DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 346, and 369

[Docket No. 80N-0050]

RIN 0905-AA06

Anorectal Drug Products for Over-the-Counter Human Use; Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) anorectal drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on anorectal drug products that have come to the agency's attention. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: August 5, 1991.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of May 27, 1980 (45 FR 35576), 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 anorectal drug products, together with the recommendations of the Advisory Review Panel on OTC Hemorrhoidal Drug Products (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by August 25, 1980. Reply comments in response to comments filed in the initial comment period could be submitted by September 24, 1980.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC anorectal drug products was published in the **Federal Register** of August 15, 1988 (53 FR 30756). Interested persons were invited to file by December 13, 1988, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by December 13, 1988. New data could have been submitted until August 15, 1989, and comments on the new data until October 15, 1989.

The OTC drug procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA is no longer using the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

As discussed in the proposed regulation for OTC anorectal drug products (53 FR 30756 at 30757), the agency advises that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the **Federal Register**. Therefore, on or after August 5, 1991, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In response to the proposed rule on OTC anorectal drug products, three manufacturers submitted comments. A request for an oral hearing before the Commissioner was also received. Copies of the comments and the hearing request received are on public display in the Dockets Management Branch (address above). Any additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

One comment, which was submitted at the very end of the period for the submission of new data, contained the results of two new clinical studies conducted to demonstrate the effectiveness of live yeast cell derivative in the relief of hemorrhoidal symptoms. These studies are currently being evaluated by the agency. The status of this ingredient does not directly relate to the other portions of the final monograph. Accordingly, in order to complete the publication of the final monograph for OTC anorectal drug products without undue delay, the agency is not addressing the data submitted on live yeast cell derivative in this document. The data will be addressed as soon as the agency's review is completed. If the data establish the effectiveness of live yeast cell derivative, the monograph will be amended accordingly. In the interim, products containing live yeast cell derivative may remain in the marketplace and are not subject to this final monograph.

The hearing request concerned the ingredient hydrocortisone. The requester asked that: (1) the definition section (§ 346.3) of the monograph be amended to provide for a drug that has anti-inflammatory properties, such as hydrocortisone; (2) hydrocortisone be allowed to be combined with other appropriate OTC ingredients at OTC strengths, including a typical anesthetic such as pramoxine; and (3) a combination of hydrocortisone and pramoxine, which is presently a prescription drug at 0.5 percent hydrocortisone and 1 percent pramoxine, be switched to OTC use and be generally recognized as safe and effective. The comment stated that general recognition of the safety and effectiveness of hydrocortisone-pramoxine combination OTC drug products exists in the published literature and cited a number of supporting references (Ref. 1). The requester also noted that the issues it raised directly relate to, and are virtually identical to, the issues in

another FDA proceeding, "In the matter of Pramoxine Hydrochloride and Hydrocortisone Acetate Drug Products," Docket No. 88N–0242, published in the **Federal Register** of July 1, 1988 (53 FR 25013).

The agency is currently reviewing the cited references and considering the request for a hearing. The agency did not include hydrocortisone in the tentative final monograph for OTC anorectal drug products (53 FR 30756 at 30766) because a claim for hydrocortisone and hydrocortisone acetate for the temporary relief of anal itching is already included in the OTC external analgesic tentative final monograph. The external analgesic tentative final monograph (48 FR 5852; February 8, 1983) includes both hydrocortisone and hydrocortisone acetate 0.25 to 0.5 percent and pramoxine hydrochloride 0.5 to 1 percent as proposed monograph ingredients. However, neither that monograph nor any other OTC drug monograph currently provides for any OTC combination drug products containing hydrocortisone and any other ingredient. Accordingly, such combination drug products are not currently legally marketed as OTC drug products. Resolution of the above issues related to hydrocortisone does not directly relate to the other conditions proposed in the tentative final monograph for OTC anorectal drug products. Accordingly, in order to complete this rulemaking with regard to the other conditions proposed in the tentative final monograph for OTC anorectal drug products without undue delay, the agency is not addressing the hearing request at this time. Resolution of the related issues in the other FDA proceeding (Docket No. 88N–0242—see above), which is currently pending the completion of studies by the interested parties, may have a bearing on the hearing request. If, after reviewing the information presented, the agency determines that a hearing should be held, it will issue a notice to that effect in a subsequent issue of the **Federal Register.**

The agency will publish its final decision on the issues related to hydrocortisone and live yeast cell derivative in OTC anorectal drug products in a future issue of the **Federal Register.** Final agency action on the remainder of the OTC anorectal drug products rulemaking occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC anorectal drug products.

Reference

(1) Comment No. HER00001, pages 61 to 65, Docket No. 80N–0050, Dockets Management Branch.

I. The Agency's Conclusions on the Comments

1. One comment suggested that § 346.14(a)(3) be revised to read: "Glycerin in solution (provided that the minimum absolute amount of glycerin is not less than 10%)." The comment contended that the language in that section as now worded (i.e., "The following active ingredients may be used as the sole protectant active ingredient in a product if the ingredient as identified constitutes 50 percent or more by weight of the final product * * *. Glycerin in a 20- to 45-percent (weight/weight) aqueous solution.") is unclear as to what is the acceptable minimum absolute amount of glycerin needed to qualify as a protectant active ingredient. The comment maintained that the intent of the section is to indicate that 50 percent of a 20-percent aqueous solution of glycerin is needed to qualify as a protectant active ingredient and, that in absolute terms, this translates to 10 percent glycerin.

The agency agrees that the comment is correct about the minimum amount of glycerin needed to qualify as a sole protectant ingredient. However, the comment's suggested change in § 346.14(a)(3) does not consider the maximum amount of glycerin that may be present in a product. If the final product consisted entirely (100 percent) of a 45-percent (weight/weight) aqueous solution of glycerin, then the product could contain 45 percent glycerin (weight/weight).

The comment's proposed revision to § 346.14(c)(3) states "glycerin in solution," but does not specify an aqueous solution. Any product containing glycerin for use as an OTC anorectal protectant in accord with the monograph cannot be formulated by including only 10 to 45 percent glycerin. Water must be present in the finished product. In discussing the importance of aqueous dilutions of glycerin (45 FR 35576 at 35631), the Panel noted that undiluted glycerin absorbs water and is somewhat dehydrating and irritating to mucous membranes and particularly to inflamed skin. The Panel determined that a lower concentration of glycerin is necessary for safe use in OTC anorectal preparations, and that there are no reports of reactions with 45 percent concentrations. The Panel also noted that undiluted glycerin is not effective as a protectant, whereas a dilution of 20 to 45 percent glycerin in water when applied to skin will lose water to epidermal tissue and acts to soften the skin (45 FR 35631). The Panel also stated at 45 FR 35627 and the agency proposed in the tentative final monograph at 45 FR 30767 that any single protectant active ingredient in a product must constitute 50 percent or more by weight of the final product. Thus, if glycerin were used as the sole protectant in a 20-percent weight/weight aqueous solution, and the glycerin in aqueous solution constituted 50 percent of the weight of the final product, the product would contain 10 percent glycerin by weight. If glycerin were used as the sole protectant in a 45-percent weight/weight aqueous solution and the glycerin in aqueous solution constituted 100 percent of the weight of the final product, the product would contain 45-percent glycerin. Therefore, the minimum concentration of glycerin in a final product would be 10 percent and the maximum concentration would be 45 percent. Accordingly, to clarify this usage, the agency is revising § 346.14(a)(3) to read as follows: "Glycerin in a 20- to 45-percent (weight/weight) aqueous solution so that the final product contains not less than 10 and not more than 45 percent glycerin (weight/weight)." The agency is adding an additional statement to § 346.14(a)(3) to make it clear that any combination product containing glycerin must contain at least this minimum amount of glycerin.

2. One comment requested final authorization regarding the anorectal use of 19 grades of Witepsol (cocoa butter substitutes, hydrogenated coco-glycerides, and hydrogenated palm kernal glycerides). The comment referred to its original citizen petition and its submissions of additional data.

The citizen petition and most of the additional submissions were fully discussed in paragraph 19 of the tentative final monograph (53 FR 30756 at 30763). The remaining information was designated in the tentative final monograph as being under review and is discussed below.

Since the petition was submitted, an official monograph for "hard fat" has been included in "The National Formulary" (NF) (Ref. 2). The agency has determined that all of the 19 grades of Witepsol ingredients meet the requirements for melting range, acid value, iodine value, saponification value, hydroxyl value, and unsaponifiable matter listed in the official NF monograph for hard fat. Accordingly, the agency is including the Witepsol ingredients in the OTC final monograph under the official NF compendial designation of "hard fat." This name replaces the descriptions

previously used or proposed by the comment, i.e, cocoa butter substitutes, hydrogenated coco-glycerides, and hydrogenated palm kernel glycerides.

The agency has the following specific comments on an effectiveness study that was conducted on one hundred subjects (Ref. 1). The volar surfaces of the arms were used as test sites, with sites of 3 square centimeters randomly assigned to each test product. Control sites were also used. Twenty materials were tested: 19 grades of Witepsol and cocoa butter. Thickness of application varied from 0.007 to 0.07 millimeters on a random basis.

Trans-epidermal water loss (an acceptable means of estimating the effectiveness of anorectal protectants) was determined by a method in which the vapor pressure above the chosen area of skin is measured without use of carrier gas currents or gravimetric analysis of the contents of an unventilated chamber (Ref. 3). The results are based on the estimation of the vapor-pressure gradient immediately above the skin and are presented in the following table:

Product (Witepsol grade)	Number of subjects	Mean percent reduction in trans-epidermal water loss	Number of subjects showing no effect
E075	94	41.5	20
E076	94	43.3	18
E085	94	50.6	14
H005	91	44.3	19
H012	91	38.5	24
H015	92	36.7	15
H019	94	45.4	18
H032	93	44.9	16
H035	95	43.2	18
H037	88	51.2	16
H039	91	46.2	19
H042	94	52.5	9
Hi75	93	43.1	19
Hi85	94	45.5	22
W025	90	41.3	17
W031	88	40.8	19
W032	92	38.4	22
W035	83	38.3	21
W045	90	35.7	22
Cocoa butter	93	30.6	28

The data demonstrate that the Witepsol-type ingredients perform in similar fashion to cocoa butter and may be considered effective as skin protectants.

Based on the above discussion, the agency has determined that the Witepsol ingredients may be included as monograph ingredients under the designation of "hard fat" in this OTC anorectal drug products final monograph. The ingredient "hard fat" is being listed in paragraph (a) of § 346.14 of the monograph under the heading "Protectant active ingredients" and should be considered in the same manner as any other protectant active ingredient listed in that paragraph.

The agency's detailed comments and evaluations of the above data are on file in the Dockets Management Branch (Ref. 4).

References

(1) Letter from B. Pagliocca, Kay-Fries, Inc., to FDA, coded LET015, Docket No. 80N-0050, Dockets Management Branch.

(2) "The United States Pharmacopoeia XXII and The National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 1931, 1989.

(3) Nilsson, G.E., "Medical and Biological Engineering and Computing," 1977.

(4) Letter from W.E. Gilbertson, FDA, to T.E. Maggio, Dynamit Nobel of America, Inc., coded LET 022, Docket No. 80N-0050, Dockets Management Branch.

II. Agency Initiated Change

In the advance notice of proposed rulemaking for OTC anorectal drug products, the Panel recommended the following warning for products containing aluminum hydroxide gel (45 FR 35576 at 35629) or kaolin (45 FR 35632): "Remove petrolatum or greasy ointment before using this product because they interfere with the ability of this product to adhere properly to the skin area." That warning was included in the Panel's recommended monograph in § 346.56(c)(1) and in the tentative final monograph in § 346.50(c)(8).

Despite the above warning, § 346.22 of the Panel's recommended monograph and § 346.22(a) of the tentative final monograph provided that any of the protectant ingredients could be combined. The agency did not receive any comments on this issue following publication of the Panel's report and the tentative final monograph. The agency has determined that aluminum hydroxide gel and kaolin should not be combined with any "greasy" ingredient. The following monograph ingredients are "greasy" in nature and therefore should not be combined with aluminum hydroxide gel or kaolin: Cocoa butter, cod liver oil, hard fat, lanolin, mineral oil, petrolatum, shark liver oil, and white petrolatum. Accordingly, the agency is stating in § 346.22(a) of this final monograph that "Any two, three, or four protectants identified in § 346.14 may be combined, except aluminum hydroxide gel in § 346.14(a)(1) and kaolin in § 346.14(a)(5) may not be combined with any ingredient in § 346.14(a) (2), (4), (6), (7), (8) and (10), and (b)(2) and (3), provided that the combined percentage by weight of all protectants in the combination is at least 50 percent of the final product (e.g., 1 gram of a 2 gram dosage unit). Any protectant ingredient included in the combination must be present at a level that contributes at least 12.5 percent by weight (e.g., 0.25 gram of a 2-gram dosage unit), except cod liver oil and shark liver oil. If an ingredient in § 346.14(b) is included in the combination, it must not exceed the concentration limit specified in § 346.14(b)."

III. Summary of Changes From the Proposed Rule

1. The agency is revising the designation of the concentrations for glycerin in § 346.14(a)(3) for clarity. (See comment 1 above.)

2. The agency is adding hard fat to § 346.14(a) of the final monograph. (See comment 2 above.)

3. The agency is revising the permitted combinations of protectants in § 346.22(a) to be consistent with the warning in § 346.50(c)(8). (See Part II. "Agency Initiated Change" above.)

IV. The Agency's Final Conclusions on OTC Anorectal Drug Products

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC anorectal drug products are generally recognized as safe and effective and not misbranded. The agency has determined that the following active ingredients are a monograph condition for their respective drug class: Local anesthetics—benzocaine, benzyl alcohol, dibucaine, dibucaine hydrochloride, dyclonine hydrochloride, lidocaine, pramoxine hydrochloride, tetracaine, and tetracaine hydrochloride; vasconstrictors—ephedrine sulfate, epinephrine, epinephrine hydrochloride, and phenylephrine hydrochloride; protectants—aluminum hydroxide gel, calamine, cocoa butter, cod liver oil, glycerin, hard fat, kaolin, lanolin, mineral oil, petrolatum, shark liver oil, topical starch, white petrolatum, and zinc oxide; analgesics, anesthetics, and antipruritics—camphor, juniper tar, and menthol; astringents—calamine, hamamelis water, and zinc oxide; and keratolytics—alcloxa and resorcinol. With the exception of hydrocortisone and live yeast cell derivative, all other ingredients for anorectal use whether or not considered in this rulemaking are considered nonmonograph ingredients. Ingredients considered in this rulemaking were: local anesthetics—diperodon and phenacaine hydrochloride; vasconstrictor—epinephrine undecylenate; protectants—bismuth oxide, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate,

and lanolin alcohols; counterirritants—camphor (greater than 3 to 11 percent), hydrastis, menthol (1.25 to 16 percent), and turpentine oil (rectified) (6 to 50 percent); astringents—tannic acid; wound healing agents—cholecalciferol, cod liver oil, peruvian balsam, shark liver oil, and vitamin A; antiseptics—boric acid, boroglycerin, hydrastis, phenol, resorcinol, and sodium salicylic acid phenolate; keratolytics—precipitated sulfur and sublimed sulfur; anticholinergics—atropine and belladonna extract; and miscellaneous ingredients—collinsonia extract, *Echerichia coli* vaccines, lappa extract, leptandra extract, and mullein. Any drug product marketed for use as an OTC anorectal drug product that is not in conformance with the monograph (21 CFR part 346) may be considered a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C 321(p)) and misbranded under section 502 of the act (21 U.S.C. 352) and may not be marketed for this use unless it is the subject of an approved application. An appropriate citizen petition to amend the monograph may also be submitted under 21 CFR 10.30.

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) The specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g). The final rule in this document is subject to the labeling provisions in § 330.1(c)(2).

The agency is removing the existing labeling requirements of § 310.201(a)(23)(v)(*b*) (21 CFR 310.201(a)(23)(v)(*b*)) relating to dyclonine hydrochloride upon the effective date of the final monograph for OTC anorectal drug products. In addition, the agency is revising § 369.20 (21 CFR 369.20) by removing the reference to rectal preparations from the entry for "BELLADONNA PREPARATIONS * * *" and by removing the entry for "RECTAL PREPARATIONS FOR EXTERNAL USE." These regulations are being revised because the above entries are superseded by this final monograph for OTC anorectal drug products.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (53 FR 30756 at 30780). The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this final rule for OTC anorectal drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96–354). That assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC anorectal drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday. This action was considered under FDA's final rule implementing the National Environmental Policy Act (21 CFR part 25).

List of Subjects

21 CFR Part 310

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

21 CFR Part 346

Anorectal drug products, Labeling, Over-the-counter drugs.

21 CFR Part 369

Labeling, Medical devices, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, subchapter D of chapter I of title 21 of the Code of Federal Regulations is amended in parts 310, 346, and 369 as follows:

PART 310—NEW DRUGS

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

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 376); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

§ 310.201 [Amended]

2. Section 310.201 Exemption for certain drugs limited by new-drug applications to prescription sale is amended by removing paragraph (a)(23)(v)(*b*) and reserving it.

3. Part 346, consisting of §§ 346.1 to 346.52 is added to read as follows:

PART 346—ANORECTAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
346.1 Scope.
346.3 Definitions.

Subpart B—Active Ingredients

346.10 Local anesthetic active ingredients.
346.12 Vasoconstrictor active ingredients.
346.14 Protectant active ingredients.
346.16 Analgesic, anesthetic, and antipruritic active ingredients.
346.18 Astringent active ingredients.
346.20 Keratolytic active ingredients.

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 321, 351, 352, 353, 355, 360, 371].

Subpart A—General Provisions

§ 346.1 Scope.

(a) An over-the-counter anorectal drug product in a form suitable for external (topical) or intrarectal (rectal) administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this part and each general condition established in § 330.1 of this chapter.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 212 unless otherwise noted.

§ 346.3 Definitions.

As used in this part:

(a) *Analgesic, anesthetic drug.* A topically (externally) applied drug that relieves pain by depressing cutaneous sensory receptors.

(b) *Anorectal drug.* A drug that is used to relieve symptoms caused by anorectal disorders in the anal canal, perianal area, and/or the lower rectal areas.

(c) *Antipruritic drug.* A topically (externally) applied drug that relieves itching by depressing cutaneous sensory receptors.

(d) *Astringent drug.* A drug that is applied topically (externally) to the skin or mucous membranes for a local and limited protein coagulant effect.

(e) *External use.* Topical application of an anorectal drug product to the skin of the perianal area and/or the skin of the anal canal.

(f) *Intrarectal use.* Topical application of an anorectal drug product to the mucous membrane of the rectum.

(g) *Keratolytic drug.* A drug that causes desquamation (loosening) and debridement or sloughing of the surface cells of the epidermis.

(h) *Local anesthetic drug.* A drug that produces local disappearance of pain, burning, itching, irritation, and/or discomfort by reversibly blocking nerve conduction when applied to nerve tissue in appropriate concentrations.

(i) *Protectant drug.* A drug that provides a physical barrier, forming a protective coating over skin or mucous membranes.

(j) *Vasoconstrictor.* A drug that causes temporary constriction of blood vessels.

Subpart B—Active Ingredients

§ 346.10 Local anesthetic active ingredients.

The active ingredient of the product consists of any of the following when used in the concentration or within the concentration range established for each ingredient:

(a) Benzocaine 5 to 20 percent.
(b) Benzyl alcohol 1 to 4 percent.
(c) Dibucaine 0.25 to 1 percent.
(d) Dibucaine hydrochloride 0.25 to 1 percent.
(e) Dyclonine hydrochloride 0.5 to 1 percent.
(f) Lidocaine 2 to 5 percent.
(g) Pramoxine hydrochloride 1 percent.
(h) Tetracaine 0.5 to 1 percent.
(i) Tetracaine hydrochloride 0.5 to 1 percent.

§ 346.12 Vasoconstrictor active ingredients.

The active ingredient of the product consists of any of the following when used in the concentration or within the concentration range established for each ingredient.

(a) Ephedrine sulfate 0.1 to 1.25 percent.
(b) Epinephrine 0.005 to 0.01 percent.
(c) Epinephrine hydrochloride 0.005 to 0.01 percent.
(d) Phenylephrine hydrochloride 0.25 percent.

§ 346.14 Protectant active ingredients.

(a) The following active ingredients may be used as the sole protectant active ingredient in a product if the ingredient as identified constitutes 50 percent or more by weight of the final product. In addition, the following active ingredients may be used in concentrations of less than 50 percent by weight only when used in combinations in accordance with § 346.22 (a), (b), or (n).

(1) Aluminum hydroxide gel.
(2) Cocoa butter.
(3) Glycerin in a 20- to 45-percent (weight/weight) aqueous solution so that the final product contains not less than 10 and not more than 45 percent glycerin (weight/weight). Any combination product containing glycerin must contain at least this minimum amount of glycerin.
(4) Hard fat.
(5) Kaolin.
(6) Lanolin.
(7) Mineral oil.
(8) Petrolatum.
(9) Topical starch.
(10) White petrolatum.

(b) The following active ingredients may not be used as a sole protectant ingredient but may be used in combination with one, two, or three other protectant active ingredients in accordance with § 346.22 (a), (b), (n), and (o) and with the following limitations:

(1) Calamine not to exceed 25 percent by weight per dosage unit (based on the zinc oxide content of calamine).

(2) Cod liver oil, provided that the product is labeled so that the amount of the product that is used in a 24-hour period represents a quantity that provides 10,000 U.S.P. units of vitamin A and 400 U.S.P. units of cholecalciferol.

(3) Shark liver oil, provided that the product is labeled so that the amount of the product that is used in a 24-hour period represents a quantity that provides 10,000 U.S.P. units of vitamin A and 400 U.S.P. units of cholecalciferol.

(4) Zinc oxide not to exceed 25 percent by weight per dosage unit.

§ 346.16 Analgesic, anesthetic, and antipruritic active ingredients.

The active ingredient of the product consists of any of the following when used within the concentration range established for each ingredient:

(a) Camphor 0.1 to 3 percent.
(b) Juniper tar 1 to 5 percent.
(c) Menthol 0.1 to 1 percent.

§ 346.18 Astringent active ingredients.

The active ingredient of the product consists of any of the following when used within the concentration range established for each ingredient:

(a) Calamine, within a concentration range of 5 to 25 percent by weight per dosage unit (based on the zinc oxide content of calamine).

(b) Hamamelis water, "The National Formulary XI," 10 to 50 percent.

(c) Zinc oxide, within a concentration range of 5 to 25 percent by weight per dosage unit.

§ 346.20 Keratolytic active ingredients.

The active ingredient of the product consists of any of the following when used within the concentration range established for each ingredient:

(a) Alcloxa 0.2 to 2 percent.
(b) Resorcinol 1 to 3 percent.

§ 346.22 Permitted combinations of anorectal active ingredients.

(a) Any two, three, or four protectants identified in (a) § 346.14 may be combined, except aluminum hydroxide gel in § 346.14(a)(1) and kaolin in § 346.14(a)(5) may not be combined with any ingredient in § 346.14(a) (2), (4), (6), (7), (8) and (10), and (b) (2) and (3), provided that the combined percentage by weight of all protectants in the combination is at least 50 percent of the

final product (*e.g.*, 1 gram of a 2-gram dosage unit). Any protectant ingredient included in the combination must be present at a level that contributes at least 12.5 percent by weight (*e.g.*, 0.25 gram of a 2-gram dosage unit), except cod liver oil and shark liver oil. If an ingredient in § 346.14(b) is included in the combination, it must not exceed the concentration limit specified in § 346.14(b).

(b) Any single anorectal ingredient identified in § 346.10, 346.12, 346.16, 346.18, or 346.20 may be combined with up to four protectants in accordance with paragraph (a) of this section.

(c) Any single local anesthetic identified in § 346.10 may be combined with any single vasoconstrictor identified in § 346.12.

(d) Any single local anesthetic identified in § 346.10 may be combined with any single astringent identified in § 346.18.

(e) Any single local anesthetic identified in § 346.10 may be combined with any single keratolytic identified in § 346.20.

(f) Any single vasoconstrictor identified in § 346.12 may be combined with any single astringent identified in § 346.18.

(g) Any single analgesic, anesthetic, and antipruritic identified in § 346.16 may be combined with any single astringent identified in § 346.18.

(h) Any single analgesic, anesthetic, and antipruritic identified in § 346.16 may be combined with any single keratolytic identified in § 346.20.

(i) Any single astringent identified in § 346.18 may be combined with any single keratolytic identified in § 346.20.

(j) Any single local anesthetic identified in § 346.10 may be combined with any single vasoconstrictor identified in § 346.12 and with any single astringent identified in § 346.18.

(k) Any single local anesthetic identified in § 346.10 may be combined with any single astringent identified in § 346.18 and with any single keratolytic identified in § 346.20.

(l) Any single vasoconstrictor identified in § 346.12 may be combined with any single analgesic, anesthetic, and antipruritic identified in § 346.16 and with any single astringent identified in § 346.18.

(m) Any single analgesic, anesthetic, and antipruritic identified in § 346.16 may be combined with any single astringent identified in § 346.18 and with any single keratolytic identified in § 346.20.

(n) Any combination of ingredients listed in paragraphs (c) through (m) of this section may be combined with up to four protectants in accordance with paragraph (a) of this section.

(o) Any product containing calamine for use as a protectant and/or as an astringent and/or containing zinc oxide for use as a protectant and/or as an astringent may not have a total weight of zinc oxide exceeding 25 percent by weight per dosage unit.

Subpart C—Labeling

§ 346.50 Labeling of anorectal drug products.

The labeling of the product contains the following information for anorectal ingredients identified in §§ 346.10, 346.12, 346.14, 346.16, 346.18, and 346.20, and for combinations of anorectal ingredients identified in § 346.22. Unless otherwise specified, the labeling in this subpart is applicable to anorectal drug products for both external and intrarectal use.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as "anorectal (hemorrhoidal)," "hemorrhoidal," "hemorrhoidal (anorectal) (insert dosage form, e.g., cream, lotion, or ointment)."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in paragraph (b) of this section, as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) ("For the temporary relief of," "Gives temporary relief of," or "Helps relieve the") (As an option, select one or both of the following: "local" or "anorectal") [select one or more of the following: "discomfort," "itching," or "itching and discomfort," followed by: "in the perianal area" or "associated with" (select one or more of the following: "hemorrhoids," "anorectal disorders," "inflamed hemorrhoidal tissues," "anorectal inflammation," "hemorrhoidal tissues," or "piles (hemorrhoids)."]]

(2) *Additional indications.* Indications applicable to each active ingredient of the product may be combined to eliminate duplicative words or phrases so that the resulting indication is clear and understandable. In addition to the indication identified in paragraph (b)(1) of this section, the labeling of the product intended for external or intrarectal use may also contain the following indications, as appropriate.

(i) *For products for external use only containing any ingredient identified in § 346.10.* "For the temporary relief of" (select one or more of the following: "pain," "soreness," or "burning").

(ii) *For products containing epinephrine or epinephrine hydrochloride identified in § 346.12 (b) and (c) for external use only, and for products containing ephedrine sulfate or phenylephrine hydrochloride identified in § 346.12 (a) and (d).*

(A) "Temporarily reduces the swelling associated with" (select one of the following: "irritated hemorrhoidal tissue and other anorectal disorders" or "irritation in hemorrhoids and other anorectal disorders").

(B) "Temporarily shrinks hemorrhoidal tissue."

(iii) *For products for external use only containing glycerin identified in § 346.14(a)(3) and for products for external and/or intrarectal use containing any protectant identified in § 346.14(a) (2), (4), (6) through (10), and (b) (1) through (4).*

(A) "Temporarily forms a protective coating over inflamed tissues to help prevent drying of tissues."

(B) "Temporarily protects irritated areas."

(C) "Temporarily relieves burning."

(D) "Provides temporary relief from skin irritations."

(E) "Temporarily provides a coating for relief of anorectal discomforts."

(F) "Temporarily protects the inflamed, irritated anorectal surface" (select one of the following: "to help make bowel movements less painful" or "from irritation and abrasion during bowel movement").

(G) "Temporarily protects inflamed perianal skin."

(H) "Temporarily relieves the symptoms of perianal skin irritation."

(iv) *For products containing aluminum hydroxide gel identified in § 346.14(a)(1) and for products containing kaolin identified in § 346.14(a)(5).* "For the temporary relief of itching associated with moist anorectal conditions."

(v) *For products for external use only containing any analgesic, anesthetic, and antipruritic identified in § 346.16.*

(A) "For the temporary relief of" (select one or both of the following: "pain" or "burning").

(B) "Can help distract from pain."

(C) "May provide a cooling sensation."

(vi) *For products for external use only containing hamamelis water identified in § 346.18(b), and for products for external use and/or intrarectal use containing calamine or zinc oxide identified in § 346.18 (a) and (c).*

(A) "Aids in protecting irritated anorectal areas."

(B) "Temporary relief of" (select one or both of the following: "irritation" or "burning").

(vii) *For products for external use only containing any ingredient identified in § 346.20.* The indication in paragraph (b)(1) of this section applies.

(c) *Warnings.* Warnings applicable to each active ingredient of the product may be combined to eliminate duplicative words or phrases so that the resulting warning is clear and understandable. The labeling of the product contains the following warnings under the heading "Warnings":

(1) "If condition worsens or does not improve within 7 days, consult a doctor."

(2) "Do not exceed the recommended daily dosage unless directed by a doctor."

(3) "In case of bleeding, consult a doctor promptly."

(4) *For products for external use only.* "Do not put this product into the rectum by using fingers or any mechanical device or applicator."

(5) *For products for intrarectal use to be used with a special applicator such as a pile pipe or other mechanical device.* "Do not use this product with an applicator if the introduction of the applicator into the rectum causes additional pain. Consult a doctor promptly."

(6) *For products for external use only containing any local anesthetic identified in § 346.10, menthol identified in § 346.16(c), or resorcinol identified in § 346.20(b).* "Certain persons can develop allergic reactions to ingredients in this product. If the symptom being treated does not subside or if redness, irritation, swelling, pain, or other symptoms develop or increase, discontinue use and consult a doctor."

(7) *For products containing any vasoconstrictor identified in § 346.12.* (i) "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(ii) "*Drug interaction precaution.* Do not use this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor."

(iii) *For products containing ephedrine sulfate identified in § 346.12(a).* "Some users of this product may experience nervousness, tremor, sleeplessness, nausea, and loss of appetite. If these symptoms persist or become worse, consult your doctor."

(8) *For products containing aluminum hydroxide gel identified in § 346.14(a)(1) and for products containing kaolin identified in § 346.14(a)(5).* "Remove petrolatum or greasy ointment before using this product because they interfere with the ability of this product to adhere properly to the skin area."

(9) *For products for external use only containing resorcinol identified in § 346.20(b).* "Do not use on open wounds near the anus."

(d) *Directions.* Directions applicable to each active ingredient of the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable. The labeling of the product contains the following information under the heading "Directions":

(1) "*Adults:* When practical, cleanse the affected area" (select one or both of the following: "with mild soap and warm water and rinse thoroughly" or "by patting or blotting with an appropriate cleansing pad"). "Gently dry by patting or blotting with toilet tissue or a soft cloth before application of this product." [Other appropriate directions in this section may be inserted here.] "Children under 12 years of age: consult a doctor."

(2) *For products for external use only.* "Apply externally to the affected area" (insert appropriate time interval of administration as identified in paragraphs (d)(6), (7), (8), or (9) of this section).

(3) *For products for external use that are pads containing anorectal ingredients.* "Gently apply to the affected area by patting and then discard."

(4) *For products for intrarectal use that are wrapped suppositories.* "Remove wrapper before inserting into the rectum."

(5) *For products for intrarectal use that are to be used with a special applicator such as a pile pipe or other mechanical device.* "FOR INTRARECTAL USE: Attach applicator to tube. Lubricate applicator well, then gently insert applicator into the rectum."

(6) *For products for external use only containing any of the local anesthetics identified in § 346.10; analgesics, anesthetics, and antipruritics identified in § 346.16; or alcloxa or resorcinol identified in § 346.20.* Apply to the affected area up to 6 times daily.

(i) *For products for external use only containing dibucaine or dibucaine hydrochloride identified in § 346.10 (c) and (d).* Apply to the affected area up to 3 or 4 times daily.

(ii) *For products for external use only containing pramoxine hydrochloride identified in § 346.10(g).* Apply to the affected area up to 5 times daily.

(7) *For products containing vasoconstrictors identified in § 346.12.* Apply to the affected area up to 4 times daily.

(8) *For products for external use only containing glycerin identified in § 346.14(a)(3) or hamamelis water identified in § 346.18(b), and for products for external and/or intrarectal use containing any protectant identified in § 346.14(a)(1), (2), (4), (5), (6), (7), and (9), and (b)(1), (2), (3), and (4), or any astringent identified in § 346.18(a) and (c).* Apply to the affected area up to 6 times daily or after each bowel movement.

(9) *For products containing petrolatum or white petrolatum identified in § 346.14(a)(8) and (10).* Apply liberally to the affected area as often as necessary.

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

§ 346.52 Labeling of permitted combinations of anorectal active ingredients.

Indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity established in § 346.50(a). For a combination drug product that does not have an established name, the labeling of the product states the statement of identity established in § 346.50(a).

(b) *Indications.* The labeling of the product states, under the heading "Indications," the indication(s) for each ingredient in the combination, as established in the indications sections of this subpart.

(c) *Warnings.* The labeling of the product states, under the heading

"Warnings," the warning(s) for each ingredient in the combination, as established in the warnings sections of this subpart.

(d) *Directions.* The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of this subpart. When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph.

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

4. The authority citation for 21 CFR part 369 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371).

§ 369.20 [Amended]

5. Section 369.20 Drugs; recommended warning and caution statements is amended by removing the statement, "See also Rectal Preparations for additional warnings," from the entry for "BELLADONNA PREPARATIONS AND PREPARATIONS OF ITS ALKALOIDS (ATROPINE, HYOSCYAMINE, AND SCOPOLAMINE (HYOSCINE)); HYOSCYAMUS, STRAMONIUM, THEIR DERIVATIVES, AND RELATED DRUG PREPARATIONS" and by removing the entry "RECTAL PREPARATIONS FOR EXTERNAL USE."

Dated: May 15, 1990.

James S. Benson,

Acting Commissioner of Food and Drugs.

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