UNITED STATES GOVERNMENT

Memorandum

U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, D.C. 20207

TO : Commissioners

DATE: December 20, 1974

FROM : Sheldon D. Butts, Assistant Secretary

THRU: Sadye E. Dunn
Secretary

SUBJECT: Vote Sheet: Proposed PPPA Standard for Iron Preparations

Attached are a draft Federal Register Notice proposing PPPA requirements for iron preparations and memoranda from OGC and PSOC containing recommendations on the proposal. Both OGC and PSOC have suggested revisions in the document; however, both agree that the proposal should be published as soon as possible.

Please indicate below your vote on the draft notice and suggested changes.

APPROVE FR NOTICE AS DRAFTED	(SIGNATURE)	(DATE)
APPROVE FR NOTICE WITH CHANGES NOTED	(SIGNATURE)	(DATE)
DISAPPROVE FR NOTICE	(SIGNATURE)	(DATE)
ABSTAIN	(SIGNATURE)	(DATE)

COMMENTS:

*U.S. GOVERNMENT PRINTING OFFICE: 1974 733-533/3604 1-3

11 pages Chairman Simpson

UNITED STATES GOVERNMENT

Memorandum

U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, D.C. 20207

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APPROVE FR NOTICE AS DRAFTED	_____ (SIGNATURE)	_____ (DATE)
APPROVE FR NOTICE WITH CHANGES NOTED per Lanpher memo	with OGC changes initialed X R. D. (SIGNATURE)	1-3-75 (DATE)
DISAPPROVE FR NOTICE	_____ (SIGNATURE)	_____ (DATE)
ABSTAIN	_____ (SIGNATURE)	_____ (DATE)

COMMENTS:

*U.S. GOVERNMENT PRINTING OFFICE: 1974 733-533/3604 1-3

DEC 23 1974

UNITED STATES GOVERNMENT

Memorandum

U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, D.C. 20207

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APPROVE FR NOTICE AS DRAFTED	(SIGNATURE)	(DATE)
APPROVE FR NOTICE WITH CHANGES NOTED	B. Franklin (SIGNATURE)	1-13-75 (DATE)
DISAPPROVE FR NOTICE	(SIGNATURE)	(DATE)
ABSTAIN	(SIGNATURE)	(DATE)

COMMENTS:

U.S. GOVERNMENT PRINTING OFFICE: 1974 733-533/1604 1-3

Commissioner Kushner (9)

UNITED STATES GOVERNMENT

Memorandum

U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, D.C. 20207

TO : Commissioners

DATE: December 20, 1974

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THRU: Sadye E. Dunn
Secretary

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APPROVE FR NOTICE AS DRAFTED	(SIGNATURE)	(DATE)
APPROVE FR NOTICE WITH CHANGES NOTED	Lawrence Kushner (SIGNATURE)	1/3/75 (DATE)
DISAPPROVE FR NOTICE	(SIGNATURE)	(DATE)
ABSTAIN	(SIGNATURE)	(DATE)

COMMENTS:

DEC 23 1974 70

*U.S. GOVERNMENT PRINTING OFFICE: 1974 733-533/3604 1-3

Commissioner Newman

UNITED STATES GOVERNMENT

Memorandum

U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, D.C. 20207

TO : Commissioners

DATE: December 20, 1974

FROM : Sheldon D. Butts, Assistant Secretary

THRU: Sadye E. Dunn
Secretary

SUBJECT: Vote Sheet: Proposed PPPA Standard for Iron Preparations

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Please indicate below your vote on the draft notice and suggested changes.

APPROVE FR NOTICE AS DRAFTED	_____ (SIGNATURE)	_____ (DATE)
APPROVE FR NOTICE WITH CHANGES NOTED (GC)	Clemmon (SIGNATURE)	1/3/75 (DATE)
DISAPPROVE FR NOTICE	_____ (SIGNATURE)	_____ (DATE)
ABSTAIN	_____ (SIGNATURE)	_____ (DATE)

COMMENTS:

DEC 23 1974

*U.S. GOVERNMENT PRINTING OFFICE: 1974 733-533/3604 1-3

Commissioner Pittle

UNITED STATES GOVERNMENT

Memorandum

DEC 23 1974

U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, D.C. 20207

TO : Commissioners

DATE: December 20, 1974

FROM : Sheldon D. Butts, Assistant Secretary

THRU: Sadye E. Dunn
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SUBJECT: Vote Sheet: Proposed PPPA Standard for Iron Preparations

Attached are a draft Federal Register Notice proposing PPPA requirements for iron preparations and memoranda from OGC and PSOC containing recommendations on the proposal. Both OGC and PSOC have suggested revisions in the document; however, both agree that the proposal should be published as soon as possible.

Please indicate below your vote on the draft notice and suggested changes.

APPROVE FR NOTICE AS DRAFTED	_____ (SIGNATURE)	_____ (DATE)
APPROVE FR NOTICE WITH CHANGES NOTED per Feinberg memo	X R. David Pittle (SIGNATURE)	1/4/75 (DATE)
DISAPPROVE FR NOTICE	_____ (SIGNATURE)	_____ (DATE)
ABSTAIN	_____ (SIGNATURE)	_____ (DATE)

COMMENTS:

*U.S. GOVERNMENT PRINTING OFFICE: 1974 733-533/3604 1-3

UNITED STATES GOVERNMENT

Memorandum

U.S. CONSUMER PRODUCT
SAFETY COMMISSION
WASHINGTON, D.C. 20207

TO : Michael Brown, OGC
Attn: Steve Lemberg

DATE: DEC 18 1974

Thru : L. J. Sharman, Dir., OSCA, A. Dimoff, Deputy EX, and F. Barrett, EX

FROM : Bernard Scharf, Technical Analysis Division, OSCA

Bernard Scharf CRC

SUBJECT: Lemberg/Dunn Memo of 12-2-74: "Proposed PPPA Standard for Iron Preparations"

The subject memorandum was circulated to the Office of the Medical Director and the Bureaus of Compliance, Biomedical Science, and Economic Analysis. The comments of these PSOC units are attached along with general observations on these comments.

All units agree that the proposed regulation be published as soon as possible. There are some reservations expressed on some of the suggested changes and these are discussed below. Since this is a proposal we can expect comments from interested parties if there are any merits to the reservations expressed.

Office of the Medical Director:

OMD has no reservations, questions, additions, or corrections. They are satisfied with the proposed changes.

Bureau of Economic Analysis:

BEA has no objections to the proposed changes. BEA expresses some concern about the "availability" of droppers for those products administered by dropper. We now know that these are available, but we do not know if sufficient quantities exist to supply the packages' requirements quantitywise. The existence of at least one dropper assembly demonstrates the technical feasibility to produce a satisfactory product. Thus, there would be no possibility for contamination as there might be with a dropper supplied separately and intended to be stored separately from the reservoir bottle between successive administrations of a product requiring dropper administration. The proposed one-year time period for the regulation to become effective after promulgation should allow manufacturers to place orders and obtain the requisite quantities. Perhaps a letter campaign to manufacturers' trade associations and pharmacists' societies, as was done in the ethylene glycol situation, prior to or simultaneously with the publication in the FEDERAL REGISTER, may obviate any potential problems in this area.

*U.S. GOVERNMENT PRINTING OFFICE: 1974 733-533/3604 1-3

Bureau of Biomedical Science:

BBS is concerned about establishing the technical feasibility, practicability, and appropriateness of packaging for other than orally administered iron preparations. Per a discussion between Steve Lemberg and B. Scharf, we were unable to locate any other dosage forms of iron preparations other than those intended for oral or injectable administration. (Physicians' Desk Reference, Pharmindex and Facts and Comparisons were consulted.)

BBS questions an apparent omission, under point four of the referenced Lemberg/Dunn memo, of coverage of dietary supplements intended for use in animals other than man and asks if this was intended. In the event that this was unintentional, BBS offers substitute wording which does not mention either man or other animals and is consistent with OGC's suggestions that iron preparations packaged for animal use be covered by the subject regulation. This would be consistent with point five of the Lemberg/Dunn memo, referenced above, and with the revised language for paragraph (12) on page 6 of the draft regulation.

BBS further points out that should the proposed veterinary prescription drug regulation be promulgated, this would result in double coverage. This would also result in a ready-made exemption to the veterinary prescription drug regulation in that those products containing less than 500 mg of iron per package would be exempt. The foregoing would also apply to non-prescription drugs if a subsequent decision is made to require non-prescription animal drugs to be packaged in Special Packaging.

BBS notes that the Technical Advisory Committee on Poison Prevention Packaging has not been consulted on this expanded coverage but concludes that such consultation, at this time, would further delay the standard's promulgation.

Bureau of Compliance:

BCM notes that the changes would make the proposed standard apply:

- to veterinary and human drugs
- to both prescription and non-prescription drugs
- to all dosage forms except injectables (this is discussed above - we have no knowledge that iron is given in forms other than for oral or injectable administration).

BCM discusses the PPPA and the history of its application by FDA with regard to orally administered drugs, aspirin, and controlled drugs. BCM points out that 1700.14(a)(10), the regulation on oral prescription drugs, already covers iron-containing prescription drugs.

Although BCM objects to the changes, they feel that the regulation should be published as soon as possible "...even in the form revised by General Counsel."

Attachments (4)

cc:
OS: Attn: S. Dunn
OEX: Attn: E. Besson
BEA
OMD
BBS
BCM

Signer/Preparer:BScharf/dml

UNITED STATES GOVERNMENT

Memorandum

U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, D.C. 20207

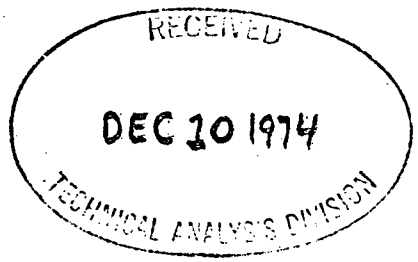
TO : Bernie Scharf, SCAT

DATE: December 10, 1974

THRU : Walter R. Hobby, Director, BEA
FROM : Judith M. Pitcher, Economist, BEA

SUBJECT: G.C. Changes to Proposed PPPA Standard for Iron Preparations.

We have no objections to the draft changes recommended by the General Counsel's Office. Since this is a proposal, we agree with Steve Lemberg that it is inappropriate for the Commission to prejudge the dropper applicator situation by including the original reference in the preamble. However, to our knowledge, CR dropper units are still not "available" in the sense that there exist sufficient production quantities to meet packagers' needs. The existence of the one CR dropper unit known to us, however, does indicate that it is technically feasible to produce this type of special packaging.



*U.S. GOVERNMENT PRINTING OFFICE: 1974 733-533/3604 1-3

UNITED STATES GOVERNMENT

Memorandum

U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, D.C. 20207

TO : Mr. Bernard Scharf, TAD, OSCA

DATE: December 6, 1974

THRU : Albert F. Esch, M.D., Director, OMD A F Esch

FROM : Leo T. Duffy, M.D., OMD L T Duffy

SUBJECT: Proposed PPPA Standard for Iron Preparations

In response to your memorandum of December 5, 1974 concerning further proposed changes suggested by OGC in the August 28, 1974 draft Federal Register Notice on the subject, this Office reviewed said draft.

Following our review we find that there are no further additions, corrections, or other comments to make concerning this subject.

cc: Georg Maisel, BBSPP

*U.S. GOVERNMENT PRINTING OFFICE: 1974 733-533/3604 1-3

MEMORANDUM

DATE: DEC 11 1974

TO : Office of Standards Coordination and Appraisal

Through: Dale C. Miller, Director, Division of Inspection and Enforcement

FROM: Robert G. Poth, BCMI RGPoth

SUBJECT: OGC's December 2, 1974 Memo Outlining Revisions of the Proposed PPPA Standard for Iron Preparations

In escence, the changes suggested by the Office of General Counsel on the subject proposed standard would (1) make it apply to veterinary as well as to human drugs; (2) make it apply to both prescription and non-prescription drugs; and (3) make it apply to all dosage forms except injectables which would include such forms as external powders, ointments, salve, suppository, etc.

The Bureau of Compliance had originally approved of the proposed standard as written. The Poison Prevention Packaging Act at Section 3(a) requires the agency in promulgating child protection packaging standards, to make a clear finding that special child-resistant packaging is necessary for the particular substance in question in order to protect young children from serious personal injury or serious illness and further that special packaging to comply with the standards is technically feasible, practicable, and appropriate for the particular substance. Prior to formation of the Consumer Product Safety Commission, the Commissioner of FDA on the advise of FDA's Bureau of Product Safety, had made the conclusions as follows: (1) human experience data available from such sources as the National Clearinghouse for Poison Control Centers failed to support a finding that special packaging is necessary to protect children from serious personal injury or serious illness as a result of handling, using, or ingesting human drugs in dosage forms intended for other than oral administration. Also at issue at that particular time was concern over a finding that special packaging to comply with the standards was technically feasible, practicable, and appropriate for ointments, suppositories, injectables, etc. Presently, BCM is unaware of any change in human experience data that might indicate a need for special packaging of other than oral dosage forms and is similarly unaware of any change in the state of the art in industry to now make available special packaging which is technically feasible, practicable, and appropriate for the non-oral dosage forms. Further, FDA's Commissioner had similarly concluded that the variation in size of dosage units and in the distribution and usage patterns between human and veterinary preparations is sufficient to warrant separate consideration under the Poison Prevention Packaging Act. Based upon those conclusions, the Commissioner of FDA had, in April of 1973, amended the previously promulgated standards for aspirin and controlled drugs limiting their application to drugs for human use in dosage forms intended for oral

administration. Similarly, the standards for prescription drugs promulgated in April of 1973 was limited in application to those for human use in dosage forms intended for oral administration.

The subject proposed standard for iron salts was limited in its application to non-prescription drugs simply because prescription drugs containing iron are already subject to the standards promulgated in April 1973 at Section 1700.14(a)(10).

Steve Lemberg in the Office of General Counsel is thoroughly aware of the reasons cited above for the proposed standard for iron preparations being written to exclude animal drugs, non-oral dosage forms, and prescription drugs. While the Bureau of Compliance obviously disagrees with the suggested revisions of the Office of General Counsel, we are more strongly concerned with the consumer safety since this particular standard is very badly needed as witnessed by the human experience data relative to iron ingestions, i.e. National Clearinghouse for Poison Control Center data shows 543 hospitalizations of children under five years of age for the period 1969 through 1973 while data from death certificates for the period 1969 through 1972 show 31 deaths of children under five years of age from accidental ingestion of these products. We would therefore concur with the publication of this proposal even in the form revised by General Counsel as quickly as possible.

Dr. L. James Shaman, SCA

December 10, 1974

THRU : Dr. Robert M. Kehir, BBS
Georg S. Haisel, BNSPP

Proposed FPPA Standard for Iron Preparations

Regarding the changes suggested by OGC (memorandum of December 2, 1974) BBS has no problems with the changes suggested. We would, however, like to address points one (1) four (4) and five (5).

We have no objections to expanding the coverage of this regulation provided that lack of such supportive data does not affect the validity of the proposal.

Point 1:

After a 3-year delay, it is vital that this standard be publicized soonest. Since the effect of the suggested changes in points 2 and 5 will include preparations intended for other than oral administration, we may not be able to support the technical feasibility, practicability, and appropriateness of such proposed packaging in every case.

Point 4:

The proposed change in the definition of Dietary Supplements appears to omit those used for animals. Is this intended?

Since OGC suggests that special packaging regulations for iron preparations cover animal as well as human drugs, the following wording is recommended for (new) paragraph 1700.1(a)(3).

> "Dietary Supplement" means any vitamin and/or mineral preparation offered in tablet, capsule, wafer or other similar uniform unit form; in powder, granular, flake, or liquid form; or in the physical form of a conventional food but which is not a conventional food; and which purports to be or is represented for special dietary use to supplement the diet by increasing the total dietary intake of one or more of the essential vitamins and/or minerals.

Point 5:

As you know, we have prepared a proposal covering veterinary prescription drugs. Since the changes mentioned above will result in certain animal drugs being included under the iron preparations proposal, certain products will be covered by both regulations. The foregoing is for your information.

We must note that the Technical Advisory Committee has not been consulted regarding this expanded coverage. Such consultation at this time, would further delay promulgation of this standard.

cc:
C. Casper (Attn: B. Scharf)
DRS
SCA File
Reading File
Central File
Subject File
BBSPP/DCWilliams:mh
Revised by: GSMaisel

Shel

UNITED STATES GOVERNMENT

Memorandum

U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, D.C. 20207

DATE: DEC 2 1974

TO : Sadye E. Dunn, Secretary

FROM : D. S. Lemberg, Office of the General Counsel DSL
THRU : Michael A. Brown, General Counsel MAB

SUBJECT: Proposed PPPA Standard for Iron Preparations

Attached is a draft Federal Register notice proposing to require child-resistant packaging for certain iron-containing preparations. A PSOC briefing package with sign-off sheets has previously been forwarded to your office. We concur with PSOC's recommendation that this proposed regulation be published as soon as possible. We are suggesting several changes which we believe should be incorporated in the final draft. However, since PSOC has not yet had the opportunity to formally comment on our suggestions, we recommend that you wait 10 working days before submitting this item to the Commissioners for action. We will transmit a copy of this memorandum to the Executive Director informing him that PSOC comments may be submitted to your office within 10 days. Any comments received may then be sent to the Commission for consideration along with our suggestions.

The changes we suggest are as follows:

1. On page 3 of the draft, eliminate all of that portion of the paragraph designated as "3." following the word "use." This paragraph will then state:

> "3. Appropriate since such special packaging is not detrimental to the integrity of the substance and will not interfere with its storage or use."

The original discussion of dropper bottles was included in this portion of the preamble because it was believed that dropper units were not available which were child-resistant. However, information now indicates that such child-resistant dropper units are available. Thus, this language would appear to be unnecessary.

*U.S. GOVERNMENT PRINTING OFFICE: 1974 733-533/3604 1-3

2. On page 4 of the draft, under "section 1700.1 Definitions", eliminate entirely the definition (3), "Non-prescription drug". The reason for this suggestion is that this definition is not necessary for the issuance of these regulations, and moreover, is not consistent with the definition of the term as used in the trade since it includes only oral drugs.

3. On page 5 of the draft redesignate the definition of "Dietary Supplement" to subsection (3) since it is recommended that the present subsection (3) be eliminated.

4. On page 5 of the draft, regarding the definition of dietary supplements, delete the word "man" on the next to the last line and replace it with the word "humans." Also delete the words "his diet" on the same line and replace with the words "their diets."

5. On page 6 of the draft, delete the entire paragraph (12), and substitute the following paragraph therefor:

> "(12) Iron preparations. Animal and human drugs (except for injectable drugs), and dietary supplements, as defined in section 1700.1(a)(3), that provide an equivalent of 500 milligrams or more of elemental iron per total package, shall be packaged in accordance with the provisions of section 1700.15(a), (b), and (c)."

This change will make definition of the term "non-prescription drugs" unnecessary, add coverage to include animal drugs and non-oral drugs (except for injectables), and simplify the language. If iron preparations found around the household present ingestion problems for young children, we see no need for excluding products which might be just as likely to be ingested.

6. On page 2 of draft, under Conclusion and proposal, change the description of the substance to be regulated to be consistent with the change suggested in 5., above.

Attachment

PRELIMINARY DRAFT AUG 20 1974

CONSUMER PRODUCT SAFETY COMMISSION

[16 CFR Part 1700]

Certain Preparations Containing Iron

Proposed Child-Resistant Packaging Standards

The purpose of this document is to propose child-resistant packaging standards for certain preparations containing iron. The accidental ingestion of such preparations has been a significant cause of hospitalizations and fatalities of children younger than 5 years of age.

Background. Acute accidental poisoning from iron began to occur with greater frequency when iron became widely used as a therapuetic agent for the treatment of anemia in 1947. Since that time, a significant number of iron poisonings in children younger than 5 years of age has occurred.

Acute iron poisoning produces a corrosion of the gastrointestinal tract (primarily the stomach and the ilium). Death may occur from shock within 4 to 6 hours or from cardiovascular collapse within 1 to 3 days.

Data from the National Clearinghouse for Poison Control Centers on accidental ingestions of iron preparations of children under 5 years of age for the period 1969-1973 show 543 hospitalizations. Data from the death certificates for 1969-1972 show 31 deaths of children younger than 5 years of age from the accidental ingestion of these products. These data do not specify the exact amounts ingested by the children, nor does the medical literature in the field recognize any precise

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lethal or toxic dose. Evidence does establish, however, that a 3-gram dose of ferrous sulfate (the most common iron salt) is fatal for a human being. On the basis of this evidence, it has been estimated that a dose of one gram of iron could produce death in a child younger than 5 years of age. This figure, however, does not leave room for variability in body weight of children under five years of age ~~(such as the 18-pound, 12-month-old crawling infant)~~ or for variable susceptibility in children ~~toddlers~~ of the same size.

Conclusion and proposal. Therefore, considering the available data on injuries and the lack of concrete data on hazardous levels of iron, and after consultation, pursuant to section 3, with the Technical Advisory Committee established in accordance with section 6 of the Poison Prevention Packaging Act of 1970, the Commission proposes that any nonprescription drug for oral administration, as defined in proposed 16 CFR 1700.1(a)(3) below, and any dietary supplement, as defined in proposed 16 CFR 1700.1(a)(4) below, that contains an equivalent of 500 milligrams or more of elemental iron per package shall require special packaging. This level provides a reasonable and necessary margin of safety in order to protect even the small toddler from serious illness. Since the Commission recognizes that neither the true toxic dose nor the lethal dose of iron has been established for children younger than 5 years of age, interested persons are invited to submit

any data that would enable the Commission to establish a more accurate level of iron below which serious illness in children younger than 5 years of age would not occur.

On the basis of preliminary contact with a number of packaging manufacturers, and pursuant to section 3(a)(2) of the act, the Commission finds that the special packaging proposed herein is:

1. Technically feasible because technology exists to produce special packaging conforming to these standards.

2. Practicable in that the special packaging is susceptible to modern mass production and assembly line techniques.

3. Appropriate since such special packaging is not detrimental to the integrity of the substance and will not interfere with its storage or use. In the case of iron preparations requiring dropper applicators, these standards do not require the use of a cap with dropper unit affixed that both comply with these requirements. It would be appropriate to utilize one of the available child-resistant closures that complies with these requirements and to market the product with a separate dropper unit.

The Commission recognizes that the packaging manufacturers' ability to supply closures prior to the effective date of special packaging standards is partially dependent upon the speed with which packagers

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of substances subject to the standards place orders for packaging. Given the number of hospitalizations and fatalities that have occurred as a result of the accidental ingestion of iron-containing preparations by children under 5 years of age, the Commission suggests that packagers of iron preparations subject to these proposed requirements begin immediately to obtain the necessary special packaging. Due to the serious danger posed by these iron preparations, the Commission intends that these regulations, if adopted, be made effective 6 months after their date of promulgation in the FEDERAL REGISTER and invites comments on this intention.

Accordingly, pursuant to the provisions of the Poison Prevention Packaging Act of 1970 (secs. 2(4), 3, 5, 84 Stat. 1670-72 (15 U.S.C. 1471(4), 1472, 1474 and under authority vested in the Commission by the Consumer Product Safety Act, the Commission proposes that 16 CFR Part 1700 be amended:

1. By adding new subparagraphs (3) and (4) to § 1700.1(a), as follows:

§ 1700.1 Definitions.

(a) * * * *

* * * *

(3) "Non-prescription drug" means any drug for human use that is in a dosage form intended for oral administration and that is not required by Federal law to be dispensed by or upon prescription of a practitioner licensed by law to administer such drug.

DRAFT

(4) "Dietary Supplement" means any vitamin and/or mineral preparation offered in tablet, capsule, wafer or other similar uniform unit form; in powder, granular, flake, or liquid form; or in the physical form of a conventional food but which is not a conventional food; and which purports to be or is represented for special dietary use by man to supplement his diet by increasing the total dietary intake of one or more of the essential vitamins and/or minerals.

2. By adding a new subparagraph (12) to § 1700.14(a), as follows (although unchanged, the introductory text of § 1700.14(a) is included below for context):

§ 1700.14 Substances requiring special packaging

(a) Substances. The Commission has determined that the degree or nature of the hazard to children in the availability of the following substances, by reason of their packaging, is such that special packaging is required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting such substances, and that the special packaging herein required is technically feasible, practicable, and appropriate for these substances:

* * * * * *

DRAFT

(12) Iron preparations. Nonprescription drugs, as defined in § 1700.1(a)(3), and/or dietary supplements, as defined in § 1700.1(a)(4), that provide an equivalent of 500 milligrams or more of elemental iron per total package, shall be packaged in accordance with the provisions of § 1700.15(a), (b), and (c).

Interested persons are invited to submit, on or before _____ _____(insert date that is 60 days after publication hereof in the FEDERAL REGISTER), written comments regarding this proposal. Comments and any accompanying data or material should be submitted, preferrably in five copies, addressed to the Secretary, Consumer Product Safety Commission, Washington, D.C. 20207. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the Office of the Secretary, 10th floor, 1750 K Street, N.W., Washington, D.C., during working hours Monday through Friday.

Dated: _____.

_____

SADYE E. DUNN,
Secretary, Consumer Product
Safety Commission.

UNITED STATES GOVERNMENT

Memorandum

U.S. CONSUMER PRODUCT
SAFETY COMMISSION
WASHINGTON, D.C. 20207

TO : Bernie Scharf, SCAT

DATE: December 10, 1974

THRU : Walter R. Hobby, Director, BEA
FROM : Judith M. Pitcher, Economist, BEA

SUBJECT: G.C. Changes to Proposed PPPA Standard for Iron Preparations.

We have no objections to the draft changes recommended by the General Counsel's Office. Since this is a proposal, we agree with Steve Lemberg that it is inappropriate for the Commission to prejudge the dropper applicator situation by including the original reference in the preamble. However, to our knowledge, CR dropper units are still not "available" in the sense that there exist sufficient production quantities to meet packagers' needs. The existence of the one CR dropper unit known to us, however, does indicate that it is technically feasible to produce this type of special packaging.

*U.S. GOVERNMENT PRINTING OFFICE: 1974 733-533/3604 1-3

UNITED STATES GOVERNMENT

Memorandum

U.S. CONSUMER PRODUCT
SAFETY COMMISSION
WASHINGTON, D.C. 20207

TO : Mr. Bernard Scharf, TAD, OSCA

DATE: December 6, 1974

THRU : Albert F. Esch, M.D., Director, OMD A F Esch

FROM : Leo T. Duffy, M.D., OMD L T Duffy

SUBJECT: Proposed PPPA Standard for Iron Preparations

In response to your memorandum of December 5, 1974 concerning further proposed changes suggested by OGC in the August 28, 1974 draft Federal Register Notice on the subject, this Office reviewed said draft.

Following our review we find that there are no further additions, corrections, or other comments to make concerning this subject.

cc: Georg Maisel, BBSPP

*U.S. GOVERNMENT PRINTING OFFICE: 1974 733-533/3604 1-3

MEMORANDUM

DATE: DEC 11 1974

TO : Office of Standards Coordination and Appraisal

Through: Dale C. Miller, Director, Division of Inspection and Enforcement

FROM: Robert G. Poth, BCMI RGPoth

SUBJECT: OGC's December 2, 1974 Memo Outlining Revisions of the Proposed PPPA Standard for Iron Preparations

In escence, the changes suggested by the Office of General Counsel on the subject proposed standard would (1) make it apply to veterinary as well as to human drugs; (2) make it apply to both prescription and non-prescription drugs; and (3) make it apply to all dosage forms except injectables which would include such forms as external powders, ointments, salve, suppository, etc.

The Bureau of Compliance had originally approved of the proposed standard as written. The Poison Prevention Packaging Act at Section 3(a) requires the agency in promulgating child protection packaging standards, to make a clear finding that special child-resistant packaging is necessary for the particular substance in question in order to protect young children from serious personal injury or serious illness and further that special packaging to comply with the standards is technically feasible, practicable, and appropriate for the particular substance. Prior to formation of the Consumer Product Safety Commission, the Commissioner of FDA on the advise of FDA's Bureau of Product Safety, had made the conclusions as follows: (1) human experience data available from such sources as the National Clearinghouse for Poison Control Centers failed to support a finding that special packaging is necessary to protect children from serious personal injury or serious illness as a result of handling, using, or ingesting human drugs in dosage forms intended for other than oral administration. Also at issue at that particular time was concern over a finding that special packaging to comply with the standards was technically feasible, practicable, and appropriate for ointments, suppositories, injectables, etc. Presently, BCM is unaware of any change in human experience data that might indicate a need for special packaging of other than oral dosage forms and is similarly unaware of any change in the state of the art in industry to now make available special packaging which is technically feasible, practicable, and appropriate for the non-oral dosage forms. Further, FDA's Commissioner had similarly concluded that the variation in size of dosage units and in the distribution and usage patterns between human and veterinary preparations is sufficient to warrant separate consideration under the Poison Prevention Packaging Act. Based upon those conclusions, the Commissioner of FDA had, in April of 1973, amended the previously promulgated standards for aspirin and controlled drugs limiting their application to drugs for human use in dosage forms intended for oral

administration. Similarly, the standards for prescription drugs promulgated in April of 1973 was limited in application to those for human use in dosage forms intended for oral administration.

The subject proposed standard for iron salts was limited in its application to non-prescription drugs simply because prescription drugs containing iron are already subject to the standards promulgated in April 1973 at Section 1700.14(a)(10).

Steve Lemberg in the Office of General Counsel is thoroughly aware of the reasons cited above for the proposed standard for iron preparations being written to exclude animal drugs, non-oral dosage forms, and prescription drugs. While the Bureau of Compliance obviously disagrees with the suggested revisions of the Office of General Counsel, we are more strongly concerned with the consumer safety since this particular standard is very badly needed as witnessed by the human experience data relative to iron ingestions, i.e. National Clearinghouse for Poison Control Center data shows 543 hospitalizations of children under five years of age for the period 1969 through 1973 while data from death certificates for the period 1969 through 1972 show 31 deaths of children under five years of age from accidental ingestion of these products. We would therefore concur with the publication of this proposal even in the form revised by General Counsel as quickly as possible.

Dr. L. James Sharman, SCA

December 10, 1974

THRU : Dr. Robert M. Kehir, FBS
Georg S. Maisel, BBSPP

Proposed FPPA Standard for Iron Preparations

Regarding the changes suggested by OGC (Memorandum of December 2, 1974) BBS has no problems with the changes suggested. We would, however, like to address points one (1) four (4) and five (5).

We have no objections to expanding the coverage of this regulation provided that lack of such supportive data does not affect the validity of the proposal.

Point 1:

After a 3-year delay, it is vital that this standard be publicized soonest. Since the effect of the suggested changes in points 2 and 5 will include preparations intended for other than oral administration, we may not be able to support the technical feasibility, practicability, and appropriateness of such proposed packaging in every case.

Point 4:

The proposed change in the definition of Dietary Supplements appears to omit those used for animals. Is this intended?

Since OGC suggests that special packaging regulations for iron preparations cover animal as well as human drugs, the following wording is recommended for (new) paragraph 1700.1(a)(3).

> "Dietary Supplement" means any vitamin and/or mineral preparation offered in tablet, capsule, wafer or other similar uniform unit form; in powder, granular, flake, or liquid form; or in the physical form of a conventional food but which is not a conventional food; and which purports to be or is represented for special dietary use to supplement the diet by increasing the total dietary intake of one or more of the essential vitamins and/or minerals.

Point 5:

As you know, we have prepared a proposal covering veterinary prescription drugs. Since the changes mentioned above will result in certain animal drugs being included under the iron preparations proposal, certain products will be covered by both regulations. The foregoing is for your information.

We must note that the Technical Advisory Committee has not been consulted regarding this expanded coverage. Such consultation at this time, would further delay promulgation of this standard.

cc:
C. Casper (Attn: B. Scharf)
DBS
SCA File
Reading File
Central File
Subject File
BBSPP/DCWilliams:mmh
Revised by: GSMaisel

Penn
GC

Dunn Sheldon
1025-KST

AUG 2 8 1974

Steve Lemberg, Office of the General Counsel

THRU : L.J. Sharman, Director, OSCA and Frederick Barrett, Executive Director
Bernard Scharf, Technical Analysis Division, OSCA

Proposed PPPA Standard For Iron Preparations

In accordance with your request for the addition of definitions of terms and the need for editing into "FEDERAL REGISTER style", I am sending you the attached, edited version of the subject regulation.

Sign-off sheets from the Office of the Medical Director and the Bureaus of Economic Analysis, Biomedical Science and Compliance are attached.

Please arrange for the necessary action by the Commissioners and the subsequent publication in the FEDERAL REGISTER at the earliest possible time.

Attachments (2)

Distribution:

OEX: A. Dimcoff, M. Doxie
OMD: A. Esch
BBS: R. Hehir
BEA: W. Hobby
BCM: E. Finch
OS: S. Dunn ✓

AUG 20 1974

CONSUMER PRODUCT SAFETY COMMISSION

[16 CFR Part 1700]

Certain Preparations Containing Iron

Proposed Child-Resistant Packaging Standards

The purpose of this document is to propose child-resistant packaging standards for certain preparations containing iron. The accidental ingestion of such preparations has been a significant cause of hospitalizations and fatalities of children younger than 5 years of age.

Background. Acute accidental poisoning from iron began to occur with greater frequency when iron became widely used as a therapuetic agent for the treatment of anemia in 1947. Since that time, a significant number of iron poisonings in children younger than 5 years of age has occurred.

Acute iron poisoning produces a corrosion of the gastrointestinal tract (primarily the stomach and the ilium). Death may occur from shock within 4 to 6 hours or from cardiovascular collapse within 1 to 3 days.

Data from the National Clearinghouse for Poison Control Centers on accidental ingestions of iron preparations of children under 5 years of age for the period 1969-1973 show 543 hospitalizations. Data from the death certificates for 1969-1972 show 31 deaths of children younger than 5 years of age from the accidental ingestion of these products. These data do not specify the exact amounts ingested by the children. Nor does the medical literature in the field recognize any precise

lethal or toxic dose. Evidence does establish, however, that a 3-gram dose of ferrous sulfate (the most common iron salt) is fatal for a human being. On the basis of this evidence, it has been estimated that a dose of one gram of iron could produce death in a child younger than 5 years of age. This figure, however, does not leave room for variability in body weight (such as the 18-pound, 12-month old crawling infant) or for variable susceptibility in toddlers of the same size.

Conclusion and proposal. Therefore, considering the available data on injuries and the lack of concrete data on hazardous levels of iron, and after consultation, pursuant to section 3, with the Technical Advisory Committee established in accordance with section 6 of the Poison Prevention Packaging Act of 1970, the Commission proposes that any nonprescription drug for oral administration, as defined in proposed 16 CFR 1700.1(a)(3) below, and any dietary supplement, as defined in proposed 16 CFR 1700.1(a)(4) below, that contains an equivalent of 500 milligrams or more of elemental iron per package shall require special packaging. This level provides a reasonable and necessary margin of safety in order to protect even the small toddler from serious illness. Since the Commission recognizes that neither the true toxic dose nor the lethal dose of iron has been established for children younger than 5 years of age, interested persons are invited to submit

any data that would enable the Commission to establish a more accurate level of iron below which serious illness in children younger than 5 years of age would not occur.

On the basis of preliminary contact with a number of packaging manufacturers, and pursuant to section 3(a)(2) of the act, the Commission finds that the special packaging proposed herein is:

1. Technically feasible because technology exists to produce special packaging conforming to these standards.

2. Practicable in that the special packaging is susceptible to modern mass production and assembly line techniques.

3. Appropriate since such special packaging is not detrimental to the integrity of the substance and will not interfere with its storage or use. In the case of iron preparations requiring dropper applicators, these standards do not require the use of a cap with dropper unit affixed that both comply with these requirements. It would be appropriate to utilize one of the available child-resistant closures that complies with these requirements and to market the product with a separate dropper unit.

The Commission recognizes that the packaging manufacturers' ability to supply closures prior to the effective date of special packaging standards is partially dependent upon the speed with which packagers

of substances subject to the standards place orders for packaging. Given the number of hospitalizations and fatalities that have occurred as a result of the accidental ingestion of iron-containing preparations by children under 5 years of age, the Commission suggests that packagers of iron preparations subject to these proposed requirements begin immediately to obtain the necessary special packaging. Due to the serious danger posed by these iron preparations, the Commission intends that these regulations, if adopted, be made effective 6 months after their date of promulgation in the FEDERAL REGISTER and invites comments on this intention.

Accordingly, pursuant to the provisions of the Poison Prevention Packaging Act of 1970 (secs. 2(4), 3, 5, 84 Stat. 1670-72 (15 U.S.C. 1471(4), 1472, 1474 and under authority vested in the Commission by the Consumer Product Safety Act, the Commission proposes that 16 CFR Part 1700 be amended:

1. By adding new subparagraphs (3) and (4) to § 1700.1(a), as follows:

§ 1700.1 Definitions.

(a) * * * *

* * * *

(3) "Non-prescription drug" means any drug for human use that is in a dosage form intended for oral administration and that is not required by Federal law to be dispensed by or upon prescription of a practitioner licensed by law to administer such drug.

(4) "Dietary Supplement" means any vitamin and/or mineral preparation offered in tablet, capsule, wafer or other similar uniform unit form; in powder, granular, flake, or liquid form; or in the physical form of a conventional food but which is not a conventional food; and which purports to be or is represented for special dietary use by man to supplement his diet by increasing the total dietary intake of one or more of the essential vitamins and/or minerals.

2. By adding a new subparagraph (12) to § 1700.14(a), as follows (although unchanged, the introductory text of § 1700.14(a) is included below for context):

§ 1700.14 Substances requiring special packaging

(a) Substances. The Commission has determined that the degree or nature of the hazard to children in the availability of the following substances, by reason of their packaging, is such that special packaging is required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting such substances, and that the special packaging herein required is technically feasible, practicable, and appropriate for these substances:

* * * * * *

(12) Iron preparations. Nonprescription drugs, as defined in § 1700.1(a)(3), or dietary supplements, as defined in § 1700.1(a)(4), that provide an equivalent of 500 milligrams or more of elemental iron per total package, shall be packaged in accordance with the provisions of § 1700.15(a), (b), and (c).

Interested persons are invited to submit, on or before _____ _____(insert date that is 60 days after publication hereof in the FEDERAL REGISTER), written comments regarding this proposal. Comments and any accompanying data or material should be submitted, preferrably in five copies, addressed to the Secretary, Consumer Product Safety Commission, Washington, D.C. 20207. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the Office of the Secretary, 10th floor, 1750 K Street, N.W., Washington, D.C., during working hours Monday through Friday.

Dated: _____.

_____

SADYE E. DUNN,
Secretary, Consumer Product
Safety Commission.

DATE: August 9, 74

TO: Those Checked Below

FROM: Bernard Scharf, Standards Coordinator, TAD/OSCA BS 8-9-74
Office of Standards Coordination and Appraisal

SUBJECT: Sign-off for the Standard/Regulation (Edited)
(standard, petition, etc.)

on Iron (subject) Dated August 8, 1974

Your signature below signifies that you have reviewed the attached material. Please denote your approval or disapproval of the material and forward this sign-off sheet to us by c/o/b 8/12/74. If you do not approve the material, reason(s) for your not approving must be attached to the sign-off sheet.

ORGANIZATION	SIGNATURE	APPROVE/DISAPPROVE	
Office of General Counsel			
Office of Field Coordination			
Office of Medical Director			
Bureau of Epidemiology			
Bureau of Engineering Sciences			
Bureau of Biomedical Sciences	[signature]	✓ 19 Aug 74	
Bureau of Information Education			
Bureau of Compliance			
Bureau of Economic Analysis			
(OSCA) Impact Analysis Division			
(OSCA) Voluntary Standards Division			

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AUG 20 1974
TECHNICAL ANALYSIS DIVISION

See Memo dtd 16 Aug '74 [signature]
to Carper via Sharma attached.

UNITED STATES GOVERNMENT

Memorandum

U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, D.C. 20207

TO : L. James Sharman, SCA
Attention: Chuck Casper, TAD

DATE: August 16, 1974

FROM : James Dimitroff, BES

SUBJECT: Proposed Child-Resistant Packaging Standards for Iron Containing Preparations

We have reviewed and approved the above-mentioned material subject to the incorporation of the following comments:

1. p.1--Data from the National Clearinghouse for Poison Control Center for the period 1969-1973 show 543 hospitalizations among children under 5 years of age due to the ingestion of iron preparations.

2. p.2--Under the heading Conclusion and Proposal lines 6 and 7, the word "ingestion" should be changed to"administration"and read:

   ...the Commission proposes that any nonprescription drug for oral administration, as defined in...

3. P.5--The definition that was supplied to OSCA for "dietary supplement" (Maisel/Bracken, June 7, 1974, copy attached) was developed after consultation with the Food and Drug Administration which has statutory responsibility for dietary supplements. The definition in toto (including the common names which were omitted in this proposal) is designed to exclude coverage of such items as breads. In as much as "conventional foods" is not defined, we suggest that OGC review the definition as currently written in the proposal, and make a determination as to its adequacy.

4. p.6--Ms. Dunn's first name is mispelled.

U.S. GOVERNMENT PRINTING OFFICE: 1974 733-533/3604 1-3

DATE: August 9, 1974

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Bureau of Biomedical Sciences			
Bureau of Information Education			
Bureau of Compliance OMS	Harry Darher	✓	
Bureau of Economic Analysis			
(OSCA) Impact Analysis Division			
(OSCA) Voluntary Standards Division			

Scharf

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Bureau of Information Education			
Bureau of Compliance			
Bureau of Economic Analysis		WMA	
(OSCA) Impact Analysis Division			
(OSCA) Voluntary Standards Division			

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TECHNICAL ANALYSIS DIVISION

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Office of Field Coordination			
Office of Medical Director	A.F. Esch 8/12/74	✓	
Bureau of Epidemiology			
Bureau of Engineering Sciences			
Bureau of Biomedical Sciences			
Bureau of Information Education			
Bureau of Compliance			
Bureau of Economic Analysis			
(OSCA) Impact Analysis Division			
(OSCA) Voluntary Standards Division			

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CLINICAL ANALYSIS DIVISION

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CLINICAL ANALYSIS DIVISION

MEMO RECD	AVOID ERRORS PUT IT IN WRITING	DATE 5-31-74
FROM: Bernard Scharf, OSCA	RECEIVED OFFICE OF THE SECRETARY JUN 3 2 28 PM '74	OFFICE
TO: Distribution		DIVISION

SUBJECT: ~~Proposed~~ PROPOSED Regulation covering Iron Preparations.

CONSUMER PRODUCT SAFETY COMMISSION

SUMMARY A copy of a memo dated May 22, 1974, from S. Lemberg to Bernie Scharf, is attached. Mr. Lemberg makes several suggestions towards improving the ~~proposed~~ subject regulation which was sent as a Briefing Package from OEX to OGC on April 15, 1974.

Please consider and let us have your comments on the third paragraph of Mr. Lemberg"s memo in which he recommends wording to replace the term "non-prescription drugs", as used in the present form of the ~~proposed~~ regulation in the Briefing Package, with a longer phrase so as to be consistent with the wording in 1700.14 (a) (10). However, it should be borne in mind that if this wording should b4 adopted, there might possibly be a need to define the term "dosage form ~~xx~~ intended for oral administration" since this term is not defined in 1700.14 (a) (10), and this lack of definition has caused some problems in the recent past with ~~xxxx~~ regard to proper application.

He also suggeststhat the term ~~xxxxxxxxx~~ "dietary supplements" presently defined in our regulation by reference to FDA's regulation 80.1 in 21 CFR, be explicitly defined in our regulation to avoid dependance on definitions of another agency which may change with time. We may not become aware of such a change and this may cause "confusion in the interpretation of our regulations." Of course, this would be the case with all of our regulations, both past and future, should they contain any reference to regulations of other agencies which may be subject to future change.

I'd like to point out that the term "dietary supplement" as used by FDA in 21 CFR, 80.1, depends on the FDA's definition of the term "United States Recommended Daily Allowance" which should also be defined at a specific level in our regulation if our definition is to parallel, at least initially, that of FDA's use of the term "U.S. Dietary Supplement."

The point on "Federal Register style", raised in the 2nd paragraph of Mr. Lemberg"s memo, will be handled by OSCA after we have received your comments and/or definitions, and, ~~where~~ ~~xxxxxxxxx~~ where indicated these comments and/or definitions will be incorporated into the Standard/Regulation

May we please have your comments, definitions, etc., by C.O.B. June 10, 1974, so that we may arrange for any necessary changes to be completed by the Rules Division of BCM?

DISTRIBUTION: OMD, BBS, BCM, BEA — Info cpys. only: OGC, OS

Attachment (1)

SIGNATURE	DOCUMENT NUMBER
Bernard Scharf	1 PAGE

FD FORM 2034 (2/72)

MEMORANDUM

CONSUMER PRODUCT SAFETY COMMISSION

DATE: MAY 22 1974

TO : Bernie Scharf, OSCA THRU: Executive Director

FROM: S. Lemberg, OGC

SUBJECT: Proposed PPPA Standards for Iron Preparations

By memorandum dated April 15, 1974, the Office of the General Counsel received a briefing package recommending publication of a proposal to require special packaging for iron preparations.

While we generally approve publication of the proposal as drafted in Tab A of the package, we hesitate to recommend it for publication for two reasons. First, we would suggest that the document be edited for Federal Register style, since Mr. J. Davis is now physically located in PSOC. Second, we would suggest that the operative language of the proposed regulation describing the substances to be subject to special packaging be expanded.

Instead of the term "non-prescription drugs," for example, we would suggest the phrase "any drug for human use that is in a dosage form intended for oral administration and that is not required by Federal law to be dispensed by or upon the prescription of a practitioner licensed by law to administer such drug." Instead of the term "dietary supplements as defined in 21 CFR 80.1, "we would suggest incorporating the referenced definition, or something similar to it, in the paragraph. The first suggestion would make the regulation parallel to paragraph (10) of § 1700.14(a), and the second suggestion is intended to clearly specify the substances subject to the standard. It is noted that the FDA definition is subject to change and that any such change could cause confusion in the interpretation of our regulations.

GC S. Dunn

April 15, 1974

Michael Brown, General Counsel
THRU: Frederick Barrett, Executive Director
L. James Sharman, Director, Office of Standards Coordination & Appraisal

Briefing Package on the proposed Poison Prevention Special Packaging Standard for Iron Preparations

The referenced Briefing Package, consisting of a Briefing Paper and draft FEDERAL REGISTER Notice, is attached.

After you have reviewed the package, please forward it to the Office of the Secretary so that arrangements may be made for its consideration by the Commissioners.

As indicated by the attached "sign-off" sheets, the package has been reviewed by the Office of the Medical Director and the Bureaus of Compliance, Biomedical Science and Economic Analysis.

Attachments (2)

cc:
Sadye Dunn, OS

DATE: April 1, 1974

TO: Those Checked Below

FROM: Bernard Scharf, Technical Analysis Division, OSCA (Rm. 912, X7606)
Office of Standards Coordination and Appraisal

SUBJECT: Sign-off for the Poison Prevention Packaging Standard
(standard, petition, etc.)

on Iron Preparations Date March 29, 1974
(subject)

Your signature below signifies that you have reviewed the attached material. Please denote your approval or disapproval of the material and forward this sign-off sheet to us by April 4, 1974. If you do not approve the material, reason(s) for your not approving must be attached to the sign-of sheet.

ORGANIZATION	SIGNATURE	APPROVE/DISAPPRO	
Office of General Counsel			
Office of Field Coordination			
✓ Office of Medical Director			
Bureau of Epidemiology			
Bureau of Engineering Sciences			
✓ Bureau of Biomedical Sciences	[signature]	✓ with attache Comments	
Bureau of Information Education			
✓ Bureau of Compliance			
✓ Bureau of Economic Analysis			
(OSCA) Impact Analysis Division			
(OSCA) Voluntary Standards Division			

DATE: April 1, 1974

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✓ Office of Medical Director			
Bureau of Epidemiology			
Bureau of Engineering Sciences			
✓ Bureau of Biomedical Sciences			
Bureau of Information Education			
✓ Bureau of Compliance			
✓ Bureau of Economic Analysis		VNA	
(OSCA) Impact Analysis Division			
(OSCA) Voluntary Standards Division			

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✓ Bureau of Biomedical Sciences			
Bureau of Information Education			
✓ Bureau of Compliance	Harry Dorber for E.B. Finch	✓	
✓ Bureau of Economic Analysis			
(OSCA) Impact Analysis Division			
(OSCA) Voluntary Standards Division			

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	Office of General Counsel			
	Office of Field Coordination			
✓	Office of Medical Director	A F Esch 4/2/74	✓	
	Bureau of Epidemiology			
	Bureau of Engineering Sciences			
✓	Bureau of Biomedical Sciences			
	Bureau of Information Education			
✓	Bureau of Compliance			
✓	Bureau of Economic Analysis			
	(OSCA) Impact Analysis Division			
	(OSCA) Voluntary Standards Division			

BRIEFING PAPER

ACTION ITEM

PROPOSED SPECIAL PACKAGING REGULATION FOR IRON PREPARATIONS

March 29, 1974

Bernard Scharf
Office of Standards Coordination
and Appraisal
496-7606

ISSUE: To propose a Special Packaging Regulation for Iron Preparations, under the Poison Prevention Packaging Act.

BACKGROUND: Data accumulated by the National Clearinghouse for Poison Control Centers (NCPCC) and other sources have indicated that children are frequently poisoned by compounds containing iron in various forms. The magnitude of these data indicate a serious problem, and effort was instituted early in 1971 to investigate this problem. This investigation has substantiated the need for regulation. Tab B contains a comprehensive chronology of the evolution of this activity, culminating in the attached proposed regulation (Tab A).

DISCUSSION: The major issues addressed during the development of the regulation are discussed in some detail in Tab C, and are briefly summarized here. This regulation covers both nonprescription drugs and dietary supplements. The term "Iron Preparations" is used in order to cover as broad a range of iron-containing products as possible, consistent with the magnitude of the problem. The proposed regulation contains a specific reference to an effective date of the Final Order. The date recommended, six months, has been somewhat controversial. (See Tab C plus additional documents in Tab D). We believe that six months is a reasonable period, especially since this activity has been ongoing for three years, and the affected industry has been apprised of the effort. However, we will closely examine all comments and data submitted on this issue, in response to publication of this proposal.

The establishment of an acceptable limit of iron content was considered. The level was first set on a single dosage unit basis and finally on a total package quantity basis. (500 mg. Iron per package). While it appears possible that children who may be particularly sensitive to iron may exhibit symptoms of toxicity at levels lower than 500 mg., the likelihood is very low. No documented cases of such an occurrence have come to our attention. Ancillary documents are attached as Tab E, in addition to the Tab C discussion.

The final major issue concerned the availability of Special Packaging to accommodate those Iron Preparations provided in dropper bottles. This is discussed in the Summary Document of Tab C and in the Ancillary Documents of Tab F. While satisfactory quantities of such packaging for dropper bottles may not presently exist, it is our judgment that sufficient quantities should be available within one year. However, it appears that droppers could be supplied separately with the stock bottle being provided with available special packaging, until combination units are available.

ALTERNATIVES:

1. Publish the Proposed Regulation as written.

A hazard to children has been demonstrated. This unreasonable risk of injury will be reduced by the promulgation and enforcement of this regulation.

2. Publish the Proposed Regulation with Modifications.

Modifications in the effective date or the acceptable iron level could be instituted.

3. Reject the Proposed Regulation.

This regulation could be returned to PSOC for further work, or the project terminated.

RECOMMENDATION:

PSOC recommends the publication of the Proposed Regulation, as written, at the earliest possible time. The need for the regulation is justified and any delay does not seem warranted.

LIST OF ATTACHMENTS

Tab A - The Proposed Regulation with Preamble.

Tab B - Chronology of Documented Events Leading to the Preparation of the Proposed Regulation.

Tab C - A Summarized Discussion of the Central Issues Considered During the Preparation of the Proposed Standard.

Tab D - Documents Bearing on the "Effective Date" Issue.

Tab E - Documents Bearing on the Quantitative Basis for Determining Coverage Under the Standard.

Tab F - Documents Bearing on the Availability of Special Packaging.

CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

Certain Preparations Containing Iron

Proposed Child-Resistant Packaging Standards

The purpose of this notice is to propose child-resistant packaging standards for certain preparations containing iron, the accidental ingestion of which has been a significant cause of hospitalizations and fatalities of children younger than 5 years of age.

Acute accidental poisoning from iron began to occur with greater frequency when iron became widely used as a therapeutic agent for the treatment of anemia in 1947. Since that time, a significant number of iron poisonings in children younger than 5 years of age has occurred.

Acute iron poisoning produces a corrosion of the gastro-intestinal tract (primarily the stomach and ilium). Death may occur from shock within 4 to 6 hours or from cardiovascular collapse within 1 to 3 days.

Data from the National Clearinghouse for Poison Control Centers on accidental ingestions of iron preparations by children younger than 5 years of age for the period 1969-1972 show 1, 568 ingestions and 429 hospitalizations. Data from the death certificates for 1969-1972 show 31 deaths of children younger

than 5 years of age from the accidental ingestion of these products. These data do not specify the exact amounts ingested by the children. Nor does the medical literature in the field recognize any precise lethal or toxic dose. However, evidence does establish three grams of ferrous sulfate (the most common iron salt) to be a fatal dose for a human being and on the basis of this evidence, it has been estimated that a dose of one gram of iron could produce death in a child younger than 5 years of age. This figure, however, does not leave room for variability in body weight (such as the 18 pound, 12 month old crawling infant) or for individual variability in susceptability in toddlers of the same size.

Therefore, considering the available data on injuries and the lack of concrete data on hazardous levels of iron and after consultation with the Technical Advisory Committee, the Commission proposes that any non-prescription drug in dosage form for oral administration in humans and any dietary supplement, as defined in 21 CFR 80.1, which contains an equivalent of 500 milligrams or more of elemental iron per package shall require special packaging. This level provides a reasonable and necessary margin of safety in order to protect even the small toddler from serious illness. However, since the Commission recognizes that neither the true toxic dose nor

the lethal dose of iron has been established for children younger than 5 years of age, interested persons are invited to submit any data which would enable the Commission to establish a more accurate level or iron, below which serious illness in children younger than 5 years of age would not occur.

The Commission has also made preliminary contact with a number of packaging manufacturers in order to determine whether production capabilities are sufficient for the products covered by this proposed regulation. It appears that presently existing forms of special packaging are compatible with the types of packaging used for iron preparations at this time. The special packaging in which products subject to this regulation will be packaged are capable of mass production and lend themselves to assembly line techniques. Moreover, the special packaging will not interfere with the storage or use of these products. In the case of iron preparations requiring dropper applicators the standards do not require the use of a cap with dropper unit affixed which complies with the regulations. It would be appropriate to utilize one of the available child-resistant closures which complies with the standards on containers and to market a dropper unit in conjunction with the package.

The Commission recognizes that the packaging manufacturers' ability to supply closures prior to the effective date of special packaging standards is partially dependent upon the speed with which packagers of substances subject to the standards place orders for packaging. Given the number of hospitalizations and fatalities which have occurred as a result of the accidental ingestion of iron-containing preparations by children under 5 years of age, the Commission suggests that packagers of iron preparations subject to this proposed standard begin immediately to obtain the necessary special packaging. Therefore, due to the serious danger posed by these iron preparations, the Commission proposes that this regulation shall become effective 6 months after publication in its final form and requests comments from the public addressed to this point.

Accordingly, pursuant to the provisions of the Poison Prevention Packaging Act of 1970 (secs. 2(4), 3, 5, 84 Stat. 1670-1672 (15 U.S.C. 1471(4), 1472, 1474)) and the Consumer Product Safety Act of 1972 (sec. 30(a), 86 Stat. 1231 (15 U.S.C. 2079(a)), a new subparagraph is proposed to be added to 1700.14 as follows:

(a) Substances. The Commission has determined that the degree or nature of the hazard to children in the availability of the following substances, by reason of their packaging, is such that special packaging is required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting such substances, and that the special packaging herein required is technically feasible, practicable, and appropriate for these substances:

* * * * * *

(12) Iron preparations. Non-prescription drugs which are in dosage forms for oral administration in humans, and dietary supplements as defined in 21 CFR 80.1, either of which provide an equivalent of 500 milligrams or more of elemental iron per total package, shall be packaged in accordance with the provisions of 1700.15(a), (b), and (c).

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Interested persons may, within 60 days after publication of this Notice in the Federal Register, file with the Office of the Secretary, Consumer Product Safety Commission, 1750 K Street, N.W., Washington, D.C., 20207, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

DATED:

Sayde E. Dunn, Secretary
Consumer Product Safety Commission

CHRONOLOGY OF EVENTS LEADING TO PREPARATION OF PROPOSED REGULATION REGARDING SPECIAL PACKAGING FOR HAZARDOUS HOUSEHOLD SUBSTANCES CONTAINING IRON

Mar. 1, 1971: Basic Research initiated by the Division of Chemical Hazards, BPS, on the basis of investigations by the Food and Drug Administration into available literature and data on human ingestion and experience data. Some of the articles cited as references include:

1) "Communications from the National Clearinghouse for Poison Control Centers" - "Accidental Poisoning in Young Children - The Hazards of Iron Medication" by Cann and Verhulst, A.M.A. Journal of Diseases of Children, May 1960, Vol. 99, pp. 688-691 and

2) "Ferrous Sulfate Poisoning" by T.J. Covey, M.D., Journal of Pediatrics, Feb. 1964, Vol. 64, No. 2, pp. 218-225

3) "A Fatal Case of Ferrous Sulfate Poisoning" by E. Charney, M.D., J.A.M.A. 1961, Oct. 21, 1961, pp. 172-173.

Human ingestion data was provided from records of the National Clearinghouse for Poison Control Centers which revealed that during the three year period from 1968 to 1970 there were 278 ferrous sulfate ingestions and 112 hospitalizations of children under five. Data obtained from death certificates for this same period show 15 deaths of children under five years of age resulting from ferrous sulfate preparations.

May 26, 1971: Initial Proposal for Standard Calling for "tablet" and "capsule" Preparations containing more than 60mg. of "Ferrous Sulfate" to be packaged in accordance with child-safety regulations. This, along with supportive data was sent by mail on this date to the TAC for their comments.

June 28, 1971: By this date all comments had been received from the TAC members. Only one member disapproved of the proposal.

Sep. 16-
Oct. 4, 1971: The Proposed Draft of the Standard has now been modified in context. Of noteworthy change was a reduction in the amount of "ferrous sulfate" per dosage unit to 30mg. The proposed, changed draft was sent to the Bureau of Drugs.

October 1971: Sometime in October, after the TAC comments had been reviewed, the proposed draft was sent to the Commissioner of FDA via the Associate Commissioner for Compliance and the General Counsel.

Oct. 19, 1971: Meeting of the following people: Commissioner and Deputy Commissioner of FDA, ACC, ACMA, BD, GC, BPS. At this meeting it was decided:

1. All proposed Standards for drugs in the future will be brought to attention of BD which will serve as a liaison with APhA and PA for expert input from these two organizations.

2. Drugs and other substances requiring Special Packaging will be treated on a limited class basis (chemically as with ferrous sulfate) or by type of product as with detergents.

3. Bureau of Drugs to explore feasibility of treating all OTC and R_x drugs as being subject to Special Packaging. Exemptions are to be published at time of original request or in response to manufacturer's substantiated requests.

4. Special Packaging Standards of blanket coverage for all R_x Drugs will have to await APhA meeting to discuss its acceptability to industry.

5. Future, proposed Standards must contain a more detailed explanation in the Action Memo and in the preamble as to the required packaging being "technically feasible, practicable, and appropriate."

6. Consideration was to be given to F/R publication of a list of all packaging manufacturers who have indicated the development of Special Packaging which would meet the testing protocol.

Nov. 9, 1971: ACC instruction to revise the proposed Standard's preamble and cover memo to better cover the technical feasibility, practicality and appropriateness. The last paragraph was to be revised to allow 60 days for comments rather than the originally provided 30 days.

Jan. 27, 1972: Responsibility for delineating Special Packaging requirements for this drug assumed by Bureau of Drugs.

Feb. 28, 1972: Bureau of Drugs considering blanketing this proposal in one covering OTC drugs.

Mar. 9, 1972: Bureau of Drugs drafts proposed Federal Register announcement soliciting comments regarding comprehensive approach to Rx and OTC drugs.

Mar. 30, 1972: BPS recommends limiting regulation to "Ferrous Sulfate".

Apr. 18, 1972: Bureau of Drugs makes the following significant suggestions for changes in the proposed Standard:

1. Use the term "elemental" iron rather than "Ferrous Sulfate" since there are many forms and salts of iron available.

2. However, iron-fortified vitamins should not be included since a finding of significant hazard cannot be made.

3. There is admittedly a problem at determining at what level of iron content per dosage form to draw the line. In addition to solid dosage forms, liquid dosage forms should be covered. Bureau of Drugs, therefore, recommends that all preparation containing 25mg. or more of "elemental" iron per tablet or capsule or per 5ml. of fluid be in Special Packaging. Five ml. is the approximate amount ingested at one swallow by a child of poisoning-prone age.

4. Discusses safety closures for dropper bottles, which do not exist. Suggests dropper be packaged separately with reservoir bottle having safety closure. Suggests that a need for a dropper-bottle safety closure will spur such development.

Apr. 20-21, 1972: In accordance with Bureau of Drugs suggestions of 4/18/72, a new proposed F/R draft was developed by BD containing provisions about the 25mg./solid dosage form limitation and the suggestion liquids being covered if they contain 25mg. or more of iron per 5ml. (1 teaspoon) dose. This draft was sent to BPS on 4/21/72 with recommendation to publish as soon as possible.

May 18, 1972: Revised draft to Bureau of Foods for review and comments. Some dietary supplement will presumably be covered if the cut-off point is 25mg. iron per dosage unit.

May 24, 1972: *In an internal memo, Bureau of Foods expresses its approval in principle with the revised draft prepared in accordance with BD suggestions. They suggest that zinc-containing supplements should have safety closures as well as iron supplements. They are investigating the possibility of suggesting that copper-containing dietary supplements also be packaged in Special Packaging.*

Bureau of Foods does not agree with 25mg. cut-off point. They would like to see all iron-containing (also zinc and copper) supplements have safety closures.

Bureau of Foods thinks that it is illogical to arbitrarily divide supplements into those requiring safety packaging and those not requiring such, particularly since a number of supplement manufacturers have already adopted safety closures on this possibility.

May 25, 1972: *Internal Bureau of Foods Memo, suggesting that BF contact BPS's Compliance Office to urge that safety closures be used on vitamin-mineral products containing iron.*

May 22, 1972: *BF in an internal memo states that the 25mg. cut-off point seems to be arbitrary, particularly in view of the then proposed FDA/RDA's which were 27mg. for children and adults and 36mg. for pregnant or lactating women.*

June 2, 1972: *The level proposed by BF is lower than BPS could support. BPS cannot justify BF's suggestion that zinc-containing products be placed in safety packaging.*

June 6, 1972: *BF and BPS comments to BD for comment.*

June 8, 1972: *BD agrees with BPS views and suggests F/R statement issue as it is.*

June 16, 1972: *Change in terminology in proposed Standard from "Ferrous Sulfate" to "Iron Salts".*

July 13, 1972: *Newly revised draft is sent to Commissioner via Deputy Commissioner, ACC and GC.*

1) Now applies specifically only to non-prescription drugs for oral administration.

2) Bureau of Drugs does not agree with Bureau of Foods that all iron preparations should be in Special Packaging, particularly since NCH data does not support this view.

July 21, 1972: FDA GC does not understand basis for iron levels set. Questions whether level should not revolve around what is available in the package rather than in the individual dosage unit (tablet or capsule), including liquids.

July 28, 1972: ACC/BPS memo pointing out GC objections and questions on draft. ACC says the PPP Act is to protect children from the contents of the entire package and that the draft, unlike previous ones, does not accomplish this. Requests comments on this from BPS re: using amount of contents of a package rather than quantity of iron in a single dosage unit or volume.

Aug. 8, 1972: BPS sends a report to BD re: "Iron Tablets Ingested by Children under 5 Years of Age". This reports on number of tablets ingested by about 200 children.

Dec. 7, 1972: Memo, Dir. BD/Dir. BPS

1. Based on a market survey it was found that numerous products are on the market in which the entire contents of a package would prove toxic to a child. Thus, the recommendation to again re-revise the draft in line with GC remarks as to a "total dose limitation."

2. The usually accepted toxic dose which might cause illness in a child is 150 mg/kg. Providing a margin of safety by lowering this limit to 100 mg/kg would place the dangerous dose to a 25 lb. "average" child to a level approximating 1200 mg. B/D, therefore, sets the toxic dose at 1000 mg. or 1 gm.

3. Thus, BD suggested keeping the 25mg. or 5ml. limits while adding a total dose limitation (entire package contents) of 1Gm. The reasoning for keeping the individual dose limitation is:

1) "very concentrated preparations will facilitate ingestion of a potentially toxic dose by a child, especially a very small child" and

2) "concentrated preparations, especially pediatric drops are more likely to be available in homes having young children."

Feb. 8, 1973: Newly revised draft sent to Commissioner thru Deputy Commissioner, GC and ACC. This now provides for 25mg./ dosage unit cut-off or 5ml./ dose in addition to 1gm. total package contents for OTC drugs with iron (including those substances classed dietary supplements and vitamin preparations). R_x items to be covered separately under an R_x Standard in preparation. Veterinary preps to be covered separately. The document now adds a 5gram non-liquid dose cut-off for such things as powders, granules, flakes, etc. as in special dietary foods.

Mar. 5, 1973: Memo from Director, BD to ACC suggesting further changes:

1) Change in last two sentences of Preamble to accurately reflect the potential toxicity of iron salts. These should read: "On the basis of available toxicity information, serious illness in a small child can be expected to occur from doses of 1.5 to 2gm. of elemental iron when ingested as any of the soluble iron salts."

2) Since proposal now includes dietary supplements the Bureau of Foods should provide comments re: established dosage unit levels and package limits.

Mar. 14, 1973: Memo, BF/ACC. Recommends:

1. Statement re: dietary supplements should read: "dietary supplements of vitamins and minerals as defined in 21 CFR 80.1." This would eliminate confusion as to other types of dietary supplements such as amino acid mixtures and items for use under medical supervision. The way draft is written it would mean that a 5 lb. box of dry, enriched infant cereal must be packaged with a safety closure.

2. In light of using 1Gm. of total contents as an index of applicability of the Standard (or better yet 500mg. or 1/2gram). There is no need to use the arbitrary 25mg./ dosage unit cut-off.

3. Recommends 500mg./ package as the upper per package total limit.

4. True toxic dose is not established nor is the lethal dose in children or toddlers.

5. The number of cases reported by the NCH is understated at the very least and is a gross underestimate of true incidence. The 1000mg. level does not leave much margin of safety as compared to 1200mg. The Standard should give protection against significant illness as well as serious illness with a potential lethal outcome.

6. Suggests applying the Standard to "Iron" rather than "Iron Salts" since not all sources are salts. Suggest Standard refer to all sources of Iron.

7. Question as to who (BPS or FDA) should receive samples.

Mar. 21, 1973: BPS internal Memo:

1. No objection to lowering total package level to 500mg. if BF can support it in case of challenge. Believes level of 1000mg. "more appropriate".

2. Does not recommend eliminating 25mg. cut-off since "child seldom ingests more than 50 tablets and almost never more than 100" and a product with 2mg. iron/ dosage form in a container of 500 would need a safety closure.

3. No indication that "iron reductum" is involved in poisonings.

May 9, 1973: ACC is now considering changing the draft to include a reference to Sect. 80.1 of CFR 21 re: dietary supplements.

May 14, 1973: A review of BF Memo of Mar. 14 by BD results in following memo from BD.

1) Agrees with reference to Sect. 80.1 in CFR 21.

2) Agrees with "across-the-board approach" to regulating all Non-Rx iron preps.

3) Recommends adoption of 500mg. as limit per package and the dropping of cut-off on individual dosage units at 25mg., particularly in regard to the confusing way in which toxicity data is presented in the literature.

4) Suggests change in wording of Standard to include reference to 80.1 CFR, 500mg. total and dropping of 25mg./ dose level.

May 18, 1973: ACC writes letter to CPSC concurring with BD memo (above) of May 14, 1973. This includes reference to CFR 21, Sect. 80.1 and "across-the-board approach" to all non-R_x iron-containing preps, elimination of arbitrary 25mg. dosage unit limit and dropping package content to 500mg. from 1000mg. ACC requests that his office be permitted to review and comment on the proposed reg. prior to publication in F/R.

May 25, 1973: CPSC internal memo:

1. Ask Off. of Med. Director what level of elemental iron will cause serious illness in 25 lb. two year old child; if CPSC can support covering all sources of iron for Special Packaging.

2. Basing Standard on total package content is the same as intended for aspirin as to 45 grain.

3. Thinks that specific mention be made in Standard of dietary supplements.

4. Says CPSC should not use level of iron which cannot be supported without FDA support.

July 17, 1973: CPSC (Med. Dir.) Memo Supports 500 total package limitation as well as other comments in May 18, 1973 memo from ACC.

Aug. 27, 1973: CPSC internal Memo (BC-BBS) Asks for:

1) Technical capabilities of packages in meeting the Iron reg. requirements.

2) Time needed for packagers to produce necessary packaging for industry and number of packagers

currently manufacturing such packaging.

Sep. 6, 1973: CPSC internal Memo (BBS-BC) reply to 8-27-73 memo.

1) Packaging is same as used for aspirin. Most other products under effective Standards.

2) Industry can meet requirements without new capacity. Only need 16 to 34 weeks notice to produce new capacity.

3) 15 companies can meet the pharmaceutical market demand. Most have indicated excess capacity to fit standard screw-neck bottles especially for most popular drug products.

4) Most iron packagers are presently using Special Packaging for other products and have production equipment on filling lines. They will need no more than 180 days notice to convert filling lines to meet Standard. This packaging is technically feasible, practicable and appropriate.

Oct. 4, 1973: Proposed reg. sent to TAC speaks in terms of "elemental iron" setting limit of 500mg. per package.

Oct. 15, 1973: Proposed reg. sent by CPSC to FDA for comments.

Nov. 1, 1973: 9 of 11 comments received from TAC by this date.

Nov. 7, 1973: Position Paper on Iron sent to OSCA by BBS.

Nov. 30, 1973: Memo, ACC/FDA to OSCA/CPSC. FDA concurs in the publication of the Standard in Iron Preparations, suggesting that references to the term "elemental" iron be deleted in three places in the introductory preamble to the Standard while retaining "elemental" in the Standard itself.

December 1973: Conference FDA-CPSC re: change to "equivalent of 500mg."

Jan. 22, 1974: A survey of manufacturers of safety packaging indicated that a minimum of nine months would be necessary to supply packagers of iron preparations. For dropper bottles, one year was estimated to be the minimum time necessary to provide child-resistant packaging.

ISSUE: The Commissioners are being presented with a proposed Special Packaging Standard on Iron Preparations, [redacted], prepared in accordance with Section 3 of the Poison Prevention Packaging Act of 1970.

BACKGROUND: We have attached a comprehensive chronology of the events and various considerations involved in the preparation of this Standard. [redacted].

Work on the proposed Standard began in March of 1971 under the auspices of the Food and Drug Administration. The primary impetus towards the recognition of the need for the promulgation of such a Standard was achieved by reference to data maintained and provided by the National Clearinghouse for Poison Control Centers (NCPCC) and by reference to the scientific literature on accidental iron poisonings in children.

With the resumption and increased use of iron-containing preparations since the thirties and forties, the incidence and frequency of accidental poisonings in children has been steadily rising.

DISCUSSION: The preparations to be covered by this Standard are those over-the-counter (nonprescription drugs and dietary supplements) products taken to counteract iron-deficiency anemia or taken for prophylactic purposes as in the case of various combinations of vitamins or multivitamins and iron with other minerals, liver, etc.

The central issues [redacted] in the formulation of this proposed Standard were four in number:

1. "Ferrous Sulfate" versus "Iron Salts" versus "Iron Preparations".

As originally contemplated, the initial draft proposals spoke in terms of "Ferrous Sulfate". Presumably, this was because much of the literature then extant on accidental iron poisonings spoke in terms of this most common of the then iron-containing preparations. It was soon realized that ferrous sulfate was only one of several iron salts being marketed for OTC use. Hence, the short-lived use of the term "Iron Salts" in subsequent memoranda and Standard drafts. It was next realized that inorganic and organic complexes of iron were being marketed in forms which could not truly be described in terms of "salts" as that term is commonly understood. Hence, the adoption of the reference to "Iron Preparations" to cover all eventualities and the use of the term "elemental iron" in discussing the total amount of iron provided per package.

2. The "Effective Date" Issue.

This second issue, which has not yet been completely resolved, is that revolving around the question of how much time to allow between the

date of the promulgation of the final order, by its publication in the FEDERAL REGISTER, and the established effective date. Periods of six, nine and twelve months have been proposed and various reasons given therefore [redacted].

The six month period is advocated by those citing the facts that:

a) The Standard has been in preparation for almost three years, and,

b) Children have been poisoned during the intervening time and are continually being exposed to the possibility of accidental poisoning by virtue of the accessibility of these products as packaged in conventional packaging.

c) In consideration of the comparatively large number of hospitalizations of and fatalities in children following accidental ingestions, iron preparations should be enclosed in Special Packaging within the shortest time possible (not sooner than 180 days after promulgation, according to Section 9 of the PPP Act unless the Commission, in the public interest and for good cause found, decides that a shorter period is necessary and has the reasons therefore published in the FEDERAL REGISTER).

d) In connection with the above three points the Bureau of Compliance feels that inasmuch as the initial availability of Special Packaging is contingent upon how quickly orders are placed by the users with packaging manufacturers, the establishment of the shortest allowable interim period will serve as a strong incentive for the affected industry to proceed, as quickly as possible, to obtain Special Packaging.

The twelve month period is advocated by those (Bureaus of Biomedical Science and Economic Analysis) who cite the facts that:

a) Surveys of packaging manufacturers indicate that quantities of Special Packaging, sufficient to accommodate industry's needs, would require a minimum of nine months to one year because of various technical and economic considerations, and,

b) This longer period will allow both the packaging manufacturers and the packagers themselves time within which to minimize changeover costs, work off existing inventory and generally allow for an orderly transition from the use of noncomplying (conventional) to complying packaging (Special Packaging).

In this connection, OSCA has determined the following relevant facts:

a) Three month extensions were necessary in the cases of five of the eight final PPP Standards Orders in which the effective date was initially set at six months following promulgation by their publication in the FEDERAL REGISTER.

b) Of the five extensions, hiatuses occurred in at least four instances (Aspirin, Methyl Salicylate, Turpentine and Methyl Alcohol). These hiatuses extended to as much as two months, (from the effective date until the extension could be published in the FEDERAL REGISTER).

c) In the case of the Methyl Alcohol Standard, the Commission received twelve petitions requesting exemptions, since even the extended effective date could not be met. These petitions caused the Commission Staff to expend a great deal of time and effeot before they were denied.

This issue is dealt with in the proposed Standard by including a provision that the Standard become effective within six months after promulgation of the Final Order. The theory in doing this is that if six months is indeed too short a period to accommodate the needs of the affected industries, this will manifest itself in the comments which are being solicited and which should be forthcoming.

If it is found necessary to extend the effective date in the Final Order to one year from the date of promulgation, an acceptable compromise may be achieved in the following way:

A statement might appear in the Final Order to the effect that "Because of the imperative need for Special Packaging in this area we expect every firm, in good faith, to begin to use such packaging as soon as it becomes available to a particular firm, the one year period notwithstanding".

A precedent was set for this type of statement in the preambles to the proposed and final orders for the Standard covering "Human Prescription Drugs in Oral Dosage Forms", published respectively in the FEDERAL REGISTERS of April 27, 1972 (Vol. 37, No. 82, p. 8461/2) and April 16, 1973 (Vol. 38, No. 72, p. 9431/33).

In the former case, the third paragraph in column 3 of page 8461 reads:

"The demands for special packaging are expected to be substantial and will increase rapidly as implementation of the Act (PPP Act) for drugs continues. Manufacturers and pharmacists are encouraged to stock adequate supplies of special packaging in order to meet the effective dates for special packaging requirements for drugs. The Food and Drug Administration encourages the pharmaceutical industry and pharmacists to cooperate and start the use of special packaging for all drug products where any potential for hazard to children exists. The objective of the Act warrants initiatives toward special packaging that should not await the time-consuming procedures necessary to establish legally enforceable requirements."

In the latter case, paragraph "J." of the preamble (p. 9433) contains this last sentence: "The Commissioner expects, however, that persons dispensing prescription drugs will begin using the special packaging in the event such packaging becomes available prior to said effective date."

Thus, those firms able to obtain Special Packaging earlier than others may begin to use them earlier.

3. Quantitative Basis for Determining Coverage Under the Standard.

The question arose early as to which preparations would be covered under the Standard. Inasmuch as a minimum toxic dose or a minimum lethal dose could not be established with certainty (due to the confusing manner in which data was presented in the literature and the insurmountable problem of determining how much iron had actually been ingested and absorbed in a particular instance), the question was approached from the beginning in an empirical manner. The initial factor as to whether Special Packaging would be required for an Iron Preparation was the amount of Ferrous Sulfate in a single dosage form or unit (tablet, capsule or teaspoonful of liquid). This quantity was first set at 60 mg. and subsequently at 30 mg. of ferrous sulfate. The final value was set at 25 mg. of "elemental" iron per solid dosage unit or per teaspoon (5 cc.) of iron-containing liquids. At one point, one faction within FDA (Bureau of Foods), suggested that all iron-containing products be contained in Special Packaging without regard to quantity of iron per dosage unit.

It was subsequently agreed upon by FDA officials (representatives of the Bureaus of Foods, Drugs and the General Counsel), that the important factor should be the total amount of iron contained in a package of an Iron Preparation. This reasoning was based on the knowledge that children have been known to ingest upwards of 90 to 100 tablets of a product and that ingestion of large numbers of tablets was not uncommon. Such a quantity would conceivably result in a child's consuming the entire contents of a package of an Iron Preparation.

But the question arose:

> "What, if any, should be the quantitative, total package level above which Special Packaging would be required and below which such packaging would not be required?"

Given the variability, from person to person and from child to child, in tolerating differing quantities of a posion, no precise lethal dose or toxic dose could be established in iron ingestions. One review article [redacted] suggested a range of 40 to 1600 mg. of Ferrous Sulfate per kilogram of body weight as having caused death in children. However, our Bureau of Biomedical Science has discredited this lower value as being incapable of support by reference to a specific source.

Using empirical methods, generally accepted toxicology values of 150 mg/Kg. as a toxic iron dose for a child and the value of 25 pounds for the average child under five, FDA's staff initially set the total quantity per package limitation at 1,000 mg. (1 Gm.) However, in order to allow for a larger "margin of safety" the limiting amount was halved to 500 mg. This was thought to provide the desired protection when considering such factors as: variability in body weight, fluctuations in the state of health and individual differences in susceptibility and reactions of a particular individual child to a given, potentially toxic dose of iron. Memoranda in support of this level are attached [redacted].

Admittedly, there is some uncertainty as to the 500 mg. level set in the Proposed Standard as that level of ingestion which would not cause toxicity, sickness, injury or death. It is difficult to "draw the line" with precision on a "Go-No Go" basis when dealing with a continuum. The exception always proves the rule. A child who, because of an individual idiosyncrasy or because of a transient or permanent physical condition, may be particularly sensitive to Iron, may exhibit symptoms of toxicity at a much lower level than at 500 mg. However, there are no documented cases which have come to our attention in this respect.

4. Availability of Special Packaging to Accommodate Dropper Bottles

It would appear that satisfactory quantities of Special Packaging for dropper bottles, which are used in an undetermined percentage of Iron Preparations does not presently exist. This was one of the prime considerations in the recommendations from the Bureaus of Biomedical Science and Economic Analysis that an effective date be set for one year after promulgation of the Standard. [redacted]. In fact, two pending petitions for exemption from compliance with the impending, effective date for the requirement of Special Packaging for Oral Prescription Drugs raise the issue of the unavailability of Special Packaging incorporating a dropper feature. Wampole Laboratories has requested an exemption for its "Organidin" Solution while Wyeth Laboratories has requested exemptions for seven penicillin-type antibiotics, one of which, "Omnipen Pediatric Drops", is also administered by dropper.

Prior to April 16, 1973 (the date of promulgation of the Special Packaging Standard for Oral Prescription Drugs), Sunbeam Plastics Corporation submitted, to the Commission, a prototype child-resistant closure which incorporated a dropper assembly. The purpose of this submission was to establish the technical feasibility of such packaging. The firm presumably has not put this into production, originally citing a lack of sufficient interest from potential users to warrant the expense of mold construction, any subsequently necessary refinements and child protocol testing.

More recently (February 1974), Doherty Brothers Company submitted test data on their dropper unit, although the company estimates that it will require one year before adequate supplies will be available for industry use.

In April 1972, the FDA's Bureau of Drugs (see chronology, Tab B) opined that droppers could be packaged separately with the stock or reservoir bottle being supplied with available Special Packaging. The problem of possible contamination of the product when in actual use was not addressed. Also not addressed was the practicability of physically keeping the dropper with the reservoir bottle for periodic use.

However, the preamble to the proposed Standard does suggest that the problem may be handled in this manner, failing the availability of dropper assemblies which offer Special Packaging with built-in dropper as a one-piece or multi-piece, combination unit.

Otherwise, contacts with packaging manufacturers indicate that except for dropper closures, Special Packaging is compatible with the packaging presently being used for Iron Preparations.

TECHNICAL ADVISORY COMMITTEE ON POISON PREVENTION PACKAGING

The proposed Standard was reviewed by the members of the TAC on PPP during June 1971 and October 1973. All members were in concurrence that the Standard was necessary and was properly written. One member, however, suggested that the Standard should apply to "medical preparations only".

ALTERNATIVES

1. Accept and publish the Proposed Standard as written:

a. The Standard meets, or upon any necessary modification thereof, (See 1.c. below) can meet all the statutory tests required by Section 3(a) of the PPP Act on the establishment, by regulation, of a Standard:

(1) Prior consultation with (and incidentally, concurrence by) the Technical Advisory Committee on Poison Prevention Packaging;

(2) The degree and nature of the hazard to children has been established and is such that Special Packaging is required to protect children from serious personal injury or serious illness;

(3) The Special Packaging to be required by such Standard is:

Technically Feasible, in that technology exists to produce such packaging in conformance with the Standard.

Practicable, in that such packaging is susceptible of modern mass production and assembly line techniques while production date indicate a capability adequate to meet the needs of affected industries.

Appropriate, in that such packaging is not detrimental to the integrity of the subject Iron Preparations and should not interfere with the storage and use of the affected products.

b. In preparing this Standard the requirements of Section 3(b) have been met in that the following have been considered:

(1) The reasonableness of the Standard is established.

(2) Available scientific, medical and engineering data concerning Special Packaging and childhood ingestions, illness, and injury caused by Iron have been reviewed and justify the promulgation of such a Standard as this.

(3) Manufacturing practices of the affected industry.

(4) The nature and use of Iron preparations.

c. Publish a modified version of the Standard when the Final Order is promulgated as a regulation.

(1) Necessary because of the uncertainties described.

(2) Depending on the comments received by the Commission following publication of the proposed Standard, there may be a need to change some provisions in the Final Order on the Standard. The Commission may then have to publish qualifications to some principles enunciated in the Preamble to the Standard. Thus, for example, the effective date may have to be extended to one year.

The suggestion that a preparation administered by dropper be enclosed in Special Packaging which does not incorporate the dropper in a single unit but where the dropper is kept separately from the reservoir bottle may have to be dropped because of claims that the product may be contaminated in this way. There may be a problem in storing a dropper supplied separately from the reservoir bottle.

Inasmuch as no Iron Preparations will be exempted under the 500 mg. per total package limiting level, and since data may be presented in answer to the request for such data concerning a level below which serious illness will not occur in children, it may prove desirable to remove this limit altogether and require that all Iron Preparations be contained in Special Packaging.

2. Reject the Proposed Standard and do not publish it.

a. The uncertainty as to the propriety of setting at 500 mg. the total package quantity level of Iron above which Special Packaging would be required and below which Special Packaging would not be required.

b. The question as to the availability, within six months of publication of the Final Order promulgating the Standard, of Special Packaging to meet the needs of inudstry, particularly as regards the availability of Special Packaging needed for products requiring delivery by dropper.

RECOMMENDATION OF THE PRODUCT SAFETY OPERATIONS CENTER:

The proposed Standard should be published, as written, at the earliest possible time. It must be borne in mind, however, that modifications may be necessary before promulgation of the Standard as a Final Order in the FEDERAL REGISTER.

MEMORANDUM

CONSUMER PRODUCT SAFETY COMMISSION

DATE: January 22, 1974

TO : Ed Finch, BC
THRU: Dr. Robert Hehir, BBS
FROM: Georg Maisel, BBSPP

SUBJECT: Proposed Regulation for the Child-Resistant Packaging of Iron Containing Preparations

We have reviewed the proposal for child-resistant packaging for iron containing preparations and have the following comments:

1. We realize that the effective date of six months after publication of the final order is a proposal based on the hazard which iron containing preparations presents to children and is subject to change depending upon information obtained through public comments and upon capabilities of packaging manufacturers at the time the final order is published. We have, however, contacted packaging manufacturers to determine whether, at this time, they feel that they would be able to supply a sufficient number of units within the six month period. December, 1974 was used as the possible effective date.

The child-resistant packaging required to supply packagers of iron preparations has been estimated at 400 million units annually. This figure was arrived at through consultation with BEA. While some manufacturers who specialize in the production of only one type of safety package - i.e., threaded closures or snap caps - indicated that they would be able to devote part of their existing mold capacity to supply packagers of iron preparations and felt that a six month effective date was feasible if orders were received promptly after publication of the final order, the larger manufacturers who manufacture both prescription vials and threaded closures indicated that a minimum of nine months to a year would be more realistic. These latter manufacturers indicated that the volume of units required would necessitate new tooling, a process which requires approximately six months before equipment is on line to begin production of packaging; a sufficient number of units would then have to be produced to satisfy initial demands of packagers. This would require two to three months. Time is also required to distribute the finished packaging nationally. The length of time necessary to produce and distribute packaging is further increased because packaging manufacturers are unwilling to build new mold capacity until sufficient orders have been received to justify the expenditure for new tools.

2. A percentage of iron-containing preparations are packaged in dropper bottles. Those manufacturers who have prototype designs for child-resistant dropper bottles were contacted and indicated that subjecting the prototypes to the testing protocol, building production machinery, and producing an initial inventory would require a minimum of one year. We realize that, at the time of the promulgation of the final order for prescription drugs, the adjudication was made that, based on information supplied to us then by packaging manufacturers, safety packaging would be developed for items in dropper bottles in time to meet the effective date of that regulation. This has not, however, proven to be true.

3. We would like to delete the sentence on page 3 of the proposed regulation stating that, "Iron containing preparations are currently packaged in glass bottles with threaded neck finishes, in vials with snap or screw type elosures, and in bottles with glass or plastic plugs. While the statement is true, iron preparations could conceivably be packaged in other types of containers i.e., bags or cans. We would prefer a general statement that iron-preparations can be packaged in existing designs of child-resistant packaging.

Copy of Reg (attached)

MEMORANDUM CONSUMER PRODUCT SAFETY COMMISSION

DATE: February 1, 1974

TO : Bill Menza, OSCA
THRU : Walter Hobbs, Acting Director, BEA
FROM: Hal Weisman, BEA

SUBJECT: Proposed Standard for Iron Preparations Under PPPA

BEA is in complete agreement with Georg Maisel's, BBSPP, memorandum of January 22, 1974 (Proposed Regulation for the Child-Resistant Packaging of Iron Containing Preparations).

We would like to emphasize that our analysis of the industry also indicates that this regulation should become effective one year after the final form of the regulation is published.

In order to help minimize changeover costs, work off existing inventory, and generally allow for an orderly transition, a one-year time period for compliance is recommended.

cc: Georg Maisel, BBSPP

Tab E

CONSUMER PRODUCT SAFETY COMMISSION

DATE: July 17, 1973

TO : Dale C. Miller
Through: Director, Bureau of Compliance
FROM: Albert F. Esch, M.D., Medical Director

SUBJECT: PPPA Proposal for Iron Salts

As requested, the PPPA Proposal for Iron Salts has been reviewed with reference to the hazardous childhood levels for these substances.

In commenting on an earlier version of the proposal, the Director, Bureau of Drugs stated (December 7, 1972) - "the usually accepted iron dose capable of causing illness in a child is about 150 mg/kg. Providing a margin of safety by lowering this limit to 100 mg/kg. would place the dangerous dose at about 1200 mg." From this it was concluded that "...a reasonable limit would seem to be about 1 gram."

The Bureau of Foods subsequently, (March 14, 1973), indicated a preference for an upper limit per total package of 500 mg. "to err on the safer side." The rationale provided was that "The 1,000 mg. limit does not leave much room for variability in body weight (such as the 18 lb. 12-month old crawler) of individual variability in susceptibility in toddlers of the same size."

On May 14, 1973 the Bureau of Drugs indicated their concurrence with the lower figure, concluding that "...establishing a conservative upper limit of package content has merit due to the rather confusing manner in which data is (i.e. are) presented in the literature concerning the toxicity of iron."

There is no means by which we can arrive expeditiously at a more precise determination of the harmful quantity of iron for a 25 lb. two year old child other than the subjective judgments made by the Bureau of Food and Drugs. I would endorse the lower figure (500 mg.) since I favor the position that a reasonable "margin of safety" should be incorporated into the Commission's medical decisions. The other points outlined in the Associate Commissioner for Compliance memorandum (May 18, 1973) appear to be a consensus of many comments elicited over the past year and should be acceptable for CPSC proposal.

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Director
Office of Standards Coordination and Appraisal
Consumer Product Safety Commission

DATE: NOV 30 1973

FROM : Associate Commissioner for Compliance, HFC-1

SUBJECT: Proposed Regulation on Child Protection Packaging for Iron Preparations

1. The Food and Drug Administration has reviewed the draft of the proposed child protection packaging standards for Iron preparations and concurs in the publishing of this proposal with the following recommended changes:

(1) The purpose of establishing a quantitative limit based on elemental iron content was to include not only the various iron salts but also chelates and complexes as well as nonionized forms of iron used in both drugs and dietary supplements. Therefore, we do not consider it appropriate to refer to the use of elemental iron in therapy or as a toxicant and recommend deletion of the term elemental on page 1, lines 2, 4 and 6 of the analysis section and revision of the standard (§ 1700.14 (a)(11)) to read as follows:

> "(11) Iron preparations. Non-prescription drugs which are in dosage forms for oral administration in humans, and dietary supplements as defined in 21 CFR 80.1, either of which provide 500 milligrams or more of elemental iron per total package, shall be packaged in accordance with the provisions of § 1700.15(a), (b) and (c)."

(2) For clarity, revise that portion of the sentence appearing at line 10, page 4 of the analysis section to read "a dose of one gram of iron could produce death in children younger."

(3) Due to the complex conditions associated with acute iron poisoning and the lack of specific identification with nervous systems, we recommend deletion of the terminology "affects the nervous system" appearing in the third paragraph, line 3, page 1 of the analysis section in the last paragraph, line 3, page 1 of the document.

(4) For clarity, revise the first sentence of the second paragraph of the document to read "Acute accidental poisoning from iron began to occur with greater frequency when iron became widely used as a therapeutic agent."

2. The above mentioned recommended changes have been made in the attached draft copy of the Federal Register notice provided by CPSC.

Sam D. Fine

Enclosures

MEMORANDUM

CONSUMER PRODUCT SAFETY COMMISSION

DATE: January 25, 1974

TO : Dr. Albert F. Esch, Office of the Medical Director

FROM: Dr. L. James Sharman, Director, Office of Standards Coordination & Appraisal

SUBJECT: Special Packaging Standard for Iron Preparations.

General Counsel has requested that we be prepared to document PSOC's recommendation that Special Packaging be required for all Iron Preparations containing 500 mg. or more of elemental iron.

We have recommendations from Drs. Done and Forbes of FDA to the effect that 500 mg. total elemental iron per package is a reasonable level allowing a sufficient margin of safety against toxicity. This view is also supported by Dr. J. M. Arena who is quoted in a review article by Dr. John J. Crothy of The National Clearinghouse for Poison Control Centers (FDA). This article, copy attached, is entitled "Acute Iron Poisoning in Children" and appears in Clinical Toxicology, 4(4), pp. 615-619, December, 1971. On page 616, 3rd paragraph, Crothy quotes Arena, in part,: "He [meaning Arena] further clarifies by noting that the minimal lethal dose is much lower since fatalities have occurred with as few as ten 5-grain tablets [2] (which would equal 650 mg. of elemental iron)."

However, the problem we would like to bring to your attention is caused by a previous sentence in this same paragraph. The 3rd sentence reads: "Death has occurred from the ingestion of ferrous sulfate in doses ranging from 40 to 1600 mg./kg. body weight." This translates out to 164.58 mg. of elemental iron (based on the fact that Iron is 36.8% by weight of Ferrous Sulfate and that the average 2 year old child weighs 25 lbs. or 11.4 kg.).

$$40 \times 36.8\% = 40 \times 0.368 = 14.7 \text{ mg. Fe}$$
$$14.7 \times 11.4 = 164.58 \text{ mg. Fe}$$

There is no doubt that the range from 40 to 1600 mg./kg. is quite large and that the 40 mg. value may represent an isolated, extremely sensitive case.

We would appreciate your opinion as to the weight we should place on this finding in view of the fact that PSOC's proposed level of 500 mg. total Iron per package is approximately 3 times as great as the lowest dosage reported to cause death.

Attachment

cc: Office of General Counsel
Marilyn Brachen, Bureau of Biomedical Science
Edward Finch, Bureau of Compliance

B. 1.2.4

January 31, 1974

Dr. Albert Kach, Office of Medical Director

Dr. L. James Sharman, Director, Office of Standards Coordination & Appraisal

Special Packaging Standard for Iron Preparations

This will serve to correct an error in computation in our memorandum to you of January 25, 1974 on the same subject.

The value "164.58 mg. Fe" should be replaced by the value "91.2 mg. Fe."

The error occurred because we were using the pure product, "Fe SO_4", upon which to base our computations. The U. S. P., however, specifies that the heptahydrate of Ferrous Sulfate, i.e., Fe $SO_4 \cdot 7H_2O$, shall be used in manufacturing Ferrous Sulfate tablets. Thus, iron amounts to 20% by weight of the hydrated Ferrous Sulfate rather than the 36.8% used in our original computation. The new calculations are:

40 (mg.) X 0.20 = 8 (mg. Fe)
8 X 11.4 = 91.2 (mg. Fe)

This also indicates a change in the last paragraph of the subject memo in that the proposed level of 500 mg. total Iron per package is approximately 5 times as great as the lowest dosage reported to cause death.

cc; Office of General Counsel
Dr. Marilyn Bracken, Bureau of Biomedical Science
Mr. Edward Finch, Bureau of Compliance

bcc:

ORU Files

Chrono

Prepare: BScharf

Signer: LJSharman:css 1/31/74

MEMORANDUM

CONSUMER PRODUCT SAFETY COMMISSION

DATE: January 31, 1974

TO : Dr. L. James Sharman, Director, Office of Standards Coordination & Appraisal

FROM: Dr. Albert F. Esch, Office of the Medical Director A. F. Esch

SUBJECT: Special Packaging Standard for Iron Preparations

Since receiving your memorandum of January 25th relating to the minimum lethal dose of ferrous sulfate, I have discussed the case in point with Mr. Lou Verhulst of the National Clearinghouse for Poison Control Centers, Dr. John Crotty of the same organization (and Author of the Article) and Mr. Georg Maisel of the Bureau of Biomedical Science.

It is my opinion that this particular literature citation does not alter the previous conclusions reached by my Office, the Bureau of Biomedical Science and the FDA in regard to a safe level for regulatory purposes. I therefore maintain my recommendation of July 17, 1973.

B. Scharf (Sent 2/13)

February 5, 1974

Michael Brown, OGC, Attn: D. Schmaltzer and S. Lemberg
THRU: Frederick Barrett, Executive Director
L. James Sharman, Director, Office of Standards Coordination & Appraisal

Telecon of January 10, 1974, between Steve Lemberg and W. Menzo,
re: PPP Standard on Iron Preparations

In the referenced telecon of January 10, 1974, General Counsel posed the following two questions:

1) Can the Bureau of Biomedical Science and/or the Office of the Medical Director support the 500 mg./total package limitation for Iron Preparations?

2) Can the Bureau of Biomedical Science support the claim that the requirement of Special Packaging for Iron Preparations is feasible, practicable and appropriate?

A. Comments on Question 1:

In answer to the first question, there seems to be ample documentation, from at least two independent, authoritative and reliable sources, to the effect that 500 mg. of "elemental" iron is a reasonable, although admittedly arbitrary, level at which to set the "per package" total limit below which Special Packaging would not be required for Iron Preparations. We admit that the level is arbitrary only because it would be nigh-on to impossible to set an exact limit below which absolutely no fatalities or serious illnesses would occur. This is because of the great variability from human to human and thus, from child to child, in the ability to tolerate acute poisonings. Much depends on the state of health of the individual and on other environmental and hereditary factors. Diet may also play an important role. However, although arbitrary we believe we are leaning to the conservative view in offering more protection to children by allowing for a greater margin of safety than available data indicate would otherwise be possible for us to set.

In a memorandum of December 7, 1972, to the Director of FDA's Bureau of Product Safety, Dr. Henry Simmons, then Director of FDA's Bureau of Drugs, stated the following on the basis of Dr. Alan Done's research: "The usually accepted iron dose capable of causing illness in a child is about 150 mg./kg. Providing a margin of safety by lowering this limit to 100 mg./kg. would place the dangerous dose at about 1200 mg. for the 25-pound child specified in the PFPA. Therefore, a reasonable limit would seem to be about 1 gram".

This theme is broached again in a memorandum of March 14, 1973, from Dr. Allen Forbes, Deputy Director of FDA's Division of Nutrition (Bureau of Foods) to FDA's Associate Commissioner for Compliance: "We originally recommended that the proposed regulation apply to all dietary supplements of vitamins and minerals and to OTC drugs containing iron, as has the Committee on Nutrition, American Academy of Pediatrics. This position was based in part on the arbitrary nature of selecting some specific amount of iron per unit or daily dose above which toxicity becomes a problem and below which it does not, when multiple units are accidentally ingested. We believe that the basic objective is attained by the novel approach of applicability of the regulation when the entire package contains in excess of a safe amount of iron. Thus, the following types of dietary supplements would require safety closures, as examples (if the safe amount per package was set at 500 mg. instead of 1,000 mg. as proposed)".....

Paragraph 3 of this memorandum goes on: "As inferred above in paragraph 4, we would prefer a safe upper limit per total package of 500 mg. to err on the safer side. The true toxic dose is not well established, nor is the lethal dose, in toddlers and older pre-school children. For many of the serious or lethal cases, the actual dose is unknown. It is reasonable to assume that the number of cases reported by the National Clearinghouse for Poison Control Centers is a gross underestimate of the true incidence (I encountered two cases in children of a colleague two weeks ago myself, promptly treated with emetics. The 1,000 mg. limit does not leave much room for variability in body weight (such as the 18 pound 12-month old crawler) or individual variability in susceptibility in toddlers of the same size. The objective should include protection against significant illness as well as against serious illness with a potential lethal outcome".

In a "Memorandum For File" of March 29, 1973, Dr. Forbes says: "The limit of 500 mg. of total iron per package, above which safety closures would be required is defensible".

Dr. Marion Finkel, Deputy Director of FDA's Bureau of Drugs, discusses Dr. Forbes' memorandum (as described above) in a memorandum of May 14, 1973, to FDA's Associate Commissioner for Compliance: "The balance of the memorandum recommending the elimination of an arbitrary unit content of dosage and establishing a conservative upper limit of package content has merit due to the rather confusing manner in which data is presented in the literature concerning the toxicity of iron. It is difficult to determine in most reported cases whether the author is referring to elemental iron or an iron salt when he attempts to present the toxic dose. If more reliable data are available on this subject, our publication of the lower 500 mg. safe upper limit of package content should prompt interested persons to present such information for our consideration prior to finalising the standard".

Under cover of his letter of May 18, 1973, to then Acting Executive Director of PSOC, John Locke, FDA's Associate Commissioner for Compliance forwarded Dr. Finkel's memorandum of May 14, 1973 (described above). In this letter Mr. Fine refers to the elimination of an arbitrary unit dosage content for iron preparations while reducing the upper limit of package content from the previously proposed 1 gram to a "more conservative upper limit of 500 milligrams of iron".

In his memorandum of July 17, 1973, to Dale Miller, Dr. Esch briefly reviews the comments from FDA's Bureaus of Foods and Drugs and concludes by saying:

"There is no means by which we can arrive expeditiously at a more precise determination of the harmful quantity of iron for a 25 pound two-year-old child other than the subjective judgments made by the Bureau of Food and Drugs. I would endorse the lower figure (500 mg.) since I favor the position that a reasonable 'margin of safety' should be incorporated into the Commission's medical decisions. The other points outlined in the Associate Commissioner for Compliance memorandum (May 18, 1973) appear to be a consensus of many comments elicited over the past year and should be acceptable for CPSC proposal".

In his review article, "Acute Iron Poisoning in Children" (Clinical Toxicology, 4(4), pp. 615-619, December, 1971), Dr. John Crotty of FDA's National Clearinghouse for Poison Control Centers writes: "Death has occurred from the ingestion of ferrous sulfate in doses ranging from 40 to 1600 mg./kg. body weight. Hoppe has estimated the fatal dose for a 2-year-old or younger child to be 900 mg./kg.[1]. More recently Arena states in his book, "Poisoning", that the average human lethal dose is about 200 to 250 mg. of iron/kg. For the average 2-year-old this means an ingestion of 3 gm. of elemental iron. He further clarifies by noting that the minimal lethal dose is much lower since fatalities have occurred with as few as ten 5-grain tablets [2] (which would equal 650 mg. of elemental iron). Although statistical data are scarce, in 1953 a British article stated: 'Cumulative experience discloses close to 50% mortality in dosages from 2-4 gm. of orally injected iron in children' [3]. In 1958, Aldrich confirmed this impression noting that after ingestion of large doses of iron the mortality rate approached 50% [4]".

A question did arise about the third sentence in Dr. Crotty's article which seemed to indicate that as little as 40 mg. Ferrous Sulfate per Kilogram body weight had produced death in children. This worked out to a total equivalent to 91.2 mg. in terms of "elemental" iron. This was brought to the attention of Dr. Albert Esch, Medical Director, Office of the Medical Director, in our memorandum of January 25, 1974. After discussing the matter with officials of FDA's National Clearinghouse for Poison Control Centers (including Dr. Crotty, author of the subject article) and with officials of the Bureau of Biomedical Science, Dr. Esch, in his memorandum of January 31, 1974, reiterates his 500 mg. per package recommendation.

Our review of iron-containing preparations of all sorts, as listed in "Facts and Comparisons", ranging from straight iron-containing products to iron and vitamin combinations and iron and liver combinations, etc., reveals that few, if any, of these products would be exempted from safety packaging on the basis of present quantities per package and a 500 mg. per package total content limitation.

RECOMMENDATION:

In view of the extensive documentation support of the 500 mg. "elemental" iron per total package limitation for iron-containing preparations, we recommend its retention in the subject proposed standard.

B. Comments on Question 2:

A memorandum, dated September 6, 1973, from Clay Sisk, then of the Bureau of Biomedical Science's Division of Poison Prevention Packaging, to Kathy O'Neill, Bureau of Compliance: Sisk discusses his contacts with a number of packaging suppliers. The gist of his findings is that these companies need only expand on production of already existing packaging materials being used for aspirin and other products already covered under the Poison Prevention Packaging Act in order to meet the needs for the special packaging of Iron Preparations. A minimum of 16 and a maximum of 34 weeks would be necessary to arrange for additional production capacity.

Sisk writes that most packagers of iron preparations are engaged in using special packaging for other drug products and already have the production equipment to assemble the child-resistant packages as part of their normal filling lines.

The publication of a proposed standard would provide enough lead time to allow affected firms to do the necessary planning and to place orders with their packaging suppliers. The packaging suppliers could, in turn, make the necessary plans to expand production accordingly.

The Bureau of Biomedical Science conducted a survey on December 12, 1973, of 5 of the largest manufacturers of safety packaging. On the assumptions that:

a. The proposed regulation would be published in January 1974;

b. The final regulation would be published in April 1974, with an effective date of 1 year from publication; and

c. Sufficient orders were received in a timely manner;

they would supply packaging in sufficient quantities to meet industry's needs. However, this is based on the provision that the final order on the Standard contains an effective date not earlier than one year after its publication in the Federal Register.

A memorandum of Jnuary 22, 1974, from Georg Haisel, BBSPP to Ed Finch, BC, reiterates the feasibility, practicability and appropriateness of Special Packaging for Iron Preparation (OTC Drugs and Special Dietary Supplements), providing that the Final Order contains an effective date not earlier than 9 months to a year after its publication in the Federal Register. This period, preferably one year, would allow industry time to develop safety packaging satisfactory for those preparations requiring the use of dropper bottles.

In its memorandum of February 1, 1974 (Hal Weisman/Bill Mensa thru Walt Hobby, BEA) the Bureau of Economic Analysis states its agreement with the views of Georg Haisel in his memorandum of January 22, 1974, to Bureau of Compliance (see above). BEA's industry analysis indicates that an effective date of one year after publication in the Federal Register is called for. This will serve to minimize changeover costs, aid in allowing existing inventory to be worked off and allow for an orderly transitional period to achieve full compliance by the effective date.

RECOMMENDATION:

It seems that the feasibility, practicability and appropriateness of special packaging for iron preparations has been established. We would recommend that industry be given the full amount of time possible, i.e., one year, in which to make appropriate arrangements to properly comply with the finalized standard. Because of the imperative need for special packaging in this area we might consider the possibility of adding a provision to the effect that although one year is allowed for firms to begin to apply safety closures to iron preparations, we would expect all firms, in good faith, to begin to use such safety packaging as soon as it becomes available to them, the one year period notwithstanding. There is a precedent for such a statement. FDA in its regulation on Impact Resistant Lenses (CFR 21, 3.85) stated in its final order: "The transition to impact-resistant lenses must be completed as promptly as possible; however, to provide for the development of an adequate supply of impact-resistant lenses and to facilitate an orderly changeover to these lenses, all lenses manufactured after January 31, 1972, must be impact-resistant"... Another, more pertinent precedent appeared in FDA's request for comments and data on "Establishment of Child-Protection Packaging Standards for Nonprescription Drugs for Humans" which was published in the Federal Register of June 20, 1972 (Vol. 37, No. 119, p. 12171 and 12172). The next to the last paragraph reads:

"The demands for special packaging are expected to be substantial and will increase rapidly when child-protection packaging standards for nonprescription drugs becomes effective. In considering the purpose of the Act, which is to protect children from poisoning accidents, the Commissioner hereby requests the pharmaceutical industry to cooperate and expand the use of special packaging to all nonprescription drug products where any potential for hazard to children exists, rather than await the time-consuming procedures necessary to establish legally enforceable requirements". Thus, those firms able to obtain safety closures earlier than others may begin to use them earlier.

cc:
Dr. Albert Kech, Director, Office of the Medical Director
Dr. Robert Nehir, Bureau of Biomedical Science, Attn: Dr. Brachen
Edward Finch, Director, Bureau of Compliance

CONCURRENCE BY:

Signed by B. Scharf
Oral Direction of A. Esch

Albert Kech, Director, Office of the Medical Director

2-12-74
Date

Dum Draff for Hehir

Robert Nehir, Director, Bureau of Biomedical Science

2-7-74
Date

bcc:
Chrono
ORU (2)

Signer: LJSharman

Preparer: BScharf:ejd 2/5/74

MEMORANDUM

CONSUMER PRODUCT SAFETY COMMISSION

DATE: February 5, 1974

TO : Dr. L. James Sharman, (OSCA)

FROM: Dr. Robert M. Hehir, (BBS)

SUBJECT: Special Packaging Standards for Iron Preparations

We would like to make the following comments with respect to your memo of January 25, 1974, to Dr. Esch, regarding the above subject.

We have reviewed the referenced article quoted by Dr. Crotty, from which the fatal level of ferrous sulfate in doses ranging from 40-1600 mg/kg body weight was taken. Although this article contains numerous cases of reported deaths from ferrous sulfate, it did not indicate the ages of the children involved, the amounts ingested, nor the method of access to the product (overdosage, therapeutic). Since this article did not give any source for the cases cited, we are unable to verify these data.

We would like to emphasize, however, as these two articles point out, there is much that is not well understood about iron, its mechanism of absorption, and even its toxicity level. For instance, ferrous sulfate exists in several stable forms, e.g., anhydrous ferrous sulfate, ferrous sulfate monohydrate, and ferrous sulfate heptahydrate, which oxidizes in moist air to form ferric sulfate. The heptahydrate is converted to the tetrahydrate at 56.6°C and to the monohydrate at 65°C. Each of these forms, depending on the amount of hydration, have different solubility levels. There is a wide variance in the reported toxic levels for ferrous sulfate (hydration unspecified), as Dr. Crotty reported.

Toxic Level	Elemental Iron Equivalent, based on $FeSO_4.7H_2O$ 1/	Source	Age
40 mg ferrous sulfate/kg	8 mg/kg	Unknown	Unknown
1600 " "	320 mg/kg	Unknown	Unknown
900 " "	180 mg/kg	Hoppe	2 Yr. Old
	200-250 mg/kg 2/	Arena	2 Yr. Old
	57 mg/kg 3/	Arena	2 Yr. Old
	44 mg/kg	Proposed standard	2 Yr. Old

The safety packaging standard for iron was initiated on March 1, 1971, by the then Bureau of Product Safety of the Food and Drug Administration and concurred in by the Bureau of Drugs. As previously noted, there is a wide range of reported toxic levels. Consequently, there was much discussion between the Bureau of Product Safety, the Bureau of Foods, and the Bureau of Drugs of the Food and Drug Administration regarding the level that was set forth in this proposal. The Food and Drug Administration, the Consumer Product Safety Commission, (Office of Medical Director and the Bureau of Biomedical Science), which are staffed with expertise in medicine, pharmacology, and toxicology, have reviewed all the available toxicity data, and agreed that the proposed dosage level (500 mg total elemental iron per package) would provide an adequate margin of safety.

There is a pressing need for this standard because of the reported fatalities due to this substance. In view of the questionable practice of persons of diverse non-technical background challenging the technical expertise of the Food and Drug Administration, the Consumer Product Safety Commission (Office of Medical Director and the Bureau of Biomedical Science), the publication of this proposed regulation is being needlessly delayed.

The implication of this challenge is even more serious: future, as well as presently drafted proposals of standards from the Food and Drug Administration and the Bureau of Biomedical Science are based on the best technical knowledge and state of the art available. There may always be suggestions of serious injury at levels below that recommended.

1/ $FeSO_4.7H_2O$ is the form of ferrous sulfate most commonly used in drugs and food supplements. These calculations are based on a 25 pound child (11.4kg).

2/ Average human lethal dose

3/ Minimal lethal dose

However, until a level is set, no protection is the rule. We recognize the shortcomings of this method and are willing to adjust such levels as further data is developed. If standards are set at the level of an isolated report, it may be impossible to support them should this be challenged. Once the data has been fully evaluated by the medical-biomedical staff and agreement reached on critical levels, this data should be submitted to the Commissioners as presented. If non-technical Bureaus wish to present additional substantiated data recommending different levels, then it should be added on as an addendum.

The Office of the Medical Director concurs with these views of the Bureau of Biomedical Science.