from CPSC noted the difficulty in assessing the extent to which elderly or handicapped persons may be hampered in accessing product packaged in conventional unit-dose packaging, because there are no ''accessibility'' standards for conventional unit-dose packaging. In their comment, CPSC provided a report of their study examining the accessibility of child-resistant and conventional unit-dose packaging with seniors, aged 60 to 75 years old. CPSC

[5] Given CPSC's child resistance requirements, FDA's action will have no effect on how difficult it is to open the package.

reported that all four child-resistant unit-dose package types passed the senior accessibility test criteria. Moreover, all 100 seniors tested were able to open the conventional unit-dose packaging.

In the iron proposal and the supplemental proposal, FDA anticipated the practical effect of the combination of new §§ 111.50 and 310.518(a) and CPSC's child-resistant packaging regulations for iron-containing drugs and dietary supplements, 16 CFR 1700.14(a)(12) and (a)(13), respectively. Manufacturers and distributors of drugs and dietary supplements containing 30 mg or more of iron per dosage unit and containing 250 mg or more of total iron per package will have two options. One option will be to package their product in child-resistant unit-dose packaging (e.g., child-resistant blisters, child-resistant pouches, or other child-resistant packaging that accomplishes the objective of making a single dosage unit available at a time). A second option will be to package their product in conventional unit-dose packaging through exercising their right to an exemption to CPSC's special packaging regulations as required by the PPPA.

FDA notes that since publication of the iron proposal, CPSC has amended its regulations in 16 CFR part 1700 (60 FR 37710, July 21, 1995) for testing the child-resistant effectiveness of packaging to require a senior adult use effectiveness of not less than 90 percent for a senior adult test panel consisting of 100 adults aged 50 to 70 years old. The intent of these amendments is to increase the use of child-resistant packaging by making it easier for adults to use them properly.

It is not FDA's intent to circumvent the aim of the PPPA to allow access by elderly and handicapped persons who may be unable to use household substances packaged in child-resistant packaging. However, in the absence of information to the contrary, FDA has no basis to conclude that iron-containing products packaged in conventional unit-dose packaging will unduly limit elderly or handicapped persons' access to such products. Therefore, FDA concludes that unit-dose packaging does not limit access to product by elderly or handicapped persons.

D. False Sense of Security

Two comments expressed their view that unit-dose packaging should not be required for products containing 30 mg or more of iron per dosage unit because such a requirement will provide a false sense of security and will not limit pediatric access to product.

FDA recognizes that no single approach is adequate to ensure the safe use of iron-containing products. However, a combination of educational programs, label warning statements, and packaging measures can reasonably be expected to be effective in reducing significantly the incidence of poisonings. As discussed in the iron proposal, FDA is sponsoring educational efforts to better inform health care providers and consumers of the risks presented by iron-containing products, and FDA is requiring label warning statements to provide information to consumers about the hazards to young children presented by iron-containing products. These two approaches will effectively alert health care providers and consumers to the hazards presented by iron-containing products. Moreover, contrary to the comments' contention that these measures, including unit-dose packaging, will provide a false sense of security, these measures more likely will support a heightened sense of concern. Persons informed of the pediatric hazard presented by iron-containing products will take extra measures to ensure that the products are handled appropriately, including ensuring that the unit-dose packaging is not compromised in any way. Therefore, FDA finds no merit in these comments.

E. CRC is Adequate

One comment expressed the view that CRC packaging is adequate for limiting pediatric access to a toxic amount of iron.

As discussed in the iron proposal, based on information available to the agency, misuse of CRC type packaging is one contributing factor to pediatric iron poisonings. For example, in 21 of the 26 pediatric iron poisoning deaths in which the type of packaging was reported, the product was packaged in CRC type packaging (Ref. 10). In the absence of information indicating that misuse of closure type packaging will no longer occur and in light of the potentially fatal consequences when a young child gains access to a lethal amount of iron, FDA is not persuaded that CRC type packaging is adequate to ensure that these products are packaged under conditions that are not injurious to health.

Another comment expressed the view that: ''FDA's current effort to go beyond the CPSC requirement for child-resistant closures with respect to iron-containing supplements should be viewed as an anomaly and not as a failure of the CRC system.''

The agency disagrees with the view that this rulemaking is an anomaly. Rather, FDA considers that this rulemaking is a special measure in response to a special circumstance, i.e., the large number of acute iron poisonings, including death in children less than 6 years of age, attributable to accidental overdoses of iron-containing products. FDA will continue to exercise its legal authority to fulfill its legislative mandate to ensure that foods, including dietary supplements, and drugs are not injurious to health.

Nonetheless, FDA agrees that this rulemaking should not be viewed as a failure of the CRC system. The agency notes that it is establishing additional packaging requirements only for products that contain 30 mg or more of iron per dosage unit because of the irreversible and potentially fatal consequences presented by these higher dose iron-containing products rather than because of a view that the CRC system has failed in any way.

F. Difficulty in Making Child-Resistant Unit-Dose Packaging

One comment stated that it is more difficult to make a child-resistant unit-dose package that is accessible and acceptable to adults than to make a conventional unit-dose package. The comment further noted that this difficulty was the reason why so few highly toxic products in the market were packaged in a unit-dose package.

FDA is not establishing packaging performance standards, child-resistant or otherwise, for iron-containing products in this rulemaking. Such standards are the responsibility of the CPSC. Rather, FDA is establishing these packaging requirements as a matter of good manufacturing practice to ensure that dietary supplements and drugs that contain 30 mg or more of iron per dosage unit are not packed under conditions whereby they may be rendered injurious to health. Therefore, FDA finds that the comment is not relevant to this rulemaking.

G. Alternative Approaches

Two comments recommended that all iron-containing drugs and dietary supplements be packaged in child-resistant unit-dose packaging to ensure that they are inaccessible to young children.

As discussed in the proposal, information available to FDA demonstrates that the iron-containing products presenting the greatest hazard to young children are those that contain 30 mg or more iron per dosage unit. As discussed above, FDA has concluded, based on the available evidence, that label warning statements and educational efforts are adequate to

address the problems with products containing less than 30 mg of iron per dosage unit, and that label warning statements, educational efforts, and unit-dose packaging are necessary to ensure that products containing 30 mg or more of iron per dosage unit are packaged under conditions that are not injurious to health. Therefore, the agency is rejecting this recommendation.

One comment recommended that, rather than requiring unit-dose packaging of products containing 30 mg or more of iron per dosage unit, FDA should limit the total number of dosage units allowed per package based on the amount of iron that is toxic. No specific upper limit on the total iron to be allowed per container was provided in this comment.

FDA notes that CPSC has taken an approach similar to that suggested by the comment by requiring child-resistant special packaging if the packaging contains more than 250 mg of total iron. In the iron proposal, FDA discussed the amount of ingested iron that is lethal to young children (i.e., to a 10 kg child) and noted that an acute ingestion of 25 mg/kg of iron may produce symptoms of poisoning, 60 mg/kg of iron may develop into clinically significant iron poisoning, and 250 mg/kg of iron may well be lethal for a young child. Because the comment did not specify an upper limit on the total iron to be allowed in the container, FDA will address the comment based on an upper limit of 250 mg of iron (i.e., the amount of iron that may produce symptoms of poisoning).

If FDA were to limit the total number of dosage units in a container based on 250 mg of iron, then a manufacturer would be able to provide up to 8 dosage units of a product containing 30 mg of iron per dosage unit (240 mg of total iron), or 3 dosage units of a product containing 65 mg of iron per dosage unit (195 mg of total iron), per container to meet this requirement. Because CPSC's child-resistant special packaging requirement has a threshold of 250 mg of total iron, such products could be packaged in conventional packaging and still be in compliance with CPSC's child-resistant special packaging regulations.

Packaging eight or fewer dosage units in closure-type packaging is impractical and actually is approaching a requirement of a ''unit-dose bottle.'' Moreover, iron-containing products frequently contain 90 to 100 dosage units per bottle, and consumers who currently purchase iron-containing products in such quantities would be likely to continue this practice, thereby purchasing 12 bottles of an iron-containing product that contains 30 mg of iron per dosage unit or 30 bottles of an iron-containing product that contains 65 mg of iron per dosage unit. Because all of the vials perform the same function, consumers are likely to store them in one place. The existence of multiple vials, particularly if the products are packaged with conventional-type closures, means that a child who discovers and gains access to one vial is likely to gain access to multiple vials. Further, to minimize the space needed for storage, consumers who bring multiple vials into the home may choose to repackage the product into as few bottles as possible, thereby defeating the intent of the regulations. Therefore, FDA concludes that limiting the total number of dosage units per container based on the total amount of iron per container will not contribute in a significant way to achieving the agency's goal of limiting pediatric access to a toxic amount of iron by ensuring that iron-containing products are packaged in a manner that will not render the product injurious to health.

The agency received two comments recommending that opaque packaging material be required for unit-dose packaging to provide additional safeguards to limit pediatric access to product. These comments noted that opaque packaging is required for child-resistant unit-dose packaging in New Zealand and throughout the European Community.

FDA recognizes that opaque packaging is one approach that may reduce pediatric access to product. However, the comments did not provide the agency with sufficient information to enable FDA to conclude that opaque unit-dose packaging is necessary to ensure that iron-containing products are packaged under conditions that are not injurious to health. Given this fact, FDA finds no basis to require the use of opaque packaging at this time. However, FDA would have no objection if manufacturers used opaque unit-dose packaging.

One comment recommended that the proposed regulation be modified to provide flexibility to permit manufacturers to try alternative packaging designs that achieve the same effect of limiting pediatric access to multiple doses of iron-containing products.

In establishing unit-dose packaging requirements for iron-containing products that contain 30 mg or more of iron per dosage unit, one of the agency's goals is to avoid restrictive requirements that unnecessarily limit technological advances that accomplish the objective of reducing pediatric access to potentially lethal amounts of iron. Under new §§ 111.50 and 310.518, the term ''unit-dose packaging'' means any type of packaging that achieves the goal of allowing access to one dosage unit at a time. The agency wants to clarify that, for the purpose of this rulemaking, several types of packaging can satisfy the definition of ''unit-dose-packaging,'' including blister-type packaging, pouches, and dispensers that deliver one dosage unit at a time. Moreover, the agency anticipates that future advances in package design will result in other types of packaging that will also meet this definition. Therefore, because the regulations as proposed provide for flexibility in the type of packaging used to achieve unit-dose, FDA is taking no action in response to this comment.

One comment asked whether the agency intends to eliminate the practice of packaging iron-containing drug products that are sold by prescription in dispensing size bottles for use by pharmacists. These bottles contain up to 1,000 tablets each. The comment stated that few pharmacists are capable of dispensing these products in unit-dose packaging and added that unit-dose packaging is not necessary for products obtained by prescription. The latter point was made by a second comment as well.

FDA does intend that change be effected in the dispensing and packaging practices of some iron-containing products, including iron-containing drug products sold by prescription. Some of the iron-containing drug products that have caused injury to children have been sold by prescription, and the agency is concerned that their being sold by prescription has not caused adults to ensure that they are kept inaccessible to children. Consequently, the agency believes that unit-dose packaging is necessary for iron-containing prescription drug products that contain 30 mg or more of iron per dosage unit. Therefore, the requirement of this final rule to package iron-containing products that contain 30 mg or more of iron per dosage unit in unit-dose packaging will result, as an unintended consequence, in an elimination of the practice of packaging such iron-containing prescription drug products in dispensing size bottles for use by pharmacists.

One comment recommended that FDA revise the proposal to specify that all iron-containing tablets sold over-the-counter be sold with CRC's. The comment suggested that packaging for iron-containing drug products sold by prescription not be changed because

pharmacies will repackage the contents. The agency understands this latter suggestion to mean that packaging for products sold by prescription should not be subject to regulation since pharmacists will repackage tablets into pharmacy vials.

FDA has not revised the regulations in response to this comment. The distinction between unit-dose packaging and CRC is essential to the rule. As explained above, decisions about child-resistant packaging are the province of CPSC. FDA is requiring unit-dose packaging for products that provide 30 mg or more of iron per dosage unit to ensure that these products are not rendered injurious to health. Serious injuries, including death, are attributable to accidental overdose of products containing this amount of iron per unit. FDA's conclusion, reached on the basis of this rulemaking, is that unit-dose packaging will limit the number of dosage units to which a child will gain access and thereby significantly limit the risk of injury. As noted above, to limit the risk of serious injury and death, the agency intends that such iron-containing drug products sold by prescription will also be packaged in unit-dose packaging.

One comment suggested that FDA review its specifications for unit-dose packaging in a public forum that would include packaging suppliers and associations to determine whether CRC might enhance safety more than unit-dose packaging.

The agency declines to accept this suggestion. As stated previously, FDA is not setting specifications for unit-dose packaging or for CRC's. Such specifications are the responsibility of the CPSC. FDA has the responsibility to ensure that products are packed under conditions that will not render them injurious to health. Young children are gaining access to toxic and potentially fatal amounts of iron from iron-containing products packaged in CRC type packaging. It is for this reason that FDA has determined that unit-dose packaging of products containing 30 mg or more of iron per dosage unit is necessary to ensure that iron containing products are packaged under conditions that will not render them injurious to health.

One comment requested that FDA review its implementation plan with industry and with individual suppliers of unit-dose packaging to discuss issues relevant to materials and machinery, including adequate supply of packaging, cost, validation, stability, and compliance.

FDA declines this request because the agency's analysis of costs and benefits (see section VI. of this document) takes into account these aspects of compliance with the rule. Based on comments received from the packaging industry, the analysis has found that: (1) There is an adequate supply of packaging, and (2) not all firms will need to purchase packaging equipment because adequate capacity exists within the contract packaging industry. The analysis also takes into account other costs of complying with the requirements of this rule, such as administrative costs, storage and transportation costs, stability testing, and label redesign costs.

One comment stated that the proposal failed to address certain regulatory concerns including the impact of the rule on product submissions currently under review by the Center for Drug Evaluation and Research (CDER) and whether new product submissions will be required by this rule.

There currently are no submissions under review by CDER for iron-containing drug products. If future submissions are made to CDER for such products, FDA expects that they will reflect any change in the stability of the products that may be caused by a change to unit-dose packaging. The rule does not, however, in and of itself, establish separate submission requirements for iron-containing drug products.

IV. Formulation and Appearance of Iron-Containing Products

The AG petition recommended that FDA prohibit the manufacture and sale of adult formulations of iron-containing products that look like candy or contain a sweet outer coating. The AAPCC petition asked FDA to urge the industry to voluntarily reformulate iron-containing products containing 30 mg or more of iron per dosage unit to be in less attractive dosage units, specifically avoiding resemblance to popular candies. NDMA asked FDA to reject the recommendation of the AG petition because any provision for ''no candy-like appearance'' would not be practical and would be difficult to administer because of the subjective nature of assessing candy-like appearance. In the proposal, FDA requested comments on whether use of ''candy'' and ''colorful'' coatings on iron-containing products is hazardous to infants and young children because of the apparent attractiveness of the products. FDA stated that the agency would consider action in this regard if the information received presented an objective basis for additional steps that FDA could take to limit the appeal of iron-containing products to young children.

FDA received several comments on the appearance of iron-containing products. Most of these comments expressed an opinion that the resemblance of certain iron-containing products, including products formulated specifically for use by children, to candy or to cartoon characters contributed to the problem of children ingesting large quantities of these products. One comment argued that experience demonstrated that children are attracted to bright, shiny, colorful objects, and that, although children will swallow most objects, they will continue to seek out objects that taste good. This comment stated that changing the sweet coating would be an additional safeguard to ensure that children do not ingest large quantities of these supplements. Another comment asserted that a candy-like appearance and taste both needlessly attract an unsuspecting child and encourage ingestion of large quantities of these products by a child who may be unlikely to chew through the sugar coat.

Another comment, from a State department of health, reported that investigation of 5 of 17 deaths revealed evidence that children chewed or sucked on the iron tablets. A comment from a State consumer protection board expressed the opinion that hazardous products with a look-alike appearance to food products that are safe to consume present conflicting messages that can confuse children about what is safe to eat, and what is not. Some comments noted that current recommendations from industry trade organizations include a recommendation that products containing 30 mg or more of iron per dosage unit should not be manufactured to have a sweet, candy-like outer coating.

In the proposal, FDA stated its tentative view that it may not be possible to objectively measure the candy-like appearance of iron-containing products. None of the comments provided a basis for FDA to change this tentative view. Therefore, FDA is not adopting any requirements relating to the formulation or appearance of iron-containing products.

V. Forms of Iron That May Be Less Toxic

A. Introduction

Three basic types of elemental iron powders are marketed for use in foods: Reduced iron, electrolytic iron, and carbonyl iron. The terms ''reduced,'' ''electrolytic,'' and ''carbonyl'' refer to the production process by which the iron is manufactured rather than the

composition of the product. In the iron proposal, FDA specifically requested comments on the appropriateness of elemental iron as a source of iron in drugs and dietary supplements. FDA stated that the agency would consider exempting iron-containing products that incorporate elemental iron from any regulations that result from the rulemaking instituted by the iron proposal if the information received was persuasive in establishing that the use of elemental iron would substantially decrease the risk of pediatric poisoning while allowing for effective dietary iron supplementation.

B. Public Workshop

In the Federal Register of March 21, 1995 (60 FR 14918), FDA published a notice announcing a public workshop on the acute toxicity of elemental forms of iron relative to that of iron salts. The purpose of the workshop was to solicit scientific data and information about the acute toxicity of elemental forms of iron with regard to whether such forms are sufficiently safe in dietary supplement and drug products to warrant exemption from the special packaging and labeling requirements that FDA had proposed for products containing iron salts.

Specifically, the notice stated that the purposes of the workshop were to: (1) Identify data that objectively describe the acute toxicity of elemental iron; (2) identify the market uses of elemental iron and any adverse reaction reporting systems or processes used by manufacturers and vendors; (3) identify any data on acute, accidental exposure of children or adults to products containing elemental iron; (4) discuss a possible conceptual framework for evaluation of the effects of elemental forms of iron upon acute exposure; and (5) discuss the validity and limitations of acute toxicity data in experimental animals in predicting the risk in young children.

The notice also stated that specific topics that may be relevant and on which discussion was invited included: (1) Physiological factors that influence toxicity of elemental forms of iron, in comparison with those for iron salts; (2) the quality, results, and relevance of animal studies on acute toxicity of elemental iron and iron salts; (3) the quality and results of human studies for evaluating the effects of elemental iron; (4) factors influencing the validity of extrapolation of experimental animal data on acute toxicity of various forms of iron for predicting the risk in young children; and (5) current uses of elemental iron in dietary supplements and drugs and the data available for predicting the risk in young children.

The workshop was held on April 20, 1995, in Rockville, MD. Statements were made by representatives of several manufacturers of iron-containing products, a trade association, a physician, and a law firm representing a manufacturer of iron-containing products. Most of the participants who made oral presentations at the public meeting also submitted written comments containing details of the information discussed at the meeting.

The data and information submitted to FDA in response to the agency's request for data in the notice announcing the public workshop, as well as the data and information submitted to FDA in comments to the iron proposal and the supplementary proposal, are discussed below. Most of the data and information submitted to FDA addressed a single form of elemental iron, namely, carbonyl iron. However, one comment provided data and information on polysaccharide iron complex (PIC), a nonionic iron complex synthesized by the neutralization of a ferric chloride carbohydrate solution. Both forms of iron will be considered below.

C. Market Uses of Elemental Iron

FDA received one comment from a manufacturer who claimed to be the sole producer of carbonyl iron in the United States and who stated that the firm had introduced a pharmaceutical/food grade of carbonyl iron into the marketplace in 1988. The comment provided information on the manufacturers of multivitamins and stand-alone iron supplements who have purchased carbonyl iron for use in those products, brand names of products containing carbonyl iron, the potency (expressed in mg of iron) of the various products, and the distributors who sold the products. The manufacturer stated that carbonyl iron had been used in more than 2 billion tablets marketed by 15 manufacturers in 35 brands of iron-containing dietary supplement and drug products.

Another comment from an industry trade association stated that there are between 1,300 and 3,000 products containing iron, including carbonyl iron, on the market.

The agency received one comment from a manufacturer of PIC, which is approximately 46 percent iron by weight and is sold in solid oral dosage forms in both dietary supplement and drug products in doses ranging from 18 mg of iron to 150 mg of iron. The comment provided information on the brand names of ten products containing PIC in solid oral dosage form and the potency (expressed in mg of iron) of the various products. The comment stated that approximately 255.8 million brand-name tablets or capsules containing PIC had been produced during the period 1993 to 1994.

FDA appreciates receiving this information, which demonstrates that certain forms of elemental iron are used as ingredients in a range of iron-containing products that are marketed for use by children and adults. This information provides a context for evaluating the impact of an agency decision to exempt any form of elemental iron from any or all of the requirements of this final rule. At this time, it appears that between 1 percent and 3 percent of iron-containing products on the market contain carbonyl iron, and that between 0.3 percent and 0.8 percent of iron-containing products on the market contain PIC.

D. Comments on the Acute Toxicity in Animals of Elemental Iron Compared to That of Iron Salts

A comment from a professor of nutrition at a research university stated that there are apparently distinct advantages to the use of carbonyl iron as an alternative to the use of iron salts because of decreased toxicity at the doses that young children are likely to ingest. Another comment from a hematologist urged that carbonyl iron be exempted because of its low acute toxicity. Neither comment, however, supplied any data to support these statements.

Several comments asserted that administering iron as carbonyl iron for the prevention and treatment of iron deficiency provides a greater margin of safety than administering iron as iron salts. One comment conceded that available data are limited but stated that while the estimated lethal dose (LD) of ferrous sulfate in rats was 200 to 300 mg of iron (Fe) (expressed in terms of iron content) per kg body weight,[6] the LD of carbonyl iron in rats and guinea pigs was 50,000 to 60,000 mg Fe/kg body weight or more[7] (Ref. 11). This comment concluded that these studies in experimental animals suggested that carbonyl iron has a 100-to 200-fold

[6] The comment did not provide a literature citation for these data. The comment also did not specify whether the data reflected LD_{50} values (i.e., the dose that is fatal to 50 percent of the animals) or LD_{100} values (i.e., the dose that is fatal to 100 percent of the animals).

[7] The data cited are LD_{100} values. The comment also noted that the LD_0 value (i.e., the dose at which all animals survive) for rats and guinea pigs was 10,000 to 15,000 mg Fe/kg body weight.

greater safety margin than ferrous sulfate.

Another comment from a manufacturer of carbonyl iron included a report, commissioned by that manufacturer, on the toxicity of carbonyl iron powder. This report acknowledged that little data were provided to directly compare the toxicity of carbonyl iron with ionic forms of iron.

FDA has reviewed the animal toxicity data cited in the comments and other available animal toxicity data (Refs. 11 through 16). Most of the reported data were expressed as LD_{50} values (i.e., the dose that is fatal to 50 percent of the animals in the study), although some data were expressed as no-adverse-effect-level (NOAEL) values. For clarity and convenience, the LD_{50} data are summarized in Tables 2 through 4. However, in most cases the data reported in these tables do not reflect studies in which the toxicity of one form of iron was directly (i.e., concurrently) compared to that of other forms of iron.

TABLE 2.—MAGNITUDE OF DIFFERENCES IN STUDIES REPORTING MEDIAN LETHAL DOSE (LD_{50}) LEVELS: CARBONYL IRON VERSUS IRON SALTS [1]

Species	LD_{50} (mg Fe/kg body weight)		Approximate fold difference
	Carbonyl iron	Iron salt	
Rat	30,000	298 to 1,000 (ferrous sulfate)	30 to 90
		580 to >2,300 (ferrous fumarate)	13 to 50
Guinea pig	20,000	300 to 350 (ferrous sulfate)	57 to 67
		263 to 350 (ferrous gluconate)	57 to 76
		350 (ferric ammonium citrate)	57
		2,000 (ferrous carbonate)	10
Dog	>25,000	160 (ferrous sulfate)	156

[1] Data summarized from published literature (Refs. 11 through 16).

TABLE 3.—MAGNUITUDE OF DIFFERENCES IN ST REPORTING MEDIAN LETHAL DOSE (LD_{50}) LEVELS: DIFFERENCES AMONG VARIOUS IRON SALTS [1]

Species	Oral LD_{50} (mg Fe/kg body weight)		Approximate fold difference
Mouse	50–900 (ferrous sulfate)	3,800 (ferrous carbonate)	4 to 25
rat	298–1,000 (ferrous sulfate)	580–>2,300 (ferrous fumarate)	2 to 8
Guinea pig	263–350 (ferrous gluconate)	2,000 (ferrous carbonate)	6 to 8

[1] bid.

TABLE 4.—MEDIAN LETHAL DOSE (LD_{50}) LEVELS REPORTED FROM ORAL EXPOSURE: SPECIES DIFFERENCES [1]

Iron source	Animal species	Oral LD_{50} (mg Fe/kg body weight)	Approximate fold difference
Ferrous sulfate	mouse	150 to 900	1.1 to 10
	rat	298 to 1,000	
	guinea pig	300 to 350	
	rabbit	600 to 720	
	dog	160	
	cat	100	
Ferrous fumarate	mouse	516 to 1,100	2 to 4.5
	rat	580 to>2,300	
Ferrous gluconate	mouse	320 to 1,100	1.3 to 4.2
	rat	518 to 865	
	guinea pig	263 to 350	
	rabbit	463 to 580	
Ferrous carbonate	mouse	3,800	1.9
	guinea pig	2,000	
	rabbit	2,220	
Ferric ammonium citrate	mouse	1,000	2.9
	guinea pig	350	
	rabbit	560	
Carbonyl iron	rat	30,000	1.5
	guinea pig	20,000	
	dog	>25,000	

[1] Ibid.

The data in Tables 2 through 4 show that the reported LD_{50} values for carbonyl iron are at least an order of magnitude greater than those of iron salts. However, although these data do suggest that the acute oral toxicity of carbonyl iron is lower than that of iron salts, FDA does not agree that these data establish that carbonyl iron has a 100- to 200-fold greater safety margin than ferrous sulfate. As explained below, the variations in reported LD_{50} values within and between species, the variations in reported LD_{50} values between different ferrous salts within the same species, and the limited data directly comparing the toxicity of carbonyl iron to that of iron salts prevent the agency from reaching such a conclusion at this time.

In evaluating the LD_{50} data, the agency compared the magnitude of the differences in the reported LD_{50} values for iron salts and for carbonyl iron (see Table 2) to the magnitude of differences in reported LD_{50} values for various iron salts (see Table 3) and to the magnitude of inter-species differences in reported LD_{50} values (see Table 4). For example, the maximum interspecies variation in reported LD_{50} values for ferrous sulfate is tenfold (see Table 4), and the maximum intraspecies variation in reported LD_{50} values for the mouse is twenty-fivefold (see Table 3). By comparison, the difference in the reported LD_{50} values for carbonyl iron and ferrous sulfate ranges from a minimum of thirtyfold in the rat to a maximum of 156-fold in the dog (see Table 2). Thus, while in laboratory animals carbonyl iron appears to be among the least toxic of iron preparations, wide variations in toxicity have been reported among different iron salts and within animal species. In some cases, the magnitude of the difference in reported LD_{50} values between carbonyl iron and iron salts is no greater than the magnitude of difference in reported LD_{50} values between various iron salts or between animal species. Given the facts that most of the LD_{50} data were reported several decades ago, that most of the studies were not conducted as concurrent comparisons of LD_{50} values for carbonyl iron and for iron salts, and that current practice is to characterize LD_{50} values within an order of magnitude range, e.g., 5 to 50 mg/kg (Ref. 17), the agency finds that it is unable to conclude, despite the higher reported LD_{50} values for carbonyl iron, that carbonyl iron provides the quantitative margin of safety compared to iron salts claimed by the comment.

In general, extrapolation from data on acute iron toxicity obtained with experimental animal species to predict acute iron toxicity in humans is not straightforward because there are large inter-species differences in response to large loads of iron. Hoppe, et al. (Ref. 16) reviewed case reports of human deaths from ingestion of ferrous sulfate and found that the average fatal dose of iron in children under 2 years of age was approximately 180 mg/kg body weight. Thus, the LD of ferrous sulfate in children is comparable to the reported LD_{50} values in the dog (160 mg/kg) and in the cat (100 mg/kg) but considerably lower than the reported LD_{50} values for the rat (300 to 1,000 mg/kg) and rabbit (600 to 720 mg/kg). Consequently, because of this variation, in attempting to predict iron toxicity in human children based on data obtained in experimental animals, it would be imprudent to rely on data derived from a single animal species.

The available iron toxicity data primarily provide acute LD levels. Most of these LD_{50} values were reported several decades ago, and details of how the studies were conducted are not available in all cases. Moreover, there are a limited number of studies in which the LD for carbonyl iron was compared directly (i.e., in the same study) to that of iron salts. The known inherent variability and lack of precision in LD_{50} values reported from one study to another (Refs. 17 and 18) make the available data unreliable for use in predicting a margin of safety that carbonyl iron would provide compared to iron salts in the event of accidental overdose. Finally, given the number of pediatric exposures, and the number of moderate and major outcomes associated with those exposures, other measures of acute toxicity, such as clinical chemistry measurements, pathology of the liver and gastrointestinal tract, and clinical signs and symptoms or injuries (e.g., vomiting) are appropriate and necessary to determine whether the acute toxicity of elemental iron is less than that of iron salts.

In summary, the magnitude of the difference in reported LD_{50} values between various iron salts, the magnitude of the inter-species difference in reported LD_{50}, the limited data directly comparing the acute toxicity of carbonyl iron to that of other iron salts, and the lack of measures of acute toxicity other than death mean that the data submitted to support reduced toxicity of carbonyl iron are not suitable for quantitative comparisons of the acute toxicity of carbonyl iron to that of iron salts. Therefore, FDA concludes that the available animal toxicity data are consistent with, but do not establish, reduced toxicity for carbonyl iron relative to that of iron salts.

E. Comments on the Acute Toxicity in Humans of Elemental Iron Compared to the Acute Toxicity of Iron Salts

Several comments cited data from a study (Ref. 19) of human volunteers who, following ingestion of a single dose of 6,000 mg of carbonyl iron (approximately 84 mg Fe/kg body weight), experienced only mild diarrhea without cramp. The comments compared these data to medical guidelines (Refs. 20 and 21) that recommend hospitalization and close observation in response to the acute ingestion of iron salts in doses of 60 mg Fe/kg body weight. One comment from a medical researcher stated that in a study conducted in his own laboratory four adult human volunteers took oral doses of 10,000 mg of carbonyl iron (approximately 140 mg Fe/kg body weight) ''without distress'' (Ref. 22). The same comment cited a published report in which a single adult human volunteer swallowed 10,000 mg of carbonyl iron ''without deleterious effects'' (Ref. 23).

The studies described by these comments are small and include so few subjects that they do not, in and of themselves, provide reliable data concerning the toxicity of carbonyl iron. As discussed below, other comments pointed that the incidence of side effects in volunteers who ingested carbonyl iron during a randomized, double-blind study designed to evaluate the bioavailability of carbonyl iron (Ref. 24) was similar to that of volunteers who ingested ferrous sulfate. However, these reports are consistent with other data that suggest that carbonyl iron may be less toxic than iron salts and could be corroborated by larger studies that are specifically designed to evaluate the safety and side effects of using carbonyl iron.

One comment from a physician noted that the reported side effects (such as diarrhea, heartburn, headache, epigastric discomfort, nausea, and abdominal cramps) from comparable doses of carbonyl iron and ferrous sulfate in a randomized, double-blind study designed to evaluate the bioavailability of carbonyl iron (Ref. 24) were similar. This comment stated that it did not make sense that similar side effects with similar dose amounts would translate to total impunity of carbonyl iron from toxic effects.

FDA agrees that reports that side effects in persons who consumed carbonyl iron as a dietary supplement or for therapeutic purposes are similar to side effects in persons who consumed

iron salts for the same purposes signify a need for caution in evaluating the limited evidence concerning the toxicity of carbonyl iron and do not translate to ''total impunity'' from toxic effects. However, these reports of similar side effects in a therapeutic setting do not necessarily mean that the physiological factors leading to injuries with accidental overdose will be the same for carbonyl iron and iron salts. Moreover, the body's response to an accidental overdose may be different from the body's response to a therapeutic dose.

The requirements of this final rule are intended to help prevent the acute iron poisonings, including deaths, in children less than 6 years of age attributable to accidental overdose of iron-containing products. Although the reports of side effects in adults who consume carbonyl iron as a dietary supplement or for therapeutic purposes raise potential questions of safety, available data are inadequate to document that these observations are necessarily predictive of acute poisoning in young children from accidental overdose of carbonyl iron. These reports, by themselves, do not provide a sufficient basis to determine that carbonyl iron is as toxic as iron salts.

F. Comments Supplying Data on Acute, Accidental Exposure of Children to Products Containing Elemental Iron

One comment from a manufacturer of carbonyl iron stated that the firm had reviewed its files and found no complaints regarding toxicity associated with its carbonyl iron products since the introduction of its pharmaceutical/food grade carbonyl iron product in 1988. The comment also stated that its carbonyl iron had been used in over 2 billion tablets marketed in 35 brands of iron-containing dietary supplement and drug products by 15 manufacturers, and that the firm was unaware of any adverse toxic effects associated with use of those products.

The same comment included data obtained from the Toxic Exposure Surveillance System (TESS) of the AAPCC. The comment summarized exposures, outcomes, symptoms, age group, and iron potency for carbonyl iron exposures and all iron exposures during the period 1989 to 1994. Table 5 compares the exposures and outcomes as summarized in the comment.

TABLE 5.—REPORTED EXPOSURES[1] FOR IRON-CONTAINING VITAMINS AND MINERALS

	Carbonyl iron (Number)	All iron (Number)
Reported exposures:		
Accidental ..	2,635	120,086
Intentional ..	58	9,854
Adverse Reaction	18	863
Unknown/other	3	15
Total	2,714	130,818
Outcomes of Exposures:[2]		
No effect[3] ..	1,081	54,837
Minor effect[4]	173	17,218
Moderate effect[5]	4	2,012
Major effect[6]	0	177
Death	0	35

[1] The data in the table reflect the data supplied in comment 150 to the iron proposal under Docket No 93P–0306.

[2] See ref. 25 of this document.

[3] The patient developed no signs or symptoms as a result of the exposure.

[4] The patient developed some signs or symptoms as a result of the exposure but they were minimally bothersome, and generally resolved rapidly with no residual disability or disfigurement.

[5] The patient developed signs or symptoms as a result of the exposure which were more pronounced, more prolonged, or more of a systemic nature than minor symptoms. Usually, some form of treatment is indicated.

[6] The patient exhibited signs or symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement.

One comment from a manufacturer of iron-containing supplements stated that the firm had not received a single report of adverse side effects or toxicity in 3 years of marketing products containing carbonyl iron.[8] Another manufacturer of iron-containing supplements submitted data on the composition of two of its multivitamin products containing 10 mg or 18 mg of carbonyl iron and summaries of 133 adverse event reports for the product containing 18 mg of carbonyl iron. This comment also provided data from a poison control center on 10 reports of exposures to a product containing carbonyl iron. Reported exposures ranged from approximately 160 mg of iron (approximately 11 mg Fe/kg) to approximately 1,975 mg of iron (unknown mg Fe/kg). The most common outcome was vomiting. The 2½-year old child who ingested 1,975 mg of carbonyl iron was treated with Ipecac and experienced headache, dizziness, hot flashes, and vomited twice. No further followup was reported for these exposures.

A trade association commented that it had conducted a confidential adverse experience survey of its members and stated that the results supported a conclusion that products containing carbonyl iron are safe and do not require special packaging and labeling. The survey results included data from members who marketed a total of seven products containing carbonyl iron. The survey found a total of 15 instances in which children aged 17 months to 4 years old ingested doses of various products in the range of 180 to 2,000 mg of iron. Only 3 of these 15 exposures resulted in minor outcomes, and none of these exposures was associated with moderate outcomes, major outcomes, or death.

One comment from a physician noted that much of the argument for exempting carbonyl iron from the requirements of the proposal was the data on accidental exposure. This comment pointed out that the absence of clinically significant effects associated with accidental exposure to carbonyl iron may reflect the fact that most of the preparations with carbonyl iron are multivitamin preparations containing lower dosages of iron compared to the preparations that have been associated with clinically significant effects. The comment expressed the opinion that there was a reasonable possibility that if carbonyl iron was exempted from the requirements of the proposal and categorized as a ''nontoxic substance,'' then experience with sublethal toxic exposure would accumulate rapidly. The author of the comment stated that he was ''not in favor of such uncontrolled experimentation.'' The comment further expressed the opinion that it would be prudent to wait until accidental exposure numerically equalled accidental exposure to other forms of iron, or at least to ferrous sulfate, when expressed in dose equivalent amounts.

FDA has evaluated the submitted information on acute, accidental exposure to products containing elemental iron. The summary information from poison control centers showed that: (1) Accidental overdose of carbonyl iron-containing products has resulted in 173 minor outcomes; (2) accidental overdose of carbonyl iron-containing products has resulted in four moderate outcomes; and (3) there were no reported exposures to carbonyl iron-

[8] The comment did not provide information about the nature of its reporting system, e.g., whether the system was systematic.

containing products that resulted in major outcomes or death. However, the total number of accidental exposures to carbonyl iron is likely to be underestimated because information on the form of iron ingested was not always reported. For example, information on the form of iron ingested is not available in the original report or followup investigation for 8 of the 37 fatalities described in the iron proposal. This likely underestimation of total accidental exposures raises the question of whether the total number of minor, moderate, major, and fatal outcomes resulting from accidental overdose of carbonyl iron is also underestimated. Moreover, the lack of reported major outcomes or death associated with accidental overdose of products known to contain carbonyl iron may be a reflection of both the small number of total exposures to date and the insensitivity of passive reporting systems.

Furthermore, information supplied in the comments concerning the identity and potency of currently available products that contain carbonyl iron indicate that only 7 of 32 brand-name products contained high doses of carbonyl iron (i.e., greater than or equal to 30 mg of iron).[9] This paucity of products containing high-potency carbonyl iron amplifies the agency's concern that the lack of reported major outcomes or death associated with accidental overdose of products known to contain carbonyl iron may be a function of the small number of total exposures to high doses of carbonyl iron (i.e., 30 mg or more of iron) rather than the low toxicity of the substance. Therefore, these data, while encouraging, must be interpreted with caution and do not by themselves provide a sufficient basis for a conclusion of reduced toxicity for carbonyl iron compared to iron salts.

Although FDA agrees that it would be prudent to defer a decision on whether carbonyl iron is sufficiently less toxic than iron salts to merit an exemption from the requirements of this final rule until the amount of data available concerning accidental human exposures to carbonyl iron approaches that for iron salts, the agency realizes that, given the current market share of carbonyl iron-containing products of 1 to 3 percent (see section V.C. of this document), such a delay is not practicable. Moreover, such a delay would not be in the interest of the public health if carbonyl iron is in fact significantly less toxic than iron salts. On the other hand, FDA recognizes that there may be some basis for the concern expressed by the comment. Therefore, although FDA is not adopting the suggestion that the agency wait until exposure to carbonyl iron numerically equals exposure to other forms of iron or to ferrous sulfate before reaching a decision on whether to exempt carbonyl iron from the requirements of this final rule, FDA will remain cautious in evaluating the existing information concerning the toxicity of carbonyl iron.

G. Comparison of Animal Toxicity Data to Human Toxicity Data

One comment from a physician stated that it may be premature to make a regulatory decision about an exemption for carbonyl iron because the toxicity data were based almost entirely on animal studies. Another comment, in a report commissioned by a manufacturer of carbonyl iron, attempted to relate data on the toxicity in humans of carbonyl iron and iron salts to animal toxicity data. First, the report stated that adult humans who were acutely exposed to a single dose of 6,000 mg (i.e., approximately 100 mg/kg) of carbonyl iron experienced no toxicity other than diarrhea,[10] and that adult humans who were acutely exposed to carbonyl iron at doses ranging from 100 to 10,000 mg (i.e., 1.4 to 142 mg/kg)[11] experienced diverse side effects (such as gastrointestinal tract disturbances and headache) but no fatality. Moreover, the report noted that the effects of exposures to carbonyl iron in rats and guinea pigs in this dose range (i.e., 1.4 to 140 mg/kg) also were not life-threatening.[12]

Second, the report noted that as the ingested dose in cases of accidental overdose of iron salts in children approached and exceeded 200 mg/kg, the likelihood of death seemed to markedly increase. By comparison, the report noted that LD_{50} values in rats for iron salts are similar (300 to 1,000 mg/kg, expressed in terms of iron content)[13] to the dose that is frequently fatal in children. The report presented the similarity in lack of toxicity for carbonyl iron in adult humans and experimental animals, and the similarity in toxicity for iron salts in children and experimental animals, as evidence that the data on experimental animals can be extrapolated to humans.

FDA has considered the reasoning in the comments that the available toxicity data in experimental animals can be extrapolated to predict whether carbonyl iron has reduced acute toxicity in children compared to that of iron salts. The available animal toxicity data qualitatively imply reduced toxicity for carbonyl iron compared to iron salts, but the data are not suited for quantitative comparisons, even among animal species. As discussed above, the quantitative toxicity information available consists for the most part of LD_{50} values calculated from nonconcurrent acute toxicity studies with few animals and few doses, and such values are neither precise nor easily compared from one study to another. The fact that most of the available LD_{50} values are derived from studies conducted more than 30 years ago, for which there are only brief details of the experimental methods and test material identity (including comparability to currently marketed forms of iron), further makes comparison of the LD_{50} values difficult. Moreover, the available information does not contain data regarding levels at which there are no toxic effects, and such data are most directly relevant to this rulemaking considering that the issue at hand is one of acute toxicity. Finally, adults are less sensitive to toxic effects than young children, and most of the available data relates to adult humans and animals. Therefore, FDA is unable to say that the available toxicity data can be extrapolated to reliably predict reduced acute toxicity in children of carbonyl iron compared to that of iron salts.

H. Comments on the Bioavailability of Elemental Iron for Dietary Iron Supplementation

FDA requested information with respect to the bioavailability of carbonyl iron to determine whether carbonyl iron provides desirable iron nutrition to those who need iron supplementation. FDA requested this information because it anticipated that an exemption for carbonyl iron from any packaging or labeling requirements in the final regulations would likely result in a shift in product formulations to replace iron salts with carbonyl iron.

Several comments asserted that administering iron as carbonyl iron is as effective for the prevention and treatment of iron deficiency as

[9] Of these seven brand-name products, three contained 50 mg iron, two contained 65 mg iron, and two contained 150 mg iron.

[10] The report did not provide a direct literature citation for this statement, but likely was referring to the study by Sacks and Crosby (Ref. 19) cited by another comment.

[11] The report did not provide a direct literature citation for this statement, but included the studies by Gordeuk et al. (Refs. 22 and 26) in a bibliography.

[12] The report did not provide a direct literature citation for this statement, but included the study by Shelanski (Ref. 11) in a bibliography.

[13] The report did not provide a direct literature citation for this statement, but LD_{50} values for iron salts are reported in this range in Ref. 12.

administering iron as iron salts. In support of this assertion, one comment from a medical researcher described several published studies in female blood donors comparing the bioavailability of carbonyl iron with that of ferrous sulfate. These published studies were also cited in several other comments.

In one study (Ref. 27) comparing treatment with carbonyl iron or ferrous sulfate with use of a placebo, the treatment was intended to replace, within 56 days, the amount (approximately 200 mg) of iron removed by phlebotomy from 75 menstruating women who were regular blood donors. Blood donor volunteers were assigned randomly to one of three treatment groups: (1) High dose (600 mg) carbonyl iron; (2) standard dose (300 mg) ferrous sulfate (equivalent to 60 mg of iron); or (3) placebo. Each treatment was administered three times daily for 1 week immediately after blood donation.

The reported incidence of side effects was similar in both groups receiving sources of iron, even though the dose of iron was 10 times higher in the group receiving carbonyl iron than in the group receiving ferrous sulfate. The authors of the study estimated total iron absorption of 95 percent, 76 percent, and 64 percent of the iron lost through blood donation by the carbonyl iron group, the ferrous sulfate group, and the placebo group, respectively, and concluded that short-term ingestion of carbonyl iron was an efficacious means of replacing iron lost through blood donation.

A followup study (Ref. 28) of the effects of short-term iron supplementation in female blood donors was designed to develop a regimen that would minimize side effects of iron supplementation compared with a placebo while replacing iron losses in all, or nearly all, donors. In this study, a treatment regimen of 100 mg of carbonyl iron given once daily at bedtime was compared with that of a placebo.[14] The conclusions of the study were that, overall, enough iron was absorbed to replace that lost at donation in 85 percent of the carbonyl iron group but in only 29 percent of the placebo group.

In another study (Ref. 24) comparing the bioavailability of carbonyl iron with that of ferrous sulfate, 49 female blood donors with iron deficiency were treated with equal doses (100 mg) of iron once daily at bedtime over a 12-week period. The doses were administered either as carbonyl iron (100 mg) or as ferrous sulfate (500 mg (equivalent to 100 mg of iron)) in a randomized, double-blind fashion. The incidence of side effects was similar in the two groups, and measures of iron status did not differ significantly throughout the study. The conclusions of the study were that estimates of net changes in total body iron suggested that the overall bioavailability of carbonyl iron is approximately 70 percent that of ferrous sulfate.

The comment also included a description of a long-term 2½-year unpublished study, in which repeated courses of 56 days of low dose (100 mg) carbonyl iron were given to one group of volunteers once daily at bedtime after each blood donation. Two other groups of volunteers were permitted unsupervised self-supplementation, with volunteers in one group donating blood in an unscheduled manner, and volunteers in the second group donating blood on a schedule identical to that of the carbonyl iron group. The conclusion of the study was that the prevalence of iron deficiency in the group receiving carbonyl iron declined substantially compared with its prevalence in the two groups who were permitted unsupervised self-supplementation. In addition, the researchers concluded that increases in measures of iron status in the subjects in the carbonyl iron group over the 30-month course of the study suggested that their iron balance was improved during the course of the study.

At the public workshop, the researcher who conducted this study pointed out that the population of subjects in this study was chosen because it is a population in which individuals are iron deficient but not for any pathological reason. The researcher categorized this population as having ''probably the highest demands on iron absorption that are seen in normal populations.''

However, the comment described as ''unexplained'' a published study (Ref. 29) conducted in Sweden in which a preparation of carbonyl iron radiolabeled with a particular isotope (^{55}Fe) was used to fortify wheat flour in which the naturally occurring iron of the wheat was extrinsically labeled with another radioisotope of iron (^{59}Fe). Doubly labeled wheat rolls prepared from this flour were served with different meals to human adult volunteers. The authors of the study claimed that the ratio of absorbed ^{55}Fe to absorbed ^{59}Fe is a direct measure of the carbonyl iron that joins the nonheme pool and is made potentially available for absorption. The authors stated that the relative bioavailability of carbonyl iron was unexpectedly low and varied from 5 percent to 20 percent when the iron fortified wheat rolls were served with different meals. The authors also stated that factors such as the baking process or the addition of ascorbic acid did not change the relative bioavailability. The authors of the study concluded that this low and variable bioavailability of carbonyl iron in humans makes it necessary to reconsider the rationale of using elemental iron powders for the fortification of foods for human consumption.

FDA recognizes the apparent discrepancy between the conclusions of the multiple studies conducted in female blood donors and the conclusions of the study conducted in human volunteers who consumed wheat rolls fortified with radiolabeled carbonyl iron. Iron bioavailability is a complex issue affected by a number of factors, including the state of physiological iron stores and state of health, in addition to the iron source and the food matrix and meal composition in which the iron is ingested. In fact, the agency has stated its intent to publish a notice of proposed rulemaking concerning the bioavailability of iron used to fortify food (final rules for the iron fortification of flour and bread, (43 FR 38575 at 38576, August 29, 1978) and (46 FR 43413, August 28, 1981)). At this time, FDA believes that following through with such a proposal makes more sense than trying to resolve such a complex issue as part of this rulemaking. Accordingly, FDA is not requiring demonstrated bioavailability as a precondition in its determination on whether to exempt carbonyl iron from the labeling requirements, packaging requirements, or both requirements of this final rule.

I. Comments on Physiological Factors That Influence Toxicity of Elemental Forms of Iron

Several comments cited animal studies (Ref. 30) that were undertaken to characterize the mechanism by which elemental iron such as carbonyl iron is absorbed (i.e., by conversion of non-ionized to ionized iron in the presence of hydrochloric acid in the stomach) and postulated that the toxicity associated with ionized iron is minimized by both the rate of gastric acid production and the equilibrium between formation of ionized iron and the discharge of the ionized iron from the stomach to the intestine. In light of

[14] The treatment was administered at bedtime to allow the carbonyl iron to remain in the gastrointestinal tract for as long as possible without food that would buffer the stomach acid required for solubilization of the elemental iron to the ferrous form.

this postulated mechanism, some of these comments also discussed the importance of the particle size of carbonyl iron in the conversion process, i.e., the smaller the particle size, the faster the conversion process.[15] A representative of a U.S. manufacturer of carbonyl iron stated that the firm manufactures approximately 40 different grades of carbonyl iron, but only 1 grade is designated for pharmaceutical or nutritional use. The average particle size of this grade is approximately 5 to 6 microns.

FDA agrees that the particle size of carbonyl iron is a key factor in the conversion of the carbonyl iron to the ionized form, and that carbonyl iron with a small particle size will be ionized (and thus absorbed) more rapidly than carbonyl iron with a large particle size. FDA also recognizes that this conversion may be necessary for the carbonyl iron to exhibit the full toxicity associated with iron salts. Therefore, the protocol of any animal studies comparing the toxicity of carbonyl iron to the toxicity of iron salts should specify the particle size of the carbonyl iron used in the studies. If FDA exempts carbonyl iron from any of the requirements of this final rule, FDA will consider including particle size, based on the particle size of the carbonyl iron used in the comparative studies, as a specification for carbonyl iron.

J. Other Comments

At the public workshop, a representative of a manufacturer of carbonyl iron expressed the opinion that, in a rulemaking proceeding, it is FDA's responsibility to establish a need for a regulation for a particular product and suggested that the agency had not presented evidence that products containing carbonyl iron need the same kind of protective measures as those that the agency has proposed for products containing iron salts. In addition, a representative of a manufacturer of iron-containing products expressed the opinion that products containing carbonyl iron and bearing a warning statement such as ''Contains iron, which can harm or cause death to a child'' would be falsely labeled and therefore misbranded under the act if the carbonyl iron is in fact a safe source of iron.

At the public workshop, in response to this statement, agency representatives pointed out that the source of the iron in some deaths attributable to iron poisoning has not been identified, and that FDA therefore cannot say with certainty that carbonyl iron was not involved in any of the poisoning deaths that were discussed in the iron proposal. Moreover, as discussed above, the lack of reported major outcomes or death associated with accidental overdose of products known to contain carbonyl iron may be attributable to the small number of total exposures to date, particularly exposures to high dosages of carbonyl iron. These comments did not dispute that accidental overdose of iron-containing products can kill a small child, and that such overdoses are a leading cause of fatal poisoning in children under the age of 6.

Faced with this information, the agency is compelled to err on the side of caution. Unless presented with convincing data demonstrating that some forms of iron are sufficiently less toxic that they are unlikely to cause injury and illness, including death, FDA must assume, to ensure that the public health is adequately protected, that all forms of iron have the potential to cause injury and illness, including serious illness and death.

K. Exemption for Carbonyl Iron From the Labeling Requirements of This Final Rule

FDA has considered the kinds of data and information that would be necessary to enable the agency to reach a decision on an exemption for any form of elemental iron, such as carbonyl iron, from the regulations on labeling of iron-containing products. In the iron proposal, FDA stated that the agency would focus on data and information in two topic areas: Toxicity and bioavailability. Specifically, FDA stated that it would focus on whether use of a source of elemental iron would decrease the risk of pediatric poisoning while providing desirable iron nutrition to those who need iron supplementation (59 FR 51030 at 51052).

As already discussed, FDA has decided not to require demonstrated bioavailability of an iron source as a criterion in exempting carbonyl iron from any of the requirements in this final rule. Therefore, the agency's decision on whether to exempt carbonyl iron from the labeling requirements of this final rule turns on whether the available data demonstrate that carbonyl iron is significantly less toxic than iron salts.

In the iron proposal, FDA tentatively concluded that it should require a label warning statement for iron-containing products because a small child is at risk of injury any time he or she gains unlimited access to any iron-containing product. Therefore, the basis for exempting products containing carbonyl iron from the labeling requirements of this final rule would be data that persuade the agency that carbonyl iron is so much less toxic than ionic forms of iron that accidental overdose of products containing carbonyl iron is unlikely to place a small child at risk of injury (including minor, moderate, and major outcomes as well as death). The most compelling information bearing on this question is the available data on the outcomes of acute, accidental exposure of children to iron-containing products because these data, in contrast to animal studies that must be interpreted and extrapolated to predict toxicity in human children, are directly relevant to the question at hand.

As discussed above, the information available from poison control centers shows that accidental overdose of carbonyl iron-containing products has resulted in 173 minor outcomes and 4 moderate outcomes. Even though there were no reported exposures to carbonyl iron-containing products that resulted in major outcomes or death, the reported occurrences of minor and moderate outcomes show that a young child who accidentally consumes an overdose of a carbonyl iron-containing product is at risk of illness or injury. Therefore, the available data on the acute, accidental exposure of children to iron-containing products do not support an exemption for carbonyl iron from the labeling requirements of this final rule. Accordingly, FDA is not exempting products containing carbonyl iron from the labeling requirements of this final rule.

L. Exemption for Carbonyl Iron From the Packaging Requirements of This Final Rule

FDA has considered the kinds of data and information that would be necessary to enable the agency to reach a decision on an exemption for any form of elemental iron, such as carbonyl iron, from the regulations on packaging of iron-containing products. As discussed with respect to an exemption from the labeling requirements of this final rule, the basis for the agency's decision on whether to exempt carbonyl iron would be data on whether the use of carbonyl iron would decrease the risk of pediatric poisoning.

In the iron proposal, FDA stated that the agency was not persuaded that full

[15] Many of the comments that addressed the influence of particle size on the physiological properties of elemental iron discussed the role of particle size from the perspective of the bioavailability of the elemental iron. However, as discussed above, FDA has decided not to require demonstrated bioavailability of an iron source as a criterion in exempting that iron source from any of the requirements of this final rule. Therefore, the discussion of the importance of particle size emphasizes its potential role in toxicity rather than bioavailability.

compliance with CPSC's CRC requirements, even in the presence of warning statements, would be adequate to ensure the safety of the use of iron-containing products. FDA proposed that iron-containing products that contain 30 mg or more of iron per dosage unit be packaged in nonreusable unit-dose packaging in light of the potentially fatal outcome that can result from pediatric iron poisoning. Moreover, many accidental overdoses of iron-containing products that do not result in fatal consequences do have life-threatening consequences. In light of the potentially fatal or life-threatening outcomes that can result from pediatric iron poisoning, the basis for exempting products containing 30 mg or more of carbonyl iron per dosage unit from the packaging requirements would be data that persuade the agency that carbonyl iron is so much less toxic than ionic forms of iron that accidental overdose of products containing a high dose of carbonyl iron is unlikely to result in major outcomes or death. The information bearing on this question is: (1) Data on the outcomes of acute, accidental exposure of children to iron-containing products; (2) data on acute toxicity in animals of carbonyl iron compared to that of iron salts; and (3) the ability to extrapolate from the acute toxicity data in animals to predict a reduced toxicity for carbonyl iron in children.

As discussed above, the information available from poison control centers shows no reported exposures to carbonyl iron-containing products that resulted in major outcomes or death. However, the data from the poison control centers did not always include the source of iron, and therefore the total number of accidental exposures to products containing carbonyl iron is likely to be underestimated. Consequently, the total number of major and fatal outcomes may also be underestimated.[16] The lack of reported exposures to carbonyl iron that resulted in major outcomes is encouraging in light of the fact that at least three major outcomes would be predicted if carbonyl iron was as toxic as iron salts. However, even if carbonyl iron was as toxic as iron salts, less than one death would be predicted from exposure to carbonyl iron. The lack of reported exposures to carbonyl iron that resulted in major outcomes or death therefore may be attributable to both the insensitivity of passive reporting systems and the small number of total exposures to carbonyl iron, particularly exposures to high doses of carbonyl iron, rather than to any reduced toxicity of carbonyl iron relative to that of iron salts. Therefore, although FDA acknowledges that the data are consistent with an interpretation that accidental overdose of carbonyl iron is unlikely to result in major outcomes or death, FDA finds that the data are too preliminary to allow it to comfortably conclude that accidental overdose of carbonyl iron-containing products is unlikely to result in major outcomes or death.

Moreover, as already discussed, the available animal toxicity data are unsuited for the agency's purpose in evaluating whether the acute toxicity in children of carbonyl iron is less than that of iron salts, and it would be premature for FDA to exempt carbonyl iron absent data that permit such an evaluation. In order to reach a decision on whether to exempt carbonyl iron from the packaging requirements of this final rule, FDA needs animal data comparing the acute toxicity of carbonyl iron to that of at least one iron salt that is commonly used in the manufacture of iron-containing supplements and drug products.

In summary, given the possibility that accidental overdose of products containing carbonyl iron could result in death of a small child, the available data on accidental exposure to carbonyl iron-containing products are too preliminary to provide a basis for an exemption for carbonyl iron from the packaging requirements of this final rule. Moreover, it would be premature for FDA to exempt carbonyl iron from the packaging requirements of this final rule given the lack of animal data that clearly establish the lower toxicity of carbonyl iron compared to at least one commonly used iron salt.

Nonetheless, FDA is encouraged by the fact that accidental overdose of products containing 30 mg or more of carbonyl iron per dosage unit thus far is not known to have caused major outcomes or death. FDA also is encouraged by the fact that the existing animal data, limited though they are, are consistent with an interpretation that carbonyl iron may be so much less toxic than iron salts that an accidental overdose of a carbonyl iron-containing product is unlikely to result in a major outcome or death. Therefore, FDA finds that it is appropriate to provide a temporary exemption from the packaging requirements of this final rule to enable interested parties to conduct appropriate animal studies that could establish a reduced toxicity for carbonyl iron relative to that of iron salts.

Accordingly, §§ 111.50(b) and 310.518(b) temporarily exempt carbonyl iron from the packaging requirements of this final rule. The temporary exemption will automatically expire 1 year after date of publication of this final rule in the Federal Register. If, during the temporary exemption period, FDA receives animal data that clearly establish that carbonyl iron is significantly less toxic than at least one commonly used iron salt, FDA will consider permanently exempting carbonyl iron from the packaging requirements of this final rule. If, following the temporary exemption period, FDA does not extend the exemption, the packaging requirements of this final rule will become effective for products containing carbonyl iron according to the same principle as for products containing other forms of iron, i.e., on the date that is 180 days after the date of expiration of the temporary exemption, or on July 15, 1998. (See discussion of the effective date in sections VI.B.7. and VIII. of this document.)

To predict the margin of safety that carbonyl iron would afford relative to iron salts in the event of accidental overdose, the agency needs data, in weanling/juvenile laboratory animals of 2 to 3 species,[17,18] in which the acute/short-term toxicity of orally administered elemental iron of known particle size [19] is compared to the acute/short term toxicity of at least one iron salt that is commonly used in the manufacture of iron supplements. The range of particle sizes of the carbonyl iron used in the comparative studies should correspond to that of the product proposed to be exempted.

[16] At the public workshop, FDA stated that the ingested substance had been identified as ferrous sulfate in ''16 or 17 out of 37 or 40 deaths.'' Review of the supporting medical records for the 37 deaths reported in the iron proposal now shows that the source of the iron involved in the accidental overdose exposures resulting in death is known in 29 of those 37 cases and that in each of these 29 cases the source was not carbonyl iron. In addition, FDA is aware that 2 additional children died of accidental overdose of an iron-containing product in 1994, and that the source of iron in both of these cases was ferrous sulfate (Refs. 1 and 2). Therefore, the number of reported pediatric deaths attributable to accidental overdose of an iron-containing product in which the source of iron is not known to FDA is 8 of 39 reported pediatric deaths.

[17] As discussed above, extrapolation from data on iron toxicity obtained with experimental animal species to predict iron toxicity in humans is not straightforward. Consequently, it would be imprudent to rely on data derived from a single animal species.

[18] The studies should be performed on at least one weanling/juvenile rodent and one weanling/juvenile nonrodent species whose gastrointestinal physiology is similar to that of infants and children (e.g., swine).

[19] As discussed above, particle size is an important factor in the rate of ionization, and thus the potential toxicity, of elemental iron.

The studies should be carried out over a range of doses, so that they can provide information relevant to the acute/short term toxicological profile, including dose responses and NOAEL's for toxic effects. The endpoints of these studies should include deposition of iron in tissues, clinical measures of iron status (e.g., hematocrit, hemoglobin, serum iron, serum ferritin, total iron binding capacity), assessment of systemic tissue damage using biomarkers (e.g., liver enzymes in serum for liver damage; blood urea nitrogen for kidney damage), gross necroscopy examination, histopathology (with emphasis on known primary target organs of acute oral toxicity of iron such as the gastrointestinal tract and liver, and on any gross lesions observed on necropsy), effects on lipid peroxidation in tissues (liver, intestines, red blood cells), and systematic evaluation and recording of clinical signs and symptoms. Such data will provide a direct comparison of the thresholds for toxic effects of carbonyl iron relative to those of ferrous salts. If the inter-species variability is large, the agency will need data in at least one species that closely resembles the human child, such as a primate species, in order to be able to extrapolate from the animal data to predict whether the toxicity of carbonyl iron in children is reduced relative to that of iron salts.

FDA intends to evaluate the animal data described above, as well as any relevant data from studies in humans that may become available, to determine whether they support a reduced toxicity for carbonyl iron such that an extension, temporary or permanent, of the exemption for carbonyl iron from the packaging requirements of this final rule is justified. However, animal data can only be used to support an interpretation that accidental exposure to a carbonyl iron-containing product is unlikely to result in a major outcome or death and cannot supersede data obtained from human exposure to carbonyl iron-containing products. Thus, animal data would not be a sufficient basis for a continued exemption in the event that FDA receives information that accidental exposure to a product containing 30 mg or more of carbonyl iron per dosage unit resulted in a major outcome or death. Accordingly, if, during the period of temporary exemption or during any period of extended or permanent exemption, FDA receives information that accidental exposure to a product containing 30 mg or more of carbonyl iron per dosage unit resulted in a major outcome or death, FDA will likely move quickly to revoke the exemption.

The temporary exemption identifies the form of iron that is exempted as carbonyl iron that conforms to § 184.1375 (21 CFR 184.1375). Section 184.1375 should accurately describe the carbonyl iron used in iron-containing dietary supplement and drug products, and, given the need for promulgation of this final rule, FDA finds that it is appropriate to incorporate it into the final regulation. However, FDA invites the submission of information on whether this description of carbonyl iron is adequate, and whether alternative or additional information is appropriate and necessary in the event that FDA decides to extend, or make permanent, the exemption. For example, FDA solicits information on whether it is appropriate and important to include a specification for the particle size of carbonyl iron that is used to manufacture dietary supplement and drug products. FDA also solicits information on factors other than particle size, such as the physical and chemical properties of the iron as well as binders and excipients, that may influence the rate of ionization of carbonyl iron and recommendations on whether it is appropriate and important to include specifications for such factors used in the manufacture of products containing carbonyl iron.

M. Other Non-Ionic Forms of Iron

The agency received one comment from a manufacturer of PIC. The comment included data obtained from the TESS database of the AAPCC on a total of 228 potentially toxic exposures to products containing PIC. None of the exposures resulted in death. One exposure, which involved a suspected suicide attempt by an adult and was accompanied by the concomitant consumption of other drug products, resulted in a major outcome. The 228 total exposures also resulted in 3 moderate outcomes and 24 minor outcomes. The comment concluded that the overall risk of accidental iron poisoning or death associated with PIC is low.

In order to determine whether PIC merits an exemption from the labeling requirements of this final rule, FDA has considered whether the information supplied in the comment supports a conclusion that accidental overdose of a PIC-containing product is unlikely to place a small child at risk of illness or injury any time he or she gains unlimited access to such products. The total number of reported acute, accidental exposures in humans to PIC is very small, but already has resulted in 3 moderate outcomes and 24 minor outcomes. Therefore, the available data on acute, accidental exposure of humans to PIC does not support an exemption for PIC-containing products from the labeling requirements of this final rule. Accordingly, FDA is not exempting products containing PIC from the labeling requirements of this final rule.

The comment also included data from an acute 14-day oral toxicity study in rats. The study was initiated with a range-finding test consisting of one male and one female rat at five doses ranging from 500 to 5,000 mg Fe/kg body weight. Following the range-finding test, a limit test was performed in which one group of five male and five female rats received a single oral administration of PIC at a dose of 5,000 mg Fe/kg body weight. Following dosing, the limit test rats were observed daily and weighed weekly. A gross necroscopy examination was performed on all limit test rats, and no gross internal findings were observed at necropsy after the 14-day exposure. No mortality occurred during the limit test, and the acute oral LD_{50} for PIC in rats therefore was estimated to be greater than 5,000 mg Fe/kg body weight.

As discussed above for carbonyl iron, the basis for exempting products containing 30 mg or more PIC per dosage unit from the packaging requirements would be data that persuade the agency that accidental overdose of products containing 30 mg or more of PIC per dosage unit is unlikely to result in major outcomes or death. The information bearing on this question is: (1) Data on the outcomes of acute, accidental exposure of children to iron-containing products; (2) data on the acute toxicity in animals of carbonyl iron compared to that of iron salts; and (3) the ability to extrapolate from the acute toxicity data in animals to predict a reduced toxicity for carbonyl iron in children.

As already discussed, the available data on accidental human overdoses are unclear as to whether there have thus far been any major outcomes resulting from exposure to PIC-containing products because the one report of major outcome was not clearly attributable to the consumption of a PIC-containing product. However, the lack of reported major outcomes or death associated with accidental overdose of products known to contain PIC may be attributable to both the insensitivity of passive reporting systems and the small number of total exposures to date. Therefore, FDA finds that the data on accidental exposures to PIC-containing iron products are too preliminary to

provide a basis for an exemption for PIC from the packaging requirements of this final rule.

Moreover, there are no animal toxicology studies directly comparing the acute toxicity of PIC in animals to that of iron salts. The available animal data therefore have limitations similar to those already discussed for the data submitted in comments discussing the toxicity of carbonyl iron and are unsuited for the agency's purpose in evaluating whether the acute toxicity in children of PIC is less than that of iron salts. It would be premature for FDA to exempt PIC absent such data. In order to reach a decision on whether to exempt PIC from the packaging requirements of this final rule, FDA needs animal data, discussed in detail above for studies with carbonyl iron, comparing the acute toxicity of PIC to that of at least one iron salt that is commonly used in the manufacture of iron-containing supplements and drug products.

At this time, the use of PIC in iron-containing products is not included in any FDA regulations. The comment did not submit sufficient information bearing on the manufacturing process, composition, and physical properties of PIC to allow the agency to adequately describe PIC in any exemption from the packaging requirements of this final rule. For example, the comment did not discuss the role, if any, of particle size and solubility of PIC, or the role of excipients and binders, as factors that may influence the toxicity of PIC. Before FDA can consider an exemption for PIC from the packaging requirements of this final rule, FDA needs information that adequately describes the manufacturing process, composition, and physical properties of PIC. If the agency reached a decision to exempt PIC from the packaging requirements of this final rule, FDA would use this information to define, in the agency's regulations, the substance that is exempt. FDA also solicits information on factors other than the properties of PIC itself, such as the physical and chemical properties of binders and excipients, that may influence the absorption and toxicity of PIC and recommendations on whether it is appropriate and important to include specifications for such factors used in the manufacture of products containing PIC.

In summary, the available data on accidental exposure to PIC-containing products are too preliminary to provide a basis for exempting PIC from the packaging requirements of this final rule. Further, FDA is concerned whether the available data on accidental exposure to PIC-containing products actually signify that PIC is no less toxic than ionic forms of iron. Moreover, it would be premature for FDA to exempt PIC from the packaging requirements of this final rule given the lack of animal data that clearly establish the lower toxicity of PIC compared to at least one commonly used iron salt. In addition, FDA lacks information that would allow the agency to describe the substance that is exempt. Therefore, at this time FDA is not exempting products containing PIC from the packaging requirements of this final rule.

Regardless of whether FDA receives animal data that support a conclusion of reduced toxicity for PIC, the agency cautions that animal data alone may not provide a sufficient basis for an exemption in light of the extremely small number of exposures in humans to date. Further, as already discussed for carbonyl iron, animal data can only be used to support an interpretation that accidental exposure to a PIC-containing product is unlikely to result in a major outcome or death and cannot supersede data that may be obtained in the future from accidental human exposure to PIC-containing products.

VI. Other Matters

One comment requested an exemption from both the labeling and unit-dose packaging requirements for the inert, iron-containing tablets that are included in packages of oral contraceptives. The inert tablets are taken on the days on which the active drug product is not taken to facilitate proper and regular use of the contraceptives by enabling women to take a pill each day rather than having to remember which day to resume after the days for which an active pill is not provided. The comment argued that meeting the requirement for an additional warning statement on the immediate container labeling of oral contraceptive products would be impossible because of the lack of space, the small size of the immediate container, and preexisting label requirements. The comment stated that oral contraceptives are a special class of prescription products that should be exempted from the labeling requirements of this rule.

The agency observes that the inert tablets in oral contraceptive products contain up to 75 mg of ferrous fumarate (equivalent to 25 mg of iron), and therefore a 1-month supply of oral contraceptives containing 7 inert tablets will contain up to 175 mg of iron. The total amount of iron in a 1-month supply of oral contraceptives is only 70 percent of the amount (250 mg) that experts have stated is sufficient to produce symptoms of poisoning in a 10 kg child (see discussion above). Moreover, FDA is not aware of any reported cases of poisoning caused by the inert, iron-containing tablets in packages of oral contraceptives. Moreover, these products are separately regulated. Therefore, FDA is granting the requested exemption from the specific labeling requirement of this final rule (see § 310.518(d)). If FDA becomes aware of poisoning caused by the ingestion of the inert, iron-containing tablets in oral contraceptive packages, it may reconsider the exemption.

The amount of iron per tablet is below the threshold level for unit-dose packaging of 30 mg of iron per dosage unit. Therefore, an exemption from the unit-dose packaging requirement is not necessary.

VII. Economic Impact

FDA has examined the economic implications of the final rule as required by Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select the regulatory approach which maximizes net benefits (including potential economic, environmental, public health and safety effects; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions including having an annual effect on the economy of $100 million or adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. If a rule has a significant impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze options that would minimize the economic impact of that rule on small businesses. Though not economically significant, FDA finds that this final rule is a ''significant regulatory action'' as defined in Section 3(f)(4) of the Executive Order because it raises novel policy issues. The agency also finds under the Regulatory Flexibility Act that the final rule is likely to have a significant impact on a substantial number of small entities. Finally, the agency, in conjunction with the Administrator of OIRA, OMB, finds that this rule is not a major rule for the purposes of congressional review (Pub. L. 104–121).

The rule will result in costs in the first year of approximately $56 million and $4.3 per year starting in year two for total discounted costs of $118 million

(discounted to infinity at 7 percent). The rule will also result in per year benefits of between $31.5 million and $61 million for total discounted benefits of between $426 million and $847 million (discounted to infinity at 7 percent). Below is a detailed description of FDA's economic analysis.

In response to the iron proposal, the agency received many comments regarding the economic impact of the proposed actions. The comments were from a variety of sources including consumer advocacy organizations, manufacturers, distributors, and trade associations.

A. Description of the Industry

In the analysis of the proposed rule, FDA stated that there are approximately 300 iron-containing products that may be affected by this action, of which approximately one-half contain 30 mg or more of iron per dosage unit. FDA received one comment from an industry trade association stating that there are between 1,300 and 3,000 iron-containing products. The comment did not specify the number or percentage of products containing 30 mg or more of iron per dosage unit.

The agency acknowledges that it originally underestimated the number of iron-containing products that may be affected by these actions. Therefore, the analysis of the final rule will be based on an estimate of 2,150 products ((1,300 + 3,000)/2). The agency will continue to assume that approximately one-half, or 1,075 products, contain 30 mg or more of iron per dosage unit.

The types of iron-containing products that have been associated with poisonings of young children are products offered in solid oral dosage form as multivitamin/mineral supplements, products intended for use as iron supplements, and drug products for therapeutic purposes. Although this final rule requiring warning statements affects all iron-containing products, the requirement for unit-dose packaging affects only products containing 30 mg or more of iron per dosage unit. Typically, multivitamin/mineral supplements provide less than 30 mg of iron per dosage unit and therefore are subject to warning statement requirements but not to packaging requirements. Iron supplements and drug products typically contain 30 mg or more of iron per dosage unit and therefore are subject to both requirements.

Iron-containing products may be purchased by consumers on their own initiative as food supplements, or they may be prescribed by physicians. Information available to the agency at the time of the proposal suggested that the overwhelming majority of iron-containing products are packaged in bottles. Additional information suggested that iron-containing products administered in hospitals are commonly packaged in unit-dose packaging. Unit-dose packaging is preferred by hospitals because use of this type of packaging provides each dosage unit with an identification and an expiration date and allows the hospital to continue to dispense product from a partially used package of drugs rather than discard a bottle opened for a specific patient after that patient is discharged. There were no comments challenging FDA's assumption that iron-containing products dispensed in hospitals are packaged in unit-dose packaging, and, therefore, this assumption is being retained in this analysis.

In the proposed analysis, FDA reported that, according to the National Center for Health Statistics, of the approximately 169 million persons of age 18 or older, 19.7 percent consume iron-containing products. If it is assumed that each individual consumes one dosage unit per day, there are approximately 12 billion dosage units of iron-containing products consumed annually in the United States. The agency does not have complete information on the number of dosage units of iron-containing products that contain 30 mg or more of iron nor did any comments provide such information. According to the recommended dietary allowance published in 1989 by the Food and Nutrition Board of the National Academy of Sciences, only pregnant women require 30 mg Fe/day. Therefore, FDA assumes that the number of higher-dosage iron-containing products consumed per year can be estimated by multiplying the number of pregnant women in the United States by the number of days in 1 year.

In the most recent year (1991) for which data is available, there were 4.1 million live births. Assuming further that each live birth resulted from a distinct pregnant woman (as opposed to more than one birth per pregnant woman), this data implies that there are about 4.1 million pregnant women on any 1 day in the United States, and that the number of dosage units per year can be estimated at 4.1 million times 365 days per year or about 1.5 billion (assumes women who give birth take iron-containing products for 3 months of nursing after delivery). The number of pregnant women may be overestimated because multiple births by one woman are ignored. The number of pregnant women may also be underestimated because using the number of live births ignores pregnancies not resulting in a live birth. In addition, all pregnant women may not necessarily take iron-containing products or begin on the first day of pregnancy, another source of potential overestimation.

B. Comments on Regulatory Options

The proposed analysis raised many possible regulatory alternatives available that may reduce the number of cases of pediatric poisonings from the accidental ingestion of iron-containing products. The options include packaging, warning statements, product reformulation, and educational efforts.

1. Packaging

In the proposal, FDA proposed to require that products containing 30 mg or more of iron per dosage unit be packaged in unit-dose containers. Because of Consumer Product Safety Commission regulations, most iron containing products currently must be packaged in CRC's. Therefore, this option would likely result in child resistant unit-dose packaging for most of these products.

a. Costs. In the analysis of the proposed actions, FDA stated that there are four types of costs associated with a mandated packaging change: Equipment, materials, transportation, and administrative costs. FDA received one comment stating that the changes in packaging will require additional storage costs of $10,800 for four products. In addition, several other comments stated that the packaging requirements would cause manufacturers to incur additional stability testing at a cost of $4,000 per product.

FDA agrees that the packaging requirements will increase storage costs and has changed its analysis to reflect that change. Using the data provided in the comment, the agency estimates storage costs to be approximately $1.4 million per year.

As discussed above, stability testing with new packaging is required under drug CGMP regulations. Therefore, FDA agrees that the packaging requirements of this final rule will increase costs for drug products containing 30 mg or more of iron per dosage unit and will change its analysis to reflect that change. There are approximately 150 drug products containing 30 mg or more iron per dosage unit. Total stability testing costs will be $0.6 million (150 drug products $\times$ $4,000).

Several comments expressed concern over the cost of equipment. One

comment from a manufacturer stated that machine tooling costs would be approximately $20,000 per product. However, one comment from a trade association stated that contract packaging firms can provide unit-dose packaging services at a cost that would be significantly less than purchasing machinery, although there was no data supporting this statement.

In the analysis of the proposed rules, FDA stated that many packagers of iron-containing products will be required to purchase new packaging equipment. Incorporating the costs provided in the comments with information used to develop the estimates used in the proposed analysis, FDA now estimates the cost of equipment used in packaging blisters, one common form of unit-dose packaging, is between $20,000 and $250,000, or on average $135,000. New equipment will not be purchased for each product sold because some manufacturers already possess unit-dose packaging equipment, and some manufacturers will use the services of contract packaging firms. FDA will not change its equipment cost per product, but it will reduce the number of products requiring new equipment based on the assumption that many firms will use contract packagers. If approximately one-third of the 1,075 products containing 30 mg or more of iron per dosage unit require the purchase of new equipment, the total equipment cost will be $48 million.

The cost of child-resistant bottles, currently the most common form of packaging, is approximately $7 per 1,000 dosage units. Child resistant blister packaging materials cost approximately $9 per 1,000 dosage units, a difference of $2 per 1,000 dosage units. FDA received no comments challenging these cost estimates.

In the proposed analysis, FDA stated that it did not have information to estimate transportation costs and requested comments. FDA received one comment providing an estimate of additional transportation costs caused by unit-dose packaging requirements to be approximately $340,000 per year.

Because no other information was provided to the agency, FDA will use this estimate in its analysis.

FDA received one comment regarding administrative costs. One manufacturer stated that its administrative cost of reviewing and implementing the regulation would be $13,000.

FDA notes that this estimate, when examined on a cost-per-product basis, is not out of line with its estimate of approximately $500 per product in the first year. Administrative costs are the dollar value of the incremental administrative effort expended in order to comply with a regulation. Administrative activities include, but are not limited to, reading and interpreting the regulation, establishing a policy to comply with the regulation (which may include, for example, challenging the regulation, compliance with direct requirements, remarketing product, or withdrawal from the market), and identifying the appropriate staff to comply with the regulation, monitoring to ensure staff efforts are consistent with corporate policy, and interacting with Federal inspectors.

The cost for equipment for unit-dose packaging for all products with 30 mg or more of iron per dosage unit is estimated to be $48 million (358 products × $135,000). The cost of materials is estimated to be $3 million per year or $43 million (discounted to infinity at 7 percent). Transportation costs are estimated to be $.34 million per year or $4.86 million (discounted to infinity at 7 percent). Storage costs will be approximately $1.4 million per year or $20 million (discounted to infinity at 7 percent). Administrative costs are estimated to be $0.54 million (1,075 × $500). Total costs associated with requiring unit-dose packaging for products containing 30 mg or more of iron per unit dose are estimated to be $116 million (discounted to infinity at seven percent) with annual costs not exceeding $54 million in any 1 year.

b. Benefits. FDA received two comments concurring with its analysis of the benefits of unit-dose packaging, and no comments challenging that analysis. In the past 8 years, there have been at least 39 cases of pediatric fatalities from the accidental ingestion of iron-containing products, or a mean of 4.9 deaths per year. Data on the dosage of the product consumed is available for 25 of these cases. In all cases for which information is available, the product consumed contained at least 40 mg of iron. In a 7-year period, there were nearly 190 poisonings that were life threatening or resulted in permanent injury, and over 2,000 poisonings that required some form of treatment. FDA believes that most, if not all, such deaths and some poisonings can be prevented by requiring that higher-dosage iron-containing products be packaged in unit-dose containers, because studies indicate that the child is less likely to consume the number of dosage units that may be fatal if the child must first remove each tablet from a unit-dose package.

Although no studies have attempted to directly estimate the value of reducing the risk of death and illness to children in particular, many studies have attempted to estimate the value of reducing these risks to adults. Most of these estimates are based on wage differences between high and low risk jobs and, thus, are derived from the labor market decisions of middle-aged adults. Although these estimates cluster around a fairly small range, $2 million to $10 million, it is not clear that these estimates are valid when applied to children.

FDA has used estimates of the value of reducing risks to adults to a level that would avoid one statistical fatality between $3 million and $5 million in past regulations, including food labeling and Hazard Analysis Critical Control Points (HACCP). One method of estimating the value of reducing risks to children is to adjust the value of reducing risks to adults by accounting for the difference in the number of life-years saved. Under this approach, an often used estimate of the value of reducing the risks to adults to a level that would avoid one statistical fatality is $5 million for a middle-aged adult. If this value does not vary with life years remaining (that is, if we assume that an infant is willing to pay the same amount to avoid risk of death as a 40 year old would be willing to pay and assuming the same distribution of wealth exists in both age groups), then $5 million is a reasonable estimate. If, however, this value does vary with life years remaining, then the corresponding value for reducing the risks to small children would be $11 million. FDA used these figures ($5 to 11 million) in the proposed analysis to provide a range of estimates. FDA received no comments objecting to these estimates and is, therefore, continuing to use these values in this analysis.

Requiring unit-dose packaging for iron-containing products at 30 mg or more of iron per dosage unit would result in benefits of reducing an average of 4.9 deaths per year, valued at between $24.5 million and $54 million per year, or between $350 million and $771 million (discounted to infinity at 7 percent).

Requiring unit-dosage packaging for iron-containing products will also reduce the number of nonfatal cases of pediatric iron poisoning. FDA has obtained from CPSC case reports for 78 iron ingestions necessitating emergency room treatment reported over 7 years, or an average of 11 illnesses per year. The dosage consumed was reported for 12 of these cases. In five of those cases, the dosage reported was under 30 mg of iron per dosage unit. AAPCC data show that from 1986 through 1992 there were nearly 190 poisonings that were life

threatening or resulted in permanent injury, and over 2,000 poisonings requiring some form of treatment as a result of accidental ingestion of adult and pediatric iron-containing products, or an average of 286 per year. FDA is unable to predict the percent of these nonfatal poisonings that would be prevented by substituting unit-dose packaging for bottles. In the proposed analysis, FDA assumed that all nonfatal poisonings would be prevented by the proposed packaging requirements. The agency received no comments on this issue and is, therefore, continuing the assumption in this final analysis.

Using a methodology developed previously for FDA to value morbidity risks, FDA is able to estimate the value of reduced risk of nonfatal poisoning. As described in the proposed analysis, by comparing similar symptoms and medical interventions, the agency has derived an estimate of the value of preventing a nonfatal pediatric iron poisoning of $20,000 per case. Seven out of twelve cases of nonfatal poisonings were a result of ingestion of products of dosages over 60 mg of iron. Assuming this proportion is extrapolated to the remaining cases for which information is unknown, and assuming unit-dose packaging will prevent all nonfatal cases (2,000 cases in 7 years), then requiring unit-dose packaging for products containing 30 mg or more of iron per unit dose will result in reduced morbidity valued $5 million per year, or $71 million (discounted to infinity at 7 percent).

The total value of the benefits of unit-dose packaging options is the sum of the value of reducing both mortality and morbidity risks. Requiring unit-dose packaging for all products containing 30 mg or more of iron per dosage unit, would result in benefits of reducing mortality risks of between $24.5 million and $54 million per year or between $350 million and $771 million (discounted to infinity at 7 percent) and reduced morbidity valued at $5 million per year or $71 million (discounted to infinity at 7 percent). Therefore, total discounted benefits are between $29.5 million and $59 million per year or between $421 million and $842 million (discounted to infinity at 7 percent).

2. Warning Labels

a. Costs. FDA received two comments providing estimates of the cost of relabeling. One manufacturer estimated graphic and design costs at $2,850 per product. Another estimated artwork costs of $240,500 for 100 products, or $2,405 per product.

In the analysis of the proposed actions, FDA estimated that the cost of relabeling was $1,500 per label. Manufacturers of iron-containing products will be required to change their labels on both the product container and the retail package to incorporate warning statements. However, because manufacturers of iron-containing products with 30 mg or more of iron per dosage unit will also be required to change their packaging, they will not incur any incremental cost of adding a warning statement to the product container. Therefore, the redesign cost per product was estimated in the proposal was estimated to be $2,250 ($1,500 x 1.5). FDA notes that this estimate is similar to redesign costs submitted in the comments. Therefore, the analysis will not be changed based on this comment. The total cost of the warning label requirements is one-time cost of $5 million (2,150 products × $2,250).

In the proposed analysis, FDA stated that an additional cost of this regulation may be an increase in iron deficiency anemia if susceptible adults react inappropriately to a warning label targeted for children. It is possible that incidence of iron-deficiency anemia may actually increase as a result of this final action. According to NHANES II, approximately 7.2 percent of women age 15 to 19 and 6.3 percent of women age 20 to 44 suffer from iron-deficiency anemia. In addition, men had a prevalence of less than 1 percent. FDA received no comments on this issue.

b. Benefits. Warning statements will only prevent pediatric iron poisonings to the extent that they lead to changes in the behavior of the adult controlling the use of the product. Whether or not the warning messages prescribed in this final rule will cause a change in behavior will depend on a number of factors, including the degree to which the statement is noticed, read, understood, and acted upon.

There is some evidence that warning statements can change behavior. For example, research indicates that the rate of increase of sales of diet soft drinks declined after saccharin warnings were put on the labels of these products (Ref. 31). However, FDA is unable to predict exactly how many cases of pediatric iron poisoning will be prevented as a result of warning statements. To the extent that warning statements will cause adults to take proper care in handling iron-containing products and to the extent that such care is not taken in the absence of warning statements, some cases of pediatric iron poisoning will be prevented.

FDA did not receive any comments challenging its estimate of the benefits of warning statements. Therefore, the analysis will not be changed by the comments. If all products containing 30 mg or more of iron per dosage unit are subject to the packaging requirements, and packaging is 100 percent effective in preventing both fatal and nonfatal cases, then there are no benefits from warning labels on these products. However, for those products still packaged in bottles, warning labels will have an impact. If each nonfatal case of iron poisoning is valued at $20,000, and the one-time cost of warning statements is $5 million, then benefits of requiring warning statements will exceed costs if warning statements prevent at least 15 nonfatal cases every year out of an average of 285.

3. Product Reformulation—Appearance

In the proposed rule, FDA requested comment on the option of reformulating iron-containing products to be less visually attractive, i.e., not look like candy. FDA received several comments on this issue. As discussed above, none of these comments presented data to support their contention that FDA should take steps to limit the appeal of iron-containing products to young children, and therefore, FDA is not including in this final rule any requirements relating to the formulation and appearance of iron-containing products.

4. Product Reformulation—Taste

In the proposed rule, FDA also requested comment on the option of adding a bitter substance to products containing iron which would discourage multiple ingestions. FDA did not receive any comments specifically addressing this issue. However, as discussed above, FDA did receive a comment expressing an opinion that a candy-like taste needlessly encourages an unsuspecting child, who may be unlikely to chew through the sugar coat, to ingest large quantities of these products. Another comment from a State department of health reported that investigation of 5 of 17 deaths revealed that children chewed or sucked on the iron tablets. However, none of these comments presented data to support a requirement by FDA for adding a bitter substance to products containing iron to discourage multiple ingestions.

5. Forms of Iron That May Be Less Toxic

Several comments requested that iron-containing products containing carbonyl iron, an elemental iron powder, be exempted from the labeling and packaging requirements. Comments stated their belief that carbonyl iron is effective in the prevention or treatment of iron deficiency and yet is less toxic

than other forms of iron commonly used in iron-containing products. Comments also stated that a permanent exemption from both packaging and labeling would dramatically reduce the costs of the regulation.

FDA agrees that such an exemption would reduce the costs of this final regulation. According to one producer of carbonyl iron, there are approximately 35 iron-containing products marketed by 15 manufacturers currently using carbonyl iron. It is likely that, if given an exemption for carbonyl iron, most, if not all, of the rest of the industry would convert their products to this form of iron. Therefore, an exemption from both labeling and packaging requirements would reduce costs by the difference between the cost of switching to carbonyl iron and the cost of making labeling and packaging changes. The cost of carbonyl iron is approximately $5.28 per lb as compared with ferrous sulfate which costs approximately $1.70 per lb. However, carbonyl iron has an iron content which is three times as high as ferrous sulfate. Therefore, on an equivalency basis, the price of the two types of iron are approximately equal ($5.28 for carbonyl iron and $5.10 for ferrous sulfate).

The cost savings from providing an exemption from packaging requirements is $54 million in the first year, or $116 million discounted to infinity at 7 percent. There are minimal cost savings from providing an exemption from labeling requirements because most labels will still be changed to reflect a change in ingredients.

However, as stated previously, although there may be some probability that carbonyl iron is less toxic, FDA is not entirely convinced that carbonyl iron is sufficiently less toxic than other commonly used forms of iron to substantially decrease the risk of pediatric poisoning. Thus, it is possible that providing an exemption from either labeling or packaging requirements, while substantially reducing costs, could also substantially reduce benefits. If carbonyl iron is not sufficiently less toxic than other forms of iron, then encouraging the industry to convert to carbonyl iron will result in lost benefits of between $426 million and $847 million (discounted to infinity at 7 percent). A permanent exemption for carbonyl iron from labeling requirements could result in a net loss to society of approximately $5 million. An exemption for carbonyl iron from packaging requirements could result in a net loss to society of between $421 million and $842 million. On the other hand, if carbonyl iron is sufficiently less toxic than other forms of iron such that accidental overdose of products containing a high dose of carbonyl iron is unlikely to result in major outcomes or death, then an exemption from the packaging requirements would result in a cost savings of $54 million annually with no corresponding loss in benefits.

Because of the uncertainty regarding the relative toxicity of carbonyl iron, FDA is temporarily exempting products containing carbonyl iron from the packaging requirements. At the end of 1 year, those products will be subject to the unit-dose packaging requirements. However, if FDA receives sufficient data to convince the agency that an exemption from carbonyl iron will not result in any loss in benefits, the exemption will be made permanent. The temporary exemption for carbonyl iron will allow manufacturers of iron containing products to delay making changes to their packaging while conducting further studies on the toxicity of carbonyl iron. This delay will result in cost savings equal to the interest on the cost of the packaging changes (7 percent of $54 million, or $4 million). The cost of the studies will depend on the species selected. FDA estimates that conducting the necessary studies will cost approximately $30,000.

6. Consumer Education Campaign

Two of the three petitions submitted advocated educational efforts for the public and health professionals. FDA agrees that the public needs to be informed of the dangers of pediatric iron poisoning. The fact that in 7 years over 2,000 poisonings requiring some kind of treatment occurred, may indicate that the public is not aware of the potential for serious harm or death in young children from accidental ingestion of iron-containing products. FDA is developing materials for a public information campaign utilizing the channels available to FDA.

7. Effective Dates

The agency proposed to make any final rule based on the proposed rule effective 6 months after date of publication of the final rule in the Federal Register. FDA received many comments objecting to this effective date.

Several comments stated that the proposed effective date is not feasible for relabeling, urging FDA to consolidate the effective date with the date for the new nutrition labeling rules for dietary supplements that would be issued as a result of the DSHEA and were statutorily mandated to be effective after December 31, 1996. This would amount to a compliance period of approximately 1 year after publication of the final rules, a delay of approximately 6 months compared to the proposed effective date. One comment requested that firms be allowed to use up existing stocks of labeling bearing the voluntary warning statement. One comment stated that revising labeling requires at least 1 year.

FDA agrees that costs of compliance with labeling requirements are reduced with extended effective dates. In general, costs of compliance for labeling are less for longer compliance periods because firms can incorporate mandatory changes to product labeling with regularly scheduled changes. In general, labeling costs are reduced by 50 percent when a compliance period is extended from 6 months to 1 year. However, benefits are also delayed.

FDA has considered the requests to extend the effective date for implementing the labeling requirements of this final rule from a period of 6 months to a period of 1 year. FDA would select the regulatory option of extending the compliance period for the warning statement requirements if the marginal benefit of the option exceeds the marginal cost. The marginal benefit of extending the compliance period to 1 year is the reduction in benefits caused by not preventing nonfatal cases for 6 months. Marginal costs will exceed marginal benefits if 125 cases are not prevented. FDA believes that it is likely that the number of additional nonfatal cases not prevented during the 6-month period will exceed this number. Thus, the savings to manufacturers from a 1-year compliance period will not be as great as the savings from injuries avoided by having the warning statement on all products. Consequently, FDA is denying the requests to extend the compliance period to 1 year.

FDA also has considered the requests to consolidate the effective date for the labeling requirements of this rule with the dietary supplement labeling requirements that would be issued as a result of the DSHEA. At this time, the effective date of this final rule is after December 31, 1996, which is the statutorily mandated date of compliance for the labeling requirements imposed by the DSHEA. However, it is questionable whether FDA's regulations implementing the DSHEA labeling requirements will be finalized before that date. FDA has previously stated its intent to provide a reasonable compliance period for the provisions of DSHEA (61 FR 16423, April 15, 1996). In light of the comments that discussed the extent of the current compliance with the industry's voluntary labeling program, FDA considers that a

reasonable response to the requests for a single compliance date, which still places public health at the forefront, is to retain the effective date of 180 days as proposed but to use enforcement discretion, consistent with its announced intent to provide a reasonable compliance period for the provisions of the DSHEA, for those products that bear a voluntary warning statement (such as the statement suggested by the NDMA). Products that do not bear any warning statement, however, must be in compliance with this final rule within 6 months of its date of publication. In the interest of fairness, the agency is likely to follow a similar approach with respect to iron-containing drug products even though iron-containing drug products are not subject to the agency's labeling regulations implementing DSHEA.

Several comments requested an extension of the effective date for the packaging requirements. One comment stated revising packaging requires at least 1 year. The comment stated that the time required to order, obtain, and implement new tooling and equipment easily exceeds 180 days. Another comment suggested that many firms would have to use outside contractors for unit-dose packaging with resultant costs and time delays but did not provide any estimates. One comment expressed uncertainty about whether the capacity of the packaging industry was sufficient to handle the extra work. One comment from the packaging industry stated that enough capacity exists to unit-dose pack all iron-containing products currently sold in the United States.

FDA agrees that costs of compliance with packaging requirements are reduced with extended effective dates. In general, extending the compliance date for packaging to 1 year would reduce costs of materials, transportation, storage, and administration. The total reduction in cost of packaging due to a 6-month extension would be approximately $5 million. However, the 6-month extension would also decrease benefits. The cost of extending the compliance date for packaging requirements for products containing 30 mg or more of iron per dosage unit is a reduction in benefits caused by not preventing fatal cases for 6 months, valued at an amount between $16 and $32 million.

FDA has considered the requests to extend the effective date for implementing the packaging requirements of this final rule. The agency's calculations show that the reduction in costs that would be expected by extending the compliance period to 1 year is small compared to the overall costs of the rule. Moreover, the reduction in benefits that would be expected by extending the compliance period to 1 year exceed the reduction in costs by a factor of 3 to 6. Therefore, FDA is denying the requests to increase the time for compliance with this final rule.

C. Regulatory Flexibility

FDA stated in the original analysis that it was not aware that any small businesses would be affected by the proposed rule and therefore determined that the rule will not result in a significant burden on small businesses. In response to those statements, FDA received comments indicating that some small businesses will be adversely affected by the rule if finalized as proposed.

One comment requested that FDA conduct an Initial Regulatory Flexibility Analysis and republish the proposed rule with that analysis, allowing for an appropriate period for public comment. FDA is denying this request. The risk of harm from accidental iron pediatric poisonings is too great for FDA to postpone rulemaking on this matter. Republishing the proposed rule would postpone action on this issue for at least 6 additional months. During that time, FDA estimates that 2 fatal cases and as many as 1,000 nonfatal cases that could be prevented by publishing the final rule rather than republishing the proposal. Further, FDA received many comments to the proposed rule providing information that FDA used to modify the provision of the rule to be less burdensome for small entities. FDA does not believe that republishing the proposed rule would result in a final rule that is significantly different from this one.

According to the Small Business Administration's (SBA) size standards, a maker of iron-containing products is small if it employees fewer than 500 persons. According to the National Nutritional Foods Association (NNFA), of approximately 100 of their members that produce iron-containing products, over 90 percent have fewer than 500 employees. However, because not all iron-containing products are produced by members of NNFA, there are probably more than 90 firms producing iron-containing supplements. According to the Bureau of the Census, approximately 84 percent, or 504 firms, of the pharmaceutical industry, which is not limited to manufacturers of iron-containing products, are small. Therefore, a significant portion of the affected industry is small by SBA's definitions. However, sources of information on the number of firms that produce iron-containing products are limited. Several sources collect information only on a subgroup of iron-containing product manufacturers, e.g., members of a particular trade organization. Other sources collect information at such an aggregated level that the information specific to iron-containing products cannot be separated out. Therefore, it is either impossible or impracticable to estimate the number of small entities that produce iron-containing products.

FDA was able to gather specific data on 10 small and 12 large producers of iron-containing supplements. The firms for which data were available sold over-the-counter iron-containing supplements through grocery stores and cannot be considered as representative of the entire industry. Many other iron-containing products are distributed through pharmacies or clinics or are marketed through other types of retail outlets and mail order catalogs. Nevertheless, because these were the only firms for which FDA could find data on the number of employees, annual revenues, and number of iron-containing products produced, the analysis was restricted to these 22 firms.

The 10 small firms employed between 4 and 440 persons (median = 111), had annual sales ranging from $450,000 to $116 million (median = $17 million), and produced between 1 and 8 iron-containing products (median = 3). A total of 35 iron-containing products were produced by small firms in the sample. The impact was heaviest on the two firms with the smallest annual revenues. For these two small firms, the regulatory cost as a percentage of annual revenues were 3 and 6 percent. The regulatory cost could be expected to raise total company expenses by 4 and 8 percent for these two small firms. In addition, the regulatory cost as a percentage of total company profits was 16 and 30 percent for these two small firms. On average, the ten small firms in the sample would experience an increase in total company expenses of 1.6 percent (median = .68 percent). The costs of the regulation as a percentage of total company profits was 6.27 percent on average for the 10 firms in the sample (median = 2.64 percent).

By comparison, the 12 large firms in the sample employed between 600 and 82,000 persons (median = 21,950), had annual sales between $60 million and $19 billion (median = $6.1 billion), and produced between 1 and 15 iron-containing products (median = 5). A total of 67 products were produced by the large firms in the sample. On average, large firms would experience

an increase in total company expenses of 0.05 percent (median = .0021 percent). Regulatory costs as a percent of annual revenues would be 0.04 percent for the average large firm (median = .0017 percent). Regulatory costs as a percent of total company profits would be 0.21 percent on average for large firms (median = .0083 percent).

D. Alternatives to Provide Regulatory Relief for Small Business

There are five alternatives that the agency considered to provide regulatory relief for small entities. First, FDA considered the option of exempting small entities from the requirements of this rule. Second, FDA considered lengthening the compliance period for small entities. Third, the agency considered exempting products containing elemental iron, such as carbonyl iron, from packaging requirements because of its low potential for toxicity. Fourth, FDA considered less restrictive warning label requirements for small entities. Finally, FDA considered the option of establishing performance rather than design standards.

1. Exempt Small Entities

One alternative for alleviating the burden for small entities would be to exempt them from the provisions of this rule. However, the majority of the firms engaged in the manufacture of iron-containing products are small. Even accounting for the fact that large firms produce more products on average than small firms, exempting small firms would exempt a large proportion of iron-containing products. Although this option would clearly eliminate the burden on small firms, it would also result in a significant decrease in the number of pediatric iron poisonings prevented. Therefore, FDA concludes that selecting this alternative would defeat the purpose of the regulation.

2. Lengthen the Compliance Period

As discussed above, the agency proposed to make any final rule effective 6 months after publication of the final rule. The DSHEA imposes certain labeling requirements on dietary supplements to be effective in December 1996. FDA could consolidate the effective date for the warning label requirements with the effective date for the new nutrition labeling format for dietary supplements, thus reducing costs. FDA received many comments stating that extending the compliance period for labeling requirements would reduce the burden for small entities without significantly reducing the benefits of the actions.

FDA agrees that extending the compliance period for the labeling requirements to coincide with the effective date for the requirements of DSHEA would significantly reduce the burden of the labeling requirements on small entities. However, a delay in the effective date for small entities would reduce the number of accidental poisonings that would be prevented by between 7 and 100 nonfatal cases. Therefore, the agency does not agree that the reduction in costs exceeds the reduction in benefits that would be expected. However, because compliance with the industry's voluntary labeling program appears to be significant, as stated previously in this document, FDA is retaining the effective date of 180 days as proposed but intends to exercise its enforcement discretion, consistent with its announced intent to provide a reasonable compliance period for the provisions of the DSHEA, for those products bearing a voluntary warning statement, such as the statement suggested by NDMA, until after the agency begins to enforce the labeling regulations implementing DSHEA. FDA believes that this response will relieve some of the burden associated with the warning statement requirements.

3. Exemption for Carbonyl Iron

Several comments to the proposed rule suggested that an exemption for carbonyl iron would reduce the impact on small entities. Because it is less expensive to switch to carbonyl iron than to comply with the packaging requirements, most or all small producers would likely take advantage of the exemption. Thus, FDA acknowledges that exempting products made with carbonyl iron would significantly reduce the burden on small entities. Because of the uncertainty regarding the relative toxicity of carbonyl iron, FDA is temporarily exempting products containing carbonyl iron from the packaging requirements for 1 year. If FDA receives sufficient data to convince the agency that an exemption from carbonyl iron will not result in a significant loss in benefits, the exemption will be made permanent. Because this exemption would apply to large firms as well as small, FDA does not believe that small entities will bear the cost of developing the necessary data.

4. Less Stringent Labeling Requirements

Elsewhere in this preamble, FDA has responded to comments from both large and small firms regarding more flexible requirements with respect to warning statements. Upon consideration of the comments, FDA has amended its proposed warning label requirements to allow as much flexibility as is possible. For example, FDA is no longer requiring that the warning statement appear on the principal display panel. FDA is also allowing firms that currently use warning statements additional time to modify their labels. Because the requirements of the final warning statements requirements are as flexible as possible, there is no room for additional flexibility for small firms.

5. Performance Standards Rather Than Design Standards

FDA considered the possibility of establishing performance rather than design standards for this final rule. Although specifically prescribing packaging and labeling changes, FDA has written performance based criteria for certain provisions of this rule. In the case of warning label statements for unit-dose containers, FDA has revised the wording of the regulation in such a way that makes clear that the manufacturer bears the responsibility in designing labeling that will meet the agency's goal of informing consumers of the dangers to small children from an accidental overdose of a product that contains iron but provides the manufacturer with flexibility in determining how it will do so. Also, FDA has decided specifically not to require any particular type of packaging, for example blister packs or pouches. Instead, FDA is allowing the manufacturer to determine the most appropriate packaging for its product provided that the packaging meets the goal of allowing access to only one dose at a time.

FDA considered the potential for establishing an acceptable toxicity for iron-containing products rather than prescribing packaging and labeling requirements to reduce risk of harm. It is not clear that this option would be less costly for small entities. For most sources of iron, the available toxicity data either does not exist or is unsuited for the purpose of evaluating the toxicity of the form of iron in humans.

E. Summary

FDA has examined the impact of the final rule in accordance with Executive Order 12866 and has determined that it is not an economically significant rule. The rule will result in costs in the first year of approximately $56 million and $4.3 per year starting in year two for total discounted costs of $118 million (discounted to infinity at 7 percent). The rule will also result in per year benefits of between $31.5 million and $61 million for total discounted benefits of

between $426 million and $847 million (discounted to infinity at 7 percent).

FDA has also examined the impact of this final rule on small businesses in accordance with the Regulatory Flexibility Act. This analysis with the rest of the preamble constitutes the Final Regulatory Flexibility Analysis. FDA has determined that this rule is likely to have a significant impact on a substantial number of small entities. However, if the temporary exemption for products made with carbonyl iron is made permanent, the impact on small entities will be significantly reduced. FDA is also reducing the impact on small entities by exempting from the labeling requirements those products bearing a voluntary warning statement until after the agency's labeling regulations implementing DSHEA take effect. FDA, in conjunction with the Administrator of OIRA, OMB, has determined that this rule is not a major rule for purposes of congressional review.

F. Public Outreach

FDA has conducted extensive outreach to a wide audience on the problem of accidental overdose of iron-containing products in small children. This outreach included independent FDA activities as well as cooperative efforts between FDA and professional trade organizations.

One focus of FDA's outreach effort was to educate consumers about the danger that iron-containing products posed to small children to foster changes in behavior with respect to safe handling of these products. This effort included direct outreach to consumers through TV and radio public service announcements in English and in Spanish; a camera-ready newspaper column in English and Spanish; multicolored posters, in English and in Spanish, distributed to retail pharmacists and clinics operated by the Women, Infants, and Children Program of the U.S. Department of Agriculture; an FDA backgrounder, which described the agency's efforts to protect children from accidental iron poisoning, that was both disseminated in printed form and made available through electronic means as a special feature in the FDA News section of the agency's home page on the World Wide Web (August 1995); an article in FDA Consumer, the agency's official consumer publication; a ''Dear Consumer'' letter distributed to more than 500 organizations with more than 10,000 affiliates; and a ''Dear Consumer Newsletter Editor'' letter to more than 150 consumer publications. FDA believed that many of these efforts would be noticed by small producers of iron supplements.

A second focus of FDA's outreach effort was to inform the professional health care community of the danger that iron-containing products posed to small children so that health care providers could help disseminate educational materials to consumers and promote the safe handling of iron-containing products. FDA notified several dozen pharmacy, medicine, and nursing organizations of the proposed regulation by telefax, including a copy of the press release, backgrounder, and summary of the regulation; mailed a ''Dear Doctor'' letter to obstetricians/gynecologists; issued a Medical Bulletin; and published columns in leading medical journals.

A third focus of FDA's outreach effort was to inform manufacturers of iron-containing products of the agency's proposed regulations on packaging and labeling such products and encourage them to work together with the agency to develop a final rule based on the proposal. The initial outreach consisted of a telefax notification, including a copy of a press release from the Department of Health and Human Services and the above-mentioned FDA backgrounder, to several trade associations to alert them to the publication of the agency's proposed rule, followed by a direct mailing of a copy of the proposed rule to those organizations. In addition, FDA met with representatives of two manufacturers' trade organizations shortly after the publication of the proposed rule to discuss specific aspects of the proposed regulation. FDA also placed a summary of key provisions of the proposed rule in the FDA News section of the agency's home page on the World Wide Web.

VIII. Environmental Impact

The agency has previously considered the environmental effects of this rule as announced in the proposed rule of October 6, 1994 (59 FR 51030). No new information or comments have been received that would affect the agency's previous determination that there is no significant impact on the human environment and that an environmental impact statement is not required.

IX. Paperwork Reduction Act

The labeling requirement of this final rule is not within the scope of the Paperwork Reduction Act of 1995, because under 5 CFR 1320.3(c)(2),[20] it is excluded from the definition of collection of information.

X. Effective Date

As discussed above (see section VII.B.7. of this document), the effective date of the labeling requirements of this final rule is 180 days after the date of its publication in the Federal Register except that the effective date for iron-containing dietary supplement and drug products bearing a voluntary warning statement (such as the statement suggested by the NDMA) is after December 31, 1996 (i.e., after the agency's labeling regulations implementing DSHEA take effect).

As also discussed above (see section VII.B.7. of this document), the effective date of the packaging requirements of this final rule is 180 days after date of its publication in the Federal Register, except that FDA is temporarily exempting products that contain carbonyl iron as the sole source of iron from these packaging requirements. The temporary exemption will automatically expire 1 year after date of publication of this final rule in the Federal Register. If, following the temporary exemption period, FDA does not temporarily or permanently extend the exemption, the packaging requirements of this final rule will become effective for products that contain carbonyl iron as their sole source of iron source according to the same principle as for products containing other forms of iron, i.e., on the date that is 180 days after date of expiration of the temporary exemption, or on July 15, 1998.

XI. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Memorandum of telephone conversation between Paul Whittaker, FDA, and Rose Ann Soloway, American Association of Poison Control Centers, dated October 13, 1995.

2. Memorandum of telephone conversation between Paul Whittaker, FDA, and Suzanne Barone, U.S. Consumer Product Safety Commission, dated November 30, 1995.

3. American Association of Poison Control Center, Inc., petition to FDA, 91P–0186/CP1, 1991.

4. Attorneys General, petition to FDA, 93P–0306/CP1, 1993.

5. Nonprescription Drug Manufacturers Association, petition to FDA, 93P–0306/CP2.

6. ''Iron,'' in *Nelson Textbook of Pediatrics*, edited by R. E. Behrman, R. M. Kliegman, W. E. Nelson, and V. C. Vaughan, W. B.

[20] Under 5 CFR 1320.3(c)(2), the public disclosure of information originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public is not included within the definition of ''collection of information.''

Saunders Co., Philadelphia, PA, 14th ed., pp.1780–1781, 1992.

7. Stewart, D. W., and I. M. Martin, ''Intended and Unintended Consequences of Warning Messages: A Review and Synthesis of Empirical Research,'' *Journal of Public Policy and Marketing*, 13(1):1–19, 1994.

8. Wilbur, C. J., ''Child Resistant Effectiveness Conventional Pouch Packaging (Non-Child Resistant),'' U.S. Consumer Product Safety Commission, C–805–9864, 1978.

9. Wilbur, C. J., ''Child Resistant Effectiveness Conventional Blister Card Packaging (Non-Child Resistant),'' U.S. Consumer Product Safety Commission, E–850–3006, 1978.

10. U.S. Consumer Product Safety Commission iron fatality case reports.

11. Shelanski, H. A., ''Acute and Chronic Toxicity Tests on Carbonyl Iron Powder,'' *Bulletin of the National Formulary Committee*, 18:87–94. 1950.

12. Life Sciences Research Office, Federation of American Societies for Experimental Biology, ''Evaluation of the Health Aspects of Iron and Iron Salts as Food Ingredients,'' (SCOGS–35). Contract No. FDA 223–75–2004, 1980.

13. National Academy of Sciences. Committee on Animal Nutrition, Subcommittee on Mineral Toxicity in Animals, ''Mineral Tolerance of Domestic Animals,'' 1980.

14. Twenty-seventh Report of the Joint Federal/World Health Expert Committee on Food Additives, ''Toxicological Evaluation of Certain Food Additives and Contaminants,'' Word Health Organization (WHO) Technical Report Series No. 696, 1983.

15. Weaver, L. C., R. W. Gardier, V. B. Robinson, and C. A. Bunde ''Comparative Toxicology of Iron Compounds,'' American Journal of the Medical Sciences, 241:296–302, 1961.

16. Hoppe, J. O., G. M. A. Marcelli, and M. L. Tainter, ''A review of the toxicity of iron compounds,'' Progress of Medical Science, 230:558–571, 1955.

17. Casarett and Doull's Toxicology, The Basic Science of Poisons, 4th ed., edited by M. O. Amdur, J. Doull, and C. C. Klaassen, Pergamon Press, New York, p. 22, 1991.

18. U.S. Food and Drug Administration, Bureau of Foods, ''Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food,'' National Technical Information Service, Springfield, VA, p. 21, 1982.

19. Sacks, P. V., and W. M. Crosby, ''Bioavailability and Toxicity of Carbonyl Iron,'' Journal of Clinical Research, 22:562, 1974.

20. Klein-Schwartz, W., G. M. Oderda, R. L. Gorman, F. Favin, and S. R. Rose, ''Assessment of Management Guidelines. Acute Iron Ingestion,'' Clinical Pediatrics, 29:316–321, 1990.

21. Mann, K. V., M. A. Picciotti, T. A. Spevack, and D. R. Durbin, ''Management of Acute Iron Overdose,'' Clinical Pharmacy, 8:428–440, 1989.

22. Gordeuk, V. R., G. M. Brittenham, C. E. McLaren, M. A. Hughes, and L. J. Keating, ''Carbonyl Iron Therapy for Iron Deficiency Anemia,'' Blood, 67:745–752, 1986.

23. Crosby, W. H., ''Prescribing Iron? Think Safety,'' Archives of Internal Medicine, 138:766–767, 1978.

24. Devasthali, S. D., V. R. Gordeuk, G. M. Brittenham, J. R. Bravo, M. A. Hughes, and L. J. Keating, ''Bioavailability of Carbonyl Iron: A Randomized, Double-blind Study,'' European Journal of Haematology, 46:272–278, 1991.

25. American Association of Poison Control Centers, Toxic Exposure Surveillance System (TESS), ''Field Definitions,'' 1992–1994.

26. Gordeuk, V. R., G. M. Brittenham, M. Hughes, L. J. Keating, and J. J. Opplt, ''High-dose Carbonyl Iron for Iron Deficiency Anemia: A Randomized, Double-blind Trial,'' American Journal of Clinical Nutrition, 46:1029–1034, 1987.

27. Gordeuk, V. R., G. M. Brittenham, M. A. Hughes, and L. J. Keating, ''Carbonyl Iron for Short-term Supplementation in Female Blood Donors,'' Transfusion, 27:80–85, 1987.

28. Gordeuk, V. R., G. M. Brittenham, J. Bravo, M. A. Hughes, and L. J. Keating, ''Prevention of Iron Deficiency With Carbonyl Iron in Female Blood Donors,'' Transfusion, 30:239–245, 1990.

29. Hallberg, L., M. Brume, and L. Rossander, ''Low Bioavailability of Carbonyl Iron in Man: Studies on Iron Fortification of Wheat Flour,'' American Journal of Clinical Nutrition, 43:59–67, 1986.

30. Huebers, H. A., G. M. Brittenham, E. Csiba, and C. A. Finch, ''Absorption of Carbonyl Iron,'' Journal of Laboratory Clinical Medicine, 108:473–478, 1986.

31. Orwin, R. G., R. E. Schucker, and R. C. Stokes, ''Evaluating the Life Cycle of a Product Warning: Saccharin and Diet Soft Drinks,'' Evaluation Review, 8 (6), 801–822, 1984.

List of Subjects

21 CFR Part 101

Food labeling, Nutrition, Reporting and recordkeeping requirements.

21 CFR Part 111

Drugs, Packaging and containers, and labeling.

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and record keeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, title 21 CFR chapter I is amended as follows:

PART 101—FOOD LABELING

1. The authority citation for 21 CFR part 101 continues to read as follows:

Authority: Secs. 4, 5, 6 of the Fair Packaging and Labeling Act (15 U.S.C. 1453, 1454, 1455); secs. 201, 301, 402, 403, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 342, 343, 348, 371).

2. Section 101.17 is amended by adding new paragraph (e) to read as follows:

§ 101.17 Food labeling warning and notice statements.

* * * * *

(e) *Dietary supplements containing iron or iron salts.* (1) The labeling of any dietary supplement in solid oral dosage form (e.g., tablets or capsules) that contains iron or iron salts for use as an iron source shall bear the following statement:

WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

(2)(i) The warning statement required by paragraph (e)(1) of this section shall appear prominently and conspicuously on the information panel of the immediate container label.

(ii) If a product is packaged in unit-dose packaging, and if the immediate container bears labeling but not a label, the warning statement required by paragraph (e)(1) of this section shall appear prominently and conspicuously on the immediate container labeling in a way that maximizes the likelihood that the warning is intact until all of the dosage units to which it applies are used.

(3) Where the immediate container is not the retail package, the warning statement required by paragraph (e)(1) of this section shall also appear prominently and conspicuously on the information panel of the retail package label.

(4) The warning statement shall appear on any labeling that contains warnings.

(5) The warning statement required by paragraph (e)(1) of this section shall be set off in a box by use of hairlines.

3. Part 111 consisting of § 111.50, is added to read as follows:

PART 111—CURRENT GOOD MANUFACTURING PRACTICE FOR DIETARY SUPPLEMENTS

Authority: Secs. 201, 402, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 342, 371).

§ 111.50 Packaging of iron-containing dietary supplements.

(a) The use of iron and iron salts as iron sources in dietary supplements offered in solid oral dosage form (e.g., tablets or capsules), and containing 30 milligrams or more of iron per dosage unit, is safe and in accordance with current good manufacturing practice only when such supplements are

packaged in unit-dose packaging. ''Unit-dose packaging'' means a method of packaging a product into a nonreusable container designed to hold a single dosage unit intended for administration directly from that container, irrespective of whether the recommended dose is one or more than one of these units. The term ''dosage unit'' means the individual physical unit of the product (e.g., tablets or capsules). Iron-containing dietary supplements that are subject to this regulation are also subject to child-resistant special packaging requirements in 16 CFR parts 1700, 1701, and 1702.

(b)(1) Dietary supplements offered in solid oral dosage form (e.g., tablets or capsules), and containing 30 milligrams or more of iron per dosage unit, are exempt from the provisions of paragraph (a) of this section until January 15, 1998, if the sole source of iron in the dietary supplement is carbonyl iron that meets the specifications of § 184.1375 of this chapter.

(2) If the temporary exemption is not extended or made permanent, such dietary supplements shall be in compliance with the provisions of paragraph (a) of this section on or before July 15, 1998.

PART 310—NEW DRUGS

The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

4. New § 310.518 is added to subpart E to read as follows:

§ 310.518 Drug products containing iron or iron salts.

Drug products containing elemental iron or iron salts as an active ingredient in solid oral dosage form, e.g., tablets or capsules shall meet the following requirements:

(a) *Packaging.* If the product contains 30 milligrams or more of iron per dosage unit, it shall be packaged in unit-dose packaging. ''Unit-dose packaging'' means a method of packaging a product into a nonreusable container designed to hold a single dosage unit intended for administration directly from that container, irrespective of whether the recommended dose is one or more than one of these units. The term ''dosage unit'' means the individual physical unit of the product, e.g., tablet or capsule. Iron-containing drugs that are subject to this regulation are also subject to child-resistant special packaging requirements in 16 CFR parts 1700, 1701, and 1702.

(b) *Temporary exemption.* (1) Drug products offered in solid oral dosage form (e.g., tablets or capsules), and containing 30 milligrams or more of iron per dosage unit, are exempt from the provisions of paragraph (a) of this section until January 15, 1998, if the sole source of iron in the drug product is carbonyl iron that meets the specifications of § 184.1375 of this chapter.

(2) If this temporary exemption is not extended or made permanent, such drug products shall be in compliance with the provisions of § 111.50(a) of this chapter on or before July 15, 1998.

(c) *Labeling.* (1) The label of any drug in solid oral dosage form (e.g., tablets or capsules) that contains iron or iron salts for use as an iron source shall bear the following statement:

WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

(2)(i) The warning statement required by paragraph (c)(1) of this section shall appear prominently and conspicuously on the information panel of the immediate container label.

(ii) If a drug product is packaged in unit-dose packaging, and if the immediate container bears labeling but not a label, the warning statement required by paragraph (c)(1) of this section shall appear prominently and conspicuously on the immediate container labeling in a way that maximizes the likelihood that the warning is intact until all of the dosage units to which it applies are used.

(3) Where the immediate container is not the retail package, the warning statement required by paragraph (c)(1) of this section shall also appear prominently and conspicuously on the information panel of the retail package label.

(4) The warning statement shall appear on any labeling that contains warnings.

(5) The warning statement required by paragraph (b)(1) of this section shall be set off in a box by use of hairlines.

(d) The iron-containing inert tablets supplied in monthly packages of oral contraceptives are categorically exempt from the requirements of paragraphs (a) and (c) of this section.

Dated: October 24, 1996.

David A. Kessler,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 97–947 Filed 1–14–97; 8:45 am]

BILLING CODE 4160–01–P