Issued in Washington, DC, on January 25, 1999.

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Acting Program Director for Air Traffic Airspace Management.

[FR Doc. 99–2136 Filed 1–28–99; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 178

Indirect Food Additives: Adjuvants, Production Aids, and Sanitizers

CFR Correction

In Title 21 of the Code of Federal Regulations, parts 170 to 199, revised as of April 1, 1998, make the following corrections:

1. In § 178.3130(b), on page 364, in the second column, in the first line of number 2 under Alkyl mono- and disulfonic acids, correct ''be'' to read ''to'', and in the same column, at the end of the fourth paragraph, after the words ''such foods have a pH'', add the words ''above 5.0''.

2. In § 178.3620(c)(3), on page 384, in the first column, in the first full paragraph, line 14, after the words ''Loosen the'' correct ''top'' to read ''topmost'' and add the following:

* * * * *

''few millimeters of each adsorbent layer with the end of a metal rod before the addition of the next layer. Continue packing in this manner until all the 14 grams of the adsorbent is added to the tube. Level off the top of the adsorbent by pressing down firmly with a flat glass rod or metal plunger to make the depth of the adsorbent bed approximately 12.5 centimeters in depth. Turn off the vacuum and remove the suction flask. Fit the 500–milliliter reservoir onto the top of the chromatographic column and prewet the column by passing 100 milliliters of isooctane through the column. Adjust the nitrogen pressure so that the rate of descent of the isooctane coming off the column is between 2–3 milliliters per minute. Discontinue pressure just before the last of the isooctane reaches the level of the adsorbent. (Caution: Do not allow the liquid level to recede below the adsorbent level at any time.) Remove the reservoir and decant the 5–milliliter isooctane concentrate solution onto the column and with slight pressure again allow the liquid level to recede to barely above the adsorbent level. Rapidly complete the transfer similarly with two 5–milliliter portions of isooctane, swirling the flask repeatedly each time to assure adequate washing of the residue. Just before the final 5–milliliter wash reaches the top of the adsorbent, add 100 milliliters of isooctane to the reservoir and continue the percolation at the 2–3 milliliters per minute rate. Just before the last of the isooctane reaches the adsorbent level, add 100 milliliters of 10 percent benzene in isooctane to the reservoir and continue the percolation at the''

* * * * *

2.In § 178.3910(a)(2) table, on pages 406 and 407, in the first column, under ''List of substances'', correct the second, third, and fifth entries to read as follows:

* * * * *

α–Butyl–Ω–hydroxypoly(oxypropyl–ene) (CAS Reg. No. 9003-13–8) having a minimum molecular weight of 1000.

α–Lauroyl–Ω–hydroxpoly (oxyethylene) (CAS Reg. No. 9004–81–3) having a minimum molecular weight of 200.

* * * * *

alpha–Alkyl–*omega*–hydroxypoly–(oxyethylene) produced by the condensation of 1 mole of C_{12} – C_{15} straight chain primary alcohols with an average of 3 moles of ethylene oxide (CAS Reg. No. 68002–97–1).

* * * * *

[FR Doc. 99–55505 filed 1–28–99; 8:45 am]

BILLING CODE 1505–01–D

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 175

Indirect Food Additives: Adhesives and Components of Coatings

CFR Correction

In Title 21 of the Code of Federal Regulations, parts 170 to 199, revised as of April 1, 1998, on page 157, second column, § 175.300 is corrected in paragraph (b)(3)(vii)(*a*) by correcting the CAS Reg. No. for 1,4–cyclohexanedicarboxylic to read ''(CAS Reg. No. 1076–97–7)''.

[FR Doc. 99–55504 filed 1–28–99; 8:45 am]

BILLING CODE 1505–01–D

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 78N–036L]

RIN 0910–AA01

Laxative Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that the over-the-counter (OTC) stimulant laxative ingredients danthron and phenolphthalein are not generally recognized as safe and effective and are misbranded. FDA is issuing this final rule as part of its ongoing review of OTC drug products after considering data and information on the safety of danthron and phenolphthalein.

EFFECTIVE DATE: January 29, 1999.

FOR FURTHER INFORMATION CONTACT: Cheryl A. Turner, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2222.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of March 21, 1975 (40 FR 12902), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC laxative, antidiarrheal, emetic, and antiemetic drug products, together with the recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products (the Panel), which was the advisory review panel that evaluated data on the active ingredients in these classes. In the advance notice of proposed rulemaking, the Panel recommended Category I (generally recognized as safe and effective and not misbranded) status for the OTC stimulant laxative ingredients danthron and phenolphthalein (40 FR 12902 at 12908 to 12910). The agency concurred with the Panel's Category I classification of these ingredients in the tentative final monograph published in the **Federal Register** of January 15, 1985 (50 FR 2124 at 2152 to 2156).

In the **Federal Register** of September 2, 1997 (62 FR 46223), FDA reopened

the administrative record and proposed to amend the tentative final monograph for OTC laxative drug products to reclassify danthron and phenolphthalein from Category I to Category II (not generally recognized as safe and effective or misbranded) and to add these ingredients to a list of nonmonograph active ingredients. Interested persons were invited to submit comments on or before October 2, 1997. Data and information received after the administrative record was reopened are on display in the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

This final rule declares OTC laxative drug products containing the active ingredients danthron or phenolphthalein to be new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)), for which an application or abbreviated application (hereinafter called application) approved under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 is required for marketing. In the absence of an approved application, products containing these drugs for laxative use also would be misbranded under section 502 of the act (21 U.S.C. 352).

The final rule amends part 310 (21 CFR part 310) to include the laxative active ingredients danthron and phenolphthalein by adding new § 310.545(a)(12)(iv)(B). Because a safety problem has been identified for OTC drug products containing danthron and phenolphthalein, this final rule is effective on the date of its publication in the **Federal Register**. Therefore, on or after January 29, 1999, no OTC drug products that are subject to this final rule may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved application.

Nineteen comments were received in response to the proposed rule on danthron and phenolphthalein. All comments addressed phenolphthalein. Copies of the comments received are on public display in the Dockets Management Branch (address above).

II. The Agency's Conclusions on the Comments

1. Three comments agreed that phenolphthalein should be removed from OTC laxative drug products because of the public health importance of this matter and the need for prompt closure by FDA. Eight comments contended that phenolphthalein should remain in OTC laxative drug products because the National Toxicology Program (NTP) data (Ref. 1) were insufficient to determine whether phenolphthalein posed a risk to humans, and because phenolphthalein has been safely and effectively used for many years. Several consumers indicated that they will not be able to find another laxative ingredient as effective as phenolphthalein, and believed that their health will be affected if they can no longer use phenolphthalein.

As stated in this document, the agency concludes that phenolphthalein is not safe and not of sufficient medical value to outweigh the potential risks associated with its OTC use. As there are at least 25 other laxative ingredients available for OTC use, the agency concludes that consumers have access to sufficient alternative laxatives.

2. Four comments offered alternatives to removing phenolphthalein from OTC laxative drug products. Three comments argued that stronger warning statements on the phenolphthalein product label and public education would adequately alert consumers of the potential health risk to humans and emphasize appropriate use of the drug.

The agency concludes that stronger warning statements and public education will not change the potential risk of using phenolphthalein and that this risk is not acceptable given the benefit for laxative use in the OTC target population.

3. Three manufacturers contended that actual carcinogenic effects of phenolphthalein in humans have not been determined and recommended that studies be conducted to evaluate the safe use of phenolphthalein in humans. One manufacturer stated that these additional data may take 2 to 3 years to obtain and recommended a moratorium on the decision to remove phenolphthalein from OTC laxative drug products. One manufacturer offered to conduct a case control human surveillance safety study. Two manufacturers recommended that FDA or another agency conduct studies to evaluate the safe use of phenolphthalein in humans.

The agency notes that it is the manufacturer's responsibility to conduct studies to determine whether phenolphthalein is safe for human use. Because of public health concerns, the agency disagrees that phenolphthalein should remain on the market while further human safety studies are being conducted and is stopping initial introduction or initial delivery for introduction into interstate commerce of OTC laxative drug products containing phenolphthalein as of the date this final rule is published in the **Federal Register**.

4. Two manufacturers submitted comments (Refs. 2 through 8) questioning the validity of the NTP data (Ref. 1). They argued that: (1) The studies failed to demonstrate a proposed mechanism of genotoxic action for phenolphthalein that is relevant to humans, (2) alternative mechanisms were not considered, (3) the data obtained from the p53 deficient mouse study are inconsistent with what was expected based on the 2-year carcinogenicity studies, (4) the NTP data do not provide a sufficient basis for FDA to draw firm conclusions regarding the potential human carcinogenicity of phenolphthalein, and (5) there are no relevant human data to draw any firm conclusions regarding potential risk of phenolphthalein in humans.

One comment submitted four consultant reports (Refs. 2 through 5), which reanalyzed the NTP data. One report by Roe (Ref. 3) directed criticisms primarily at the p53 deficient mouse study and the ''null'' mouse, which lacks both wild type p53 alleles. Roe dismissed the positive genotoxicity results as apparent only under conditions of toxicity or in some cases as an estrogenic effect. Roe also rejected the findings of genotoxicity demonstrated for phenolphthalein in the Chinese Hamster Ovary (CHO) cell chromosome aberrations assays, in the several positive in vivo micronucleus assays, and in the mutation and chromosomal aberration findings in the Syrian hamster embryo cells (SHE) transformation assay by Tsutsui et al. (Ref. 9).

Two reports from CanTox U.S., Inc., (Refs. 2 and 4) concurred with the estrogenic mechanism of carcinogenesis proposed by Roe. CanTox proposed that an aneugenic effect may be involved and questioned the validity of the mutagenicity data presented by Tsutsui et al. (Ref. 9) for the SHE cell assay, noting that the control data were not different from the treated groups.

One comment included a position paper on phenolphthalein from the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products (CPMP) (Ref. 7). The CPMP argued that while carcinogenicity and genotoxicity for phenolphthalein were confirmed by data from a transgenic mouse model, the systemic exposures to active drug, both in the conventional rodent bioassays and p53 mouse, appeared to be well in excess of those likely to be encountered in normal human use. CPMP stated that the extent of risk to humans cannot be established without adequate mechanistic data addressing whether a threshold exists for the carcinogenic

effects in mice and the in vivo genotoxic effects. CPMP added that it was unable to verify from original data FDA's statement that the ''systemic exposures in rodents were approximately fortyfold to seventyfold and sixtyfold to hundredfold the human exposure for rats and mice, respectively.''

Another comment (Ref. 8) also reanalyzed the NTP data and concluded that phenolphthalein was a genotoxic carcinogen in rodents. No new information was submitted.

The comments did not submit any new data, but focused on interpreting findings that already were available. The issue of carcinogenicity through a genotoxic mechanism was discussed in the proposed rule (62 FR 46223 at 46224) and at the April 30, 1997, FDA Center for Drug Evaluation and Research (CDER) Carcinogenicity Assessment Committee (CAC) meeting (Ref. 10). The CAC concluded that the study in p53 heterozygous mice supports other evidence that phenolphthalein may be carcinogenic through a genotoxic mechanism. There was a clear dose-dependent increase in the incidence of thymic lymphoma in the p53 assay, confirming one of the primary tumors of concern to the CAC based on its original evaluation of the 2-year assay data. These tumors occurred at doses that showed no other signs of toxicity. Further, the CAC believed that the results of several of the assays and data support a genotoxic clastogenic mechanism. Phenolphthalein was positive in chromosome aberration tests and showed chromosomal abnormality and hypoxanthine phosphoribosyltransferase (hprt) mutations in the SHE cell assay, where nontoxic doses caused cell transformation, mutations, and chromosome aberration. The p53 protein accumulation in the nucleus of thymic lymphoma cells of the original 2-year mouse bioassay, coupled with the deletion of the wild type p53 allele in the thymic lymphomas of p53 mice, is indicative of interaction with the p53 gene as a target site. In vivo, repeated exposure resulted in micronuclei in both the original bioassay and in p53 mice studies. In the p53 mice, an increase in peripheral blood micronucleus occurred even at the low doses (about 15 times the human exposure) with increased duration of treatment without establishing a no effect dose. Further, the exposures used to demonstrate these in vivo and in vitro genotoxic effects were in the range that could occur with human laxative use.

With regard to use of the p53 assay and its usefulness for quantitative risk assessment, NTP used the p53 heterozygous mouse assay to test phenolphthalein; therefore, many of the comments in Roe's report regarding the ''null'' mouse (which lacks both wild type p53 alleles) do not apply. Information is available regarding the responsiveness of the p53 model and the types of compounds to which it responds. To date, when using a 6-month protocol design, the p53 mouse only appears to respond to compounds known to be carcinogenic and genotoxic, and not to compounds that are carcinogenic and nongenotoxic. There is also no evidence to date that the p53 heterozygous mouse assay that was used responds to carcinogens at significantly lower doses than are positive in standard bioassays. Data for the micronucleus response from Tice et al. (Ref. 11) indicate that, while the maximal response in the p53 mouse is greater than for other strains of mice, response below 2,000 milligram/kilogram/day is similar to that of normal CD-1 mice similarly treated with phenolphthalein. Furthermore, the tumor response to phenolphthalein in the p53 model occurred over a dose range that could have been predicted based on the results of the 2-year bioassay in mice (assuming a genotoxic mechanism). Thus, the agency considers it reasonable to use the p53 model as a part of the weight of evidence in assessing a drug suspected of being a genotoxic carcinogen.

The agency further notes that the CAC's evaluation was not a quantitative assessment for either the standard bioassays or the p53 assay, rather the data were viewed qualitatively considering exposure. The evidence from several experimental studies indicating that phenolphthalein acts through a genotoxic mechanism via deoxyribonucleic acid (DNA) structural damage decreases the utility of a direct quantitative risk assessment. The genotoxicity data were also considered in the evaluation of the 2-year bioassay results, which contributed significantly to the conclusion of a relevant risk to humans. The p53 mouse assay was conducted under test conditions where factors such as target organ toxicity did not confound its interpretation, and where exposures and pharmacodynamic effects were well characterized. Thus, the results of the p53 mouse assay appear to be more likely relevant to humans than the results from the 2-year bioassay as conducted.

Further, the agency disagrees with Roe's dismissal of the genotoxic findings in the CHO cell chromosome aberration, micronucleus, and SHE cell transformation assays as apparent under conditions of toxicity or in some cases as an estrogenic effect. The agency is aware that phenolphthalein is known to have estrogenic activity. The information available on phenolphthalein indicates that its potency for binding at estrogen receptors and for induction of estrogenic effects is low compared to endogenous estrogens (by about a factor of 10^3 and 10^4 less than estradiol). Given the concentrations of phenolphthalein achieved in the bioassays, this action may be considered to have little overall contribution to the estrogenic load in the rodent models tested. The types of tumors observed for phenolphthalein are generally unlike those observed with other estrogenic chemicals. While there may be some contribution by estrogenic effects in the tumor response, the estrogenic effects appear most relevant for the ovarian tumors observed only in the 2-year mouse bioassay.

The genotoxic effects of phenolphthalein were observed under conditions compatible with the International Conference on Harmonization (ICH) guidance for the conduct of such genotoxicity studies. Although the repeat dose micronucleus assay that was originally reported was conducted at doses causing bone marrow toxicity, which could be viewed as confounding the results, the micronucleus assay conducted in the p53 mouse exhibited little evidence of toxicity and yielded results essentially identical to those of the prior assays. Thus, excessive toxicity is not essential to the micronucleus response for phenolphthalein. Further, this assay, although not part of the standard ICH test battery, is believed by many in the scientific community to be a more comprehensive assessment than the acute dose micronucleus assay, as it allows for any metabolic induction processes that might occur in vivo. This assay also allows exposures to achieve steady state conditions and reduces the uncertainty of appropriate sampling times, which can confound the standard acute assessments. Use of such tests is in accordance with ICH recommended guidelines for additional genotoxicity testing where positive findings have been observed in carcinogenicity studies.

The agency notes that there was an error in the Tsutui et al. report (Ref. 9), in that the number of mutations found in the control group for the SHE cell transformation assay should have been reported as $<0.25 \times 10^{-6}$. The Tsutui et al. findings for the control treatment are consistent with historical experience and less than 1/16 the response in phenolphthalein treated cells. The positive control produced an effect only

threefold greater than phenolphthalein. Thus, these data indicate a mutational effect for phenolphthalein.

The data also indicate that both aneuploidy and structural damage are caused by phenolphthalein. Tice et al. (Ref. 11) showed a possible increase in aneuploidy based on the kinetochore analysis. There was also significant evidence of structural damage; phenolphthalein treatment caused an approximate fourfold increase in micronuclei with structural damage and an eightfold increase in aneugenic damage calculated based on the ratio of normochromatic erythrocytes and polychromatic erythrocytes, and the increase in micronuclei. Also, an effect on aneuploidy was not observed in the study by Tsutsui et al. (Ref. 9) with SHE cells, whereas DNA structural damage and mutation were reported. The view that aneuploidy is the primary mechanism of genetic damage related to the carcinogenic effect also ignores the evidence of structural damage observed in the CHO cell chromosomal aberration studies, including those done by NTP, with responses approaching those seen with the positive control. Although the loss of heterozygosity observed in tumors from the p53 mouse could be explained by an aneugenic mechanism, it could also be the result of a chromosome break or deletion of a significant segment of the p53 region targeted by the assay. This allele loss was also specific for the p53 wild-type gene, with no effect on the null allele. Such a selective effect would not be anticipated from chromosome loss by an aneugenic mechanism functioning at the spindle apparatus.

One CanTox report (Ref. 5) presented information on the effects of phenolphthalein on thymidylate synthase (TS) activity and the potential relationship to the genotoxic and carcinogenic effects observed following phenolphthalein treatment in various systems. This report was evaluated by FDA's Executive CAC and Genetic Toxicology Committees (the Committees) (Ref. 12), which noted that the TS enzyme inhibitory activity was reported for a bacterial source and could differ between the bacterial and human or other mammalian forms, but there is no information available for assessing increased or decreased sensitivity. The Committees found no available information for estimation of intracellular versus extracellular concentrations of phenolphthalein to determine whether the in vivo phenolphthalein concentrations are within a reasonable range of those that were studied in vitro for TS inhibition. The inhibitor effects, however, appear to occur at plasma concentrations of phenolphthalein tenfold to hundredfold greater than the plasma concentrations associated with in vivo effects. There was also no information available on the TS activity of the glucuronide or other metabolites of phenolphthalein. In addition, the nucleotide pool disruption model lacked in vivo data and other information showing that a disruption of nucleotide pools was caused by phenolphthalein or that nucleotide pool effects were involved in the observed responses to phenolphthalein. The Committees noted that the effects of phenolphthalein on induction of micronuclei could be considered consistent with an effect on TS, based on comparisons of effects with 5-fluorouracil (5-FU) and methotrexate (MTX) treatment. However, the TS inhibitory activity does not appear consistent with or explain the other observed effects of phenolphthalein. In contrast to the assays conducted on phenolphthalein, 5-FU and MTX failed to increase SHE cell transformation. This suggests that, if phenolphthalein is active as a TS inhibitor at the tested concentrations, its effects on SHE cells (such as transformation, mutation, and chromosomal aberration) appear independent of the TS activity. Also, phenolphthalein is associated with increased chromosomal aberrations in CHO cells only in the presence of metabolic activation. This contrasts with the ability of phenolphthalein to directly inhibit TS. The comment's suggestion that the effect in CHO cells is due to fragile site damage in the CHO cell genome is not consistent with data provided by Witt et al. (Ref. 6), nor with the observations on CHO cells discussed at the April 2, 1996, CAC meeting (Ref. 13). In both data sets, there were increases in both complex and simple chromosomal breaks. In the latter data set, the proportionate response of simple and complex breaks appears similar to that caused by cyclophosphamide (a known genotoxicant used as the positive control for the assay). There was no discussion by the comment as to why a fragile site response would not be relevant for human adverse effects. The Committees noted that in a chromosomal aberration assay on human peripheral blood lymphocytes tested in vitro (Ref. 14), there was evidence of a clastogenic response from one of two subjects tested. While there is evidence that phenolphthalein can inhibit TS in some in vitro systems, the Committees stated that the data do not support the argument that TS inhibition explains all of the genetic damage observed in tests conducted on phenolphthalein, and that TS inhibition is the underlying mechanism of tumor formation in the three in vivo assays conducted. The Committees concluded that the data on TS inhibition do not refute the potential relevance of phenolphthalein's toxicologic effects for humans.

The CPMP (Ref. 7) contended that the extent of risk in humans cannot be established because the mechanistic data are inadequate and the phenolphthalein doses used in the study were excessive. The agency is not aware of any available data that would suggest that the mechanisms thought to account for tumor induction by phenolphthalein in experimental animals would not also operate in humans. Further, the phenolphthalein exposures used to demonstrate the in vivo and vitro genotoxic effects were in the range of those that humans use to cause laxation. The agency also notes that the exposure information for phenolphthalein that the CPMP could not verify was based on data obtained from a kinetic study (Ref. 15) sponsored by the 1992–1993 Nonprescription Drug Manufacturers Association Phenolphthalein Study Group.

After review of all the available data, the agency concludes that phenolphthalein caused chromosome aberrations, cell transformation, and mutagenicity in mammalian cells. Because benign and malignant tumor formation occurs at multiple tissue sites in multiple species of experimental animals, phenolphthalein is reasonably anticipated to have human carcinogenic potential.

III. References

1. Comment No. RPT7, Docket No. 78N–036L, Dockets Management Branch.

2. CanTox U.S., Inc., ''Discussion of New Data Related to Phenolphthalein Presented at the April 30, 1997 Meeting of the Carcinogenicity Assessment Committee of the U.S. Food and Drug Administration,'' June 9, 1997, in Comment No. C167, Docket No. 78N–036L, Dockets Management Branch.

3. Roe, F. J., ''Opinion on the Safety of Phenolphthalein as an Ingredient of OTC Laxative Preparations,'' August 28, 1996, in Comment No. C180, Docket No. 78N–036L, Dockets Management Branch.

4. CanTox U.S., Inc., ''Evaluation of the Rodent Carcinogenicity of Phenolphthalein,'' October 1, 1997, in Comment No. C180, Docket No. 78N–036L, Dockets Management Branch.

5. CanTox U.S., Inc., ''The Relevance of the Role of Phenolphthalein as an Inhibitor of Thymidylate Synthase for the Interpretation of the Genotoxic Potential and Carcinogenicity Assessment of this Compound,'' December 4, 1997, in Comment No. C186, Docket No. 78N–036L, Dockets Management Branch.

6. Witt, K. L. et al., ''Phenolphthalein: Induction of Micronucleated Erythrocytes in Mice,'' Mutation Research, 341:151–160, 1995, in Comment No. C186, Docket No. 78N–036L, Dockets Management Branch.
7. Comment No. C189, Docket No. 78N–036L, Dockets Management Branch.
8. Comment No. RPT9, Docket No. 78N–036L, Dockets Management Branch.
9. Tsutsui, T. et al., ''Cell Transforming Activity and Genotoxicity of Phenolphthalein in Cultured Syrian Hamster Embryo Cells,'' unpublished manuscript, 1997, in Comment No. RPT7, Docket No. 78N–036L, Dockets Management Branch.
10. Comment No. MM13, Docket No. 78N–036L, Dockets Management Branch.
11. Tice, R. R. et al., ''Tumorigenicity Studies of Dietary Phenolphthalein (CAS No. 77–09–8) in TSG-p53 Transgenic Female Mice,'' final report, April 11, 1997, in Comment No. RPT7, Docket No. 78N–036L, Dockets Management Branch.
12. Comment No. MM15, Docket No. 78N–036L, Dockets Management Branch.
13. Comment No. MM12, Docket No. 78N–036L, Dockets Management Branch.
14. Comment No. RPT10, Docket No. 78N–036L, Dockets Management Branch.
15. BTC Study No. P0392002 in Comment No. RPT11, Docket No. 78N–036L, Dockets Management Branch.

5. One comment expressed concern about the availability of an acceptable bowel cleansing system for use by physicians if the use of phenolphthalein is banned. The comment argued that its bowel cleansing system containing phenolphthalein, magnesium citrate, and bisacodyl should not be considered an OTC laxative. The comment stated that if phenolphthalein cannot be used, patients may be misdiagnosed because adequate bowel cleansing was not achieved prior to undergoing a bowel examination. The comment requested that the agency allow the continued sale of phenolphthalein in bowel cleansing systems if the product is adequately labeled, limited to a one-time application, and purchased and used under a physician's supervision.

This final rule prohibits the use of phenolphthalein in OTC laxative drug products. If an OTC bowel cleansing system is reformulated to contain a different laxative ingredient, data must be submitted to the rulemaking for OTC laxative ingredients to support the safety and effectiveness of the reformulated bowel cleansing system. Bowel cleansing systems that contain phenolphthalein and are limited to purchase and use under a physician's supervision may be submitted for agency review in a new drug application.

6. One comment stated that if phenolphthalein is reclassified as a Category II ingredient in the final rule, an immediate effective date would be unfair because it would cause significant economic harm to manufacturers of phenolphthalein. The comment recommended that a 1-year transition period be allowed for manufacturers to reformulate their laxative products, which will involve the purchase and production of new materials and, possibly, new equipment. The comment did not present any information that was not previously addressed in the proposed rule.

Because over 1 year has passed since the proposal was published, providing adequate time for reformulation, the agency denies the comment's request. In the preamble to the proposed rule (58 FR at 46226 to 46227), FDA found good cause under 5 U.S.C. 553(d) and 21 CFR 10.40(c)(4) for an immediate effective date for this final rule. In the reasons given in that preamble, as well as the fact that an additional period of more than 1 year has passed; the agency confirms the finding of good cause for an immediate effective date for this final rule.

IV. The Agency's Final Conclusions on Danthron and Phenolphthalein

Based on new data and information, the agency is reclassifying the stimulant laxative ingredients danthron and phenolphthalein from Category I (monograph) to Category II (nonmonograph) and is adding danthron and phenolphthalein to the list of stimulant laxatives in § 310.545(a)(12)(iv). The current list in that section is redesignated as § 310.545(a)(12)(iv)(A) and danthron and phenolphthalein are being included in new § 310.545(a)(12)(iv)(B). As a result of this reclassification of danthron and phenolphthalein, the amendments proposed in §§ 334.18, 334.30, 334.32, 334.60, and 344.66 (62 FR 46223 at 46227) will be finalized in the final rule for OTC laxative drug products, to be published in a future issue of the **Federal Register**.

V. Analysis of Impacts

One comment was received in response to the agency's request in the proposal for specific comment on the economic impact of this rulemaking (62 FR 46223 at 46225). (See comment 6 of this document.)

FDA has examined the impacts of this final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities.

Title II of the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*) requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

The agency believes that this final rule is consistent with the principles set out in the Executive Order and in these two statutes. The purpose of this final rule is to establish conditions under which the OTC stimulant laxative ingredients danthron and phenolphthalein are not generally recognized as safe and effective. Cessation of marketing of OTC laxative drug products containing danthron occurred in 1987. Therefore, no reformulation or relabeling will be necessary for this ingredient.

Products containing phenolphthalein will need to be reformulated to replace the ingredient with another laxative active ingredient. A number of laxative ingredients in proposed part 334 (50 FR 2124 at 2152) could be used. In addition, most OTC laxative drug products containing phenolphthalein have already been reformulated since the proposal was published.

When the proposed rule was published, the agency was aware of only one phenolphthalein dosage form, a flavored chewable tablet. Sales of this dosage form by all manufacturers were about $20 million in 1995 (most attributed to one large manufacturer), comprising about 3 percent of the total retail market for laxative products. The major manufacturer of this product informed the agency on August 29, 1997 (Ref. 1), that it planned to reformulate the product with another OTC laxative ingredient within 60 days.

Because these products must be manufactured in compliance with the pharmaceutical current good manufacturing practices (21 CFR parts 210 and 211), all firms have the necessary skills and personnel to perform the tasks of reformulation, validation, and relabeling either in-house or by contractual arrangement. The rule will not require any new reporting and recordkeeping activities. No additional professional skills are needed. There are no other Federal rules

that duplicate, overlap, or conflict with this rule.

Based on the agency's understanding that most manufacturers have already reformulated or otherwise are in the process of reformulating, the agency expects that this final rule will not be economically significant under Executive Order 12866, nor would it impose an Unfunded Mandate (as that term is described in the Unfunded Mandate Reform Act). The agency also believes that it has undertaken steps to reduce the burden to small entities. Nevertheless, some entities may incur significant impacts, especially manufacturers that still must reformulate their phenolphthalein products and, to a lesser extent, private label manufacturers that provide labeling for a number of the affected products. Danthron was removed from OTC laxative drug products in 1987 and has not been available for approximately 10 years. Therefore, it is unlikely that reclassification of danthron as a nonmonograph ingredient would have any economic impact. This economic analysis, together with other relevant sections of this document, serves as the agency's final regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

VI. Reference

1. Comment No. C173, Docket No. 78N–036L, Dockets Management Branch.

VII. Paperwork Reduction Act of 1995

This final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VIII. Environmental Impact

The agency has determined under 21 CFR 25.31(c) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 310

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 is amended as follows:

PART 310—NEW DRUGS

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

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

2. Section 310.545 is amended by redesignating paragraph (a)(12)(iv) as paragraph (a)(12)(iv)(A) and by revising the newly redesignated heading, by adding paragraphs (a)(12)(iv)(B) and (d)(29), and by revising paragraph (d) introductory text and paragraph (d)(1) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(12) * * *

(iv)(A) Stimulant laxatives—Approved as of May 7, 1991. * * *

(iv)(B) Stimulant laxatives—Approved as of January 29, 1999.

Danthron

Phenolphthalein

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(29) of this section.

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(2)(i), (a)(3) through (a)(4), (a)(6)(i)(A), (a)(6)(ii)(A), (a)(7) (except as covered by paragraph (d)(3) of this section), (a)(8)(i), (a)(10)(i) through (a)(10)(iii), (a)(12)(i) through (a)(12)(iv)(A), (a)(14) through (a)(15)(i), and (a)(16) through (a)(18) of this section.

* * * * *

(29) January 29, 1999, for products subject to paragraph (a)(12)(iv)(B) of this section.

Dated: January 20, 1999.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 99–1938 Filed 1–28–99; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 520

Oral Dosage Form New Animal Drugs

CFR Correction

In Title 21 of the Code of Federal Regulations, parts 500 to 599, revised as of April 1, 1998, on page 176, second column, § 520.2158b is corrected by adding paragraph (d) to read as follows:

§ 520.2158b Dihydrostreptomycin tablets.

* * * * *

(d) *Conditions of use. Calves*—(1) *Amount.* 150 milligrams of dihydrostreptomycin and 1.5 grams of chlorhexidine dihydrochloride per 100 pounds of body weight per day.

(2) *Indications for use.* Treatment of bacterial scours in calves.

(3) *Limitations.* Administer orally once a day for 5 days; withdraw 3 days before slaughter.

[FR Doc. 99–55506 filed 1–28–99; 8:45 am]

BILLING CODE 1505–01–D

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 31

[TD 8815]

RIN 1545–AT99

Federal Unemployment Tax Act (FUTA) Taxation of Amounts Under Employee Benefit Plans

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Final regulations.

SUMMARY: This document contains final regulations under section 3306(r)(2) of the Internal Revenue Code (Code), that provide guidance as to when amounts deferred under or paid from a nonqualified deferred compensation plan are taken into account as wages for purposes of the employment taxes imposed by the Federal Unemployment Tax Act (FUTA). Section 3306(r)(2), relating to treatment of certain nonqualified deferred compensation, was added to the Code by section 324 of the Social Security Amendments of 1983. These regulations provide guidance to employers who maintain nonqualified deferred compensation plans.

DATES: *Effective Date:* These regulations are effective January 29, 1999.

Applicability Date: These regulations are applicable on and after January 1, 2000. In addition, these regulations provide certain transition rules for amounts deferred and benefits paid before January 1, 2000, including allowing employers to use a reasonable, good faith interpretation of section 3306(r)(2).

FOR FURTHER INFORMATION CONTACT: Janine Cook, Linda E. Alsalihi, or Margaret A. Owens, (202) 622–6040 (not a toll-free number).

SUPPLEMENTARY INFORMATION:

Background

These final regulations amend the Employment Tax Regulations (26 CFR