21 CFR Part 310

[Docket No. 80N–0050]

RIN 0905–AA06

Anorectal 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 afinal rule establishing that any over-the-counter (OTC) drug product containing live yeast cell derivative (LYCD) for anorectal use is not generally recognized as safe and effective and is misbranded. This final rule evaluates data on LYCD that were still under review when an earlier final rule on OTC anorectal drug products was issued. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: September 2, 1994.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5000.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of May 27, 1980 (45 FR 35576), FDA published 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 the data on the active ingredients in this class of drugs. The agency's tentative final monograph on OTC anorectal drug products was published in the **Federal Register** of August 15, 1988 (53 FR 30756). LYCD was considered safe for use as an OTC wound-healing agent for limited use (1 week or less), but was classified as Category III (available data are insufficient to classify as effective for use as an OTC woundhealing agent in the anorectal area, and further testing is required) (53 FR 30765).

One comment, submitted at the end of the period for the submission of new data, contained the results of two new clinical studies in support of the effectiveness of LYCD in the relief of hemorrhoidal symptoms (Ref. 1). These studies remained under review at the time of publication of the agency's final rule on OTC anorectal drug products in the **Federal Register** of August 3, 1990 (55 FR 31776); that rule did not address the final status of LYCD. The agency stated that in order to complete the publication of the final monograph for OTC anorectal drug products without undue delay, the agency was not addressing the data submitted on LYCD in that document, and that the data would be addressed as soon as the agency's review was completed. The agency's evaluation of those data now completes the anorectal drug products rulemaking with respect to LYCD. The only other pending issues relating to hydrocortisone, as discussed in the final rule (55 FR 31776), will be addressed in a future issue of the **Federal Register** to complete the rulemaking on OTC anorectal drug products.

In its final conclusions on OTC anorectal drug products (55 FR 31776), the agency listed a number of anorectal ingredients that it considered to be nonmonograph ingredients. The agency stated that on or after August 5, 1991 (12 months after the final rule was published), 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.

When the final rule was issued in August 1990, none of the nonmonograph ingredients were listed in a regulation. Since then, the agency has established 21 CFR 310.545, which contains a list of certain active ingredients that are not generally recognized as safe and effective for certain OTC drug uses. The agency is adding § 310.545(a)(26) to include the nonmonograph anorectal active ingredients discussed in the final rule of August 3, 1990, as well as LYCD. The date of nonmonograph status for all of the ingredients, except for LYCD, listed in § 310.545(a)(26) was August 5, 1991. The date of nonmonograph status of LYCD is September 2, 1994. This timeframe for LYCD is consistent with that provided for other nonmonograph ingredients in the August 3, 1990, final rule. The agency's detailed comments on the data are on file in the Dockets Management Branch (Ref. 1).

Reference

(1) Comment No. C19, Docket No. 80N–0050, Dockets Management Branch (HFA–305),Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

II. The Agency's Final Conclusions on Live Yeast Cell Derivative for Anorectal Use

One comment submitted the results of two studies (WBI–1987 and WM–444B) to support the effectiveness of LYCD for relief of hemmorhoidal symptoms of pain, itching, burning, or irritation, and for shrinking swelling of hemorrhoidal tissue caused by inflammation (Ref. 1). The comment also referred to other data that it had submitted to the rulemaking on OTC skin protectant drug products in support of LYCD's effectiveness as a wound healing agent (Ref. 2). The comment stated its belief that the skin protectant data also support the use of LYCD as a wound healing agent in the anorectal area. The comment cited the Panel's discussion of the nature of data required to support the effects of wound-healing agents on anorectal wounds in the advance notice of proposed rulemaking (45 FR 35576 at 35658), where it stated "* * * an agent that causes a significant increase in the healing of wounds at other sites, and also relieves anorectal clinical symptoms over a similar time period can be considered an anorectal wound-healing agent." The comment concluded that the agency would accept evidence of wound-healing efficacy from tissues other than in the anorectal area.

The agency has evaluated the two studies and determined that they are incapable of demonstrating the effectiveness of LYCD for relief of hemorrhoidal symptoms of pain, itching, burning, or irritation. The studies also do not contain data showing that LYCD shrinks swelling of hemorrhoidal tissue caused by inflammation. The conduct of studies WBI–1987 and WM–444B was independently inspected by agency field investigators who found evidence that the data submitted were unreliable.

A. Study WBI–1987

This study was a double-blind, randomized, parallel group comparison of LYCD versus ointment vehicle for the relief of hemorrhoidal discomfort. The purpose was to show the effectiveness of LYCD in an ointment as a wound healing agent. On case report forms, subjects were to record (by vertical marks on 100 millimeter (mm) visual analog scales) their assessment of two qualities of hemorrhoidal pain, i.e., irritation and burning, immediately before treatment, and 5, 15, 30, 45, and 60 minutes after treatment. The two qualities of hemorrhoidal pain were analyzed as separate scores. Hemorrhoidal pain relief was assessed at each post-treatment evaluation by the

participant circling one of six adjectives ranging from "complete relief" to "no relief." On the 100 mm analog scale, improvement from baseline for the active preparation and for the control, respectively, were 65.0 and 44.1 for irritation, and 72.7 versus 46.0 for burning, according to the sponsor's analysis. Comparison of the two treatments for both parameters was analyzed by the two-sample t-test, which showed statistically significant differences for both parameters ($p < 0.001$). Mean total pain relief on a six-category scale was reported as 3.8 for the active preparation and 2.8 for the control ($p < 0.001$).

A global assessment of efficacy was also to be provided at the conclusion of the 1-hour study. The subject graded the overall effectiveness of the medication by circling the appropriate number on a scale where 1 represented "poor" and 10 represented "excellent." All 20 subjects treated with the active preparation gave a global evaluation score of 8 or better, and 13 subjects graded it as excellent (10). Mean global assessment rated was 9.6 for the active preparation and 7.3 for the control ($p < 0.001$). None of the control subjects graded the treatment as excellent.

While these results seem to infer effectiveness, it does not appear that the case report forms, on which all critical data were to be recorded by the subject, were in fact contemporaneously filled out by the subjects. The circles and vertical lines used to record scores were all of two easily distinguishable types; they did not show the diversity that would be expected if each subject filled out his or her own clinical report form. For one subject who was included in the study twice, there were clear differences in the manner and style of the subject's markings on the visual analog scales on two different occasions. The differences would be unlikely if the subject had actually filled out the form. Thus, it appears that study personnel filled out the forms, which is a clear violation of the protocol and which raises major questions as to the blinding and integrity of the study. If the forms were not filled out by subjects at the time of that rating, as the protocol required, there can be no assurance that the forms represent actual reports by the subjects at the appropriate measurement time and not, for example, ratings filled out by study personnel aware of treatment assignments.

Questions concerning who filled out the forms and when they were filled out were asked of the investigator. He responded to the agency by letter dated November 19, 1991 (Ref. 3), but the response did not address the issue of who filled out the forms. The investigator dealt with other problems and emphasized future improvements in his practices. Thus, although the reported results of the study might support effectiveness, the significant discrepancy between the reported and the actual method of data collection does not allow the agency to conclude that bias on the part of the investigator or analyst has been shown to be minimized.

B. Study WM–444B

This study was a double-blind, parallel group clinical trial using a methodology similar to Study WB–1987, but with the subjective assessment testing period extended to include 75–, 90–, 105–, and 120–minute assessment times. The purpose of this study was also to demonstrate the effectiveness of LYCD ointment in relief of hemorrhoidal pain. Of 100 subjects eligible to enter the study, 50 were allocated to the active preparation and 50 to the vehicle. The effect of the active preparation was significantly greater than that of the vehicle for all variables at all evaluation points.

Unfortunately, this study cannot be considered an adequate and well-controlled study because the method of blinding provides no assurance that the study was, in fact, blinded successfully. The tear-off portions of the label (under which the tube's contents were revealed) were closed by rubber cement. There was no way to tell whether the tear-off section had been opened because the rubber cement closure could be replaced readily. Agency reviewers found that they could easily open the labels to reveal the identity of the medication, re-close them, and then attach them on the case report form of the respective subjects, without altering their appearance. Thus, there is no assurance that the study was blinded, as planned. Ordinarily, in studies that are adequately double-blinded, once labels are opened they cannot be closed again without appearing altered. In the absence of secure blinding, there is no evidence that the subjects were not biased by suggestions from the nurses, the coordinator, or the principal investigator.

Study WM–444B also had other deficiencies and significant departures from commonly accepted investigational practices: (1) There was no record of lot numbers on the tubes for the product tested; thus there was no assurance that the drug product used in the clinical trial was the same formulation as the drug product proposed for marketing, and (2) the allocation of samples for each test site was not addressed.

Standards for effectiveness of an OTC drug that is generally recognized as safe and effective are set forth in 21 CFR 330.10(a)(4)(ii), which states that proof of effectiveness of such an OTC drug shall consist of controlled clinical investigations as defined in § 314.126(b)(21 CFR 314.126(b)), unless this requirement is waived as not reasonably applicable or essential and another method is adequate. Based on inadequate measures taken by the investigative team to minimize bias on the parts of the subjects and the observers, the agency finds that the studies were not conducted in conformance with 21 CFR 314.126(b)(5).

In conclusion, the agency does not consider either study capable of demonstrating the effectiveness of LYCD for any anorectal uses. Therefore, the studies are inadequate to support the use of LYCD to relieve symptoms of hemorrhoidal pain, itching, burning, or irritation, or to shrink hemorrhoids.The agency's detailed comments on the data are on file in the Dockets Management Branch (address above) (Ref. 4).

References

(1) Comments No. C19 and SUP5, Docket No. 80N–0050, Dockets Management Branch.

(2) Comments No. C34, AMD, C57, SUP, and LET11 through LET14, Docket No. 78N–0021, Dockets Management Branch.

(3) Second attachment to letter from W. E. Gilbertson, FDA, to J. R. Jacobs, Whitehall Laboratories, coded LET25, Docket No. 80N-0050, Dockets Management Branch.

(4) Letter from W. E. Gilbertson, FDA, to J. R. Jacobs, Whitehall Laboratories, coded LET25, Docket No. 80N–0050, Dockets Management Branch.

C. Data Submitted to the Skin Protectant Rulemaking

The comment's data on LYCD as a skin protectant wound healing agent were not used in arriving at the agency's conclusion on LYCD's effectiveness as an anorectal wound healing agent. The Panel stated that studies to test the effects of agents on wound healing must be designed with the use site in mind, i.e., where there is compression (due to sitting), stretching of surface and subcutaneous tissue on a sporadic basis (due to walking, bowel movement), increased moisture, chafing (due to clothing and opposed body surfaces), and gross contamination by aerobic and/or anaerobic bacteria and yeast (45 FR 35576 at 35658). The Panel compared testing under those conditions with testing on many body wounds that can be maintained at a relative degree of cleanliness, immobilized, and covered consistently or exposed to air. The Panel further pointed out that although the wound-healing process may be similar

in the anorectal and other areas, the natural impediments are not and thus any experimental design germaine to the anorectal area must consider these impediments. The agency agrees with the Panel's conclusions and further notes that the data in support of LYCD as a skin protectant wound-healing agent consisted of studies on subjects with burns and with surgically induced abrasions (Ref. 1). Testing in these studies did not take into account the differences in treatment area as described by the Panel. Accordingly, these studies are not acceptable to support the use of LYCD as a wound-healing agent in the anorectal area.

Reference

(1) Comments No. C34, AMD, C57, SUP, and LET11 through LET14, Docket No. 78N–0021, Dockets Management Branch.

The agency has determined that LYCD for any OTC anorectal use is not generally recognized as safe and effective. The agency is amending § 310.545(a) and (d) to establish that LYCD and certain other active ingredients are not generally recognized as safe and effective and are misbranded for use in OTC anorectal drug products. Therefore, LYCD as an ingredient for OTC anorectal use is considered a nonmonograph ingredient and misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352) and is a new drug within the meaning of section 201(p) of the act (21 U.S.C. 321(p)) for which an approved application or abbreviated application under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations (21 CFR part 314) is required for marketing. In appropriate circumstances, a citizen petition to amend the monograph (21 CFR part 346) and containing new data to support LYCD's use as an anorectal active ingredient may be submitted under 21 CFR 10.30 in lieu of an application. Any drug product containing LYCD as an anorectal active ingredient for OTC use initially introduced or initially delivered for introduction into interstate commerce or repackaged or relabeled after the effective date of this final rule is not in compliance with the regulation and is subject to regulatory action.

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. This final rule only affects the status of LYCD for OTC anorectal use. The agency is aware of only a few LYCD-containing OTC anorectal drug products that are currently marketed. These products also contain shark liver oil, petrolatum, or cocoa butter, acceptable anorectal protectants (Refs. 1, 2, and 3). Thus, the products can be reformulated to delete the LYCD and be relabeled to delete any claims specifically related to LYCD. Anorectal protectant ingredients and claims in accord with §§ 346.14 and 346.50 can be used. For all other active nonmonograph ingredients listed in this final rule, the effective date of August 5, 1991, has already occurred. 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 determined under 21 CFR 25.24(c)(6) 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.

References

(1) Physicians' Desk Reference for Nonprescription Drugs, 13th ed., Medical Economics Co., Inc., Oradell, NJ, 1992, pp. 752–753.

(2) Physicians' Desk Reference for Nonprescription Drugs, 13th ed., Medical Economics Co., Inc., Oradell, NJ, 1992, p. 777.

(3) Drug Facts and Comparisons, 46th ed., Facts and Comparisons, St. Louis, 1992, p. 2163.

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

2. Section 310.545 is amended by adding new paragraph (a)(26), by revising the introductory text of paragraph (d), and by adding new paragraphs (d)(13) and (d)(14) to read as follows:

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

(a) * * *

(26) *Anorectal druq products*—(i) *Anticholinergic drug products.*

Atropine
Belladonna extract

(ii) *Antiseptic drug products.*

Boric acid
Boroglycerin
Hydrastis
Phenol
Resorcinol
Sodium salicylic acid phenolate

(iii) *Astringent drug products.*

Tannic acid

(iv) *Counterirritant drug products.*

Camphor (greater than 3 to 11 percent)
Hydrastis
Menthol (1.25 to 16 percent)
Turpentine oil (rectified) (6 to 50 percent)

(v) *Keratolytic drug products.*

Precipitated sulfur
Sublimed sulfur

(vi) *Local anesthetic drug products.*

Diperodon
Phenacaine hydrochloride

(vii) *Other druq products.*

Collinsonia extract
Escherichia coli vaccines
Lappa extract
Leptandra extract
Live yeast cell derivative
Mullein

(viii) *Protectant druq products.*

Bismuth oxide
Bismuth subcarbonate
Bismuth subgallate
Bismuth subnitrate
Lanolin alcohols

(ix) *Vasoconstrictor druq products.*

Epinephrine undecylenate

(x) *Wound healinq druq products.*

Cholecalciferol

Cod liver oil
Live yeast cell derivative
Peruvian balsam
Shark liver oil
Vitamin A
* * * * *

(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)(14) of this section.
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(13) August 5, 1991, for products subject to paragraphs (a)(26) of this section, except for those that contain live yeast cell derivative.

(14) September 2, 1994, for products subject to paragraph (a)(26)(vii) and (a)(26)(x) of this section that contain live yeast cell derivative.

Dated: August 27, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 93–21370 Filed 9–1–93; 8:45 am]
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21 CFR Part 310

[Docket No. 80N–0146]

RIN 0905–AA06

Nailbiting and Thumbsucking Deterrent 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 any nailbiting and thumbsucking deterrent drug product for over-the-counter (OTC) human use is not generally recognized as safe and effective and is 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 OTC nailbiting and thumbsucking deterrent drug products that have come to the agency's attention. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: March 2, 1994.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of October 17, 1980 (45 FR 69122), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), a proposed rule to establish a monograph for OTC nailbiting and thumbsucking deterrent drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous External 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 January 15, 1981. Reply comments in response to comments filed in the initial comment period could be submitted by February 16, 1981.

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. 1–23, 12420 Parklawn Dr., 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 nailbiting and thumbsucking deterrent drug products was published in the **Federal Register** of September 3, 1982 (47 FR 39096). Interested persons were invited to file by November 2, 1982, written comments, objections, or requests for a 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 January 2, 1983. New data could have been submitted until September 3, 1983, and comments on the new data until November 3, 1983.

In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency published a final rule in 21 CFR part 310 establishing that certain active ingredients that had been under consideration in a number of OTC drug rulemaking proceedings were not generally recognized as safe and effective. That final rule was effective on May 7, 1991 and included, in § 310.545(a)(13), denatonium benzoate, an active ingredient under consideration in the rulemaking for OTC nailbiting and thumbsucking deterrent drug products. This ingredient was determined to be nonmonograph because no additional data had been submitted establishing that it was generally recognized as safe and effective as a nailbiting and thumbsucking deterrent. Final agency action on all other OTC nailbiting and thumbsucking deterrent drug products occurs with the publication of this final rule.

In the proposed rule, the agency did not propose any OTC nailbiting and thumbsucking deterrent active ingredient as generally recognized as safe and effective and not misbranded. However, the agency proposed monograph labeling in the event that data were submitted that resulted in the upgrading of any ingredient to monograph status in the final rule. In this final rule, however, no active ingredient has been determined to be generally recognized as safe and effective for use in OTC nailbiting and thumbsucking deterrent drug products. Therefore, proposed subpart C of 21 CFR part 358 for OTC nailbiting and thumbsucking deterrent drug products is not being issued as a final regulation.

This final rule declares OTC drug products containing OTC nailbiting and thumbsucking deterrent active ingredients to be new drugs under 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 this use also would be misbranded under section 502 of the act (21 U.S.C. 352). In appropriate circumstances, a citizen petition to establish a monograph may be submitted under 21 CFR 10.30 in lieu of an application.

This final rule amends 21 CFR part 310 to include drug products containing nailbiting and thumbsucking deterrent ingredients by adding to subpart E new § 310.536 (21 CFR 310.536). The inclusion of OTC nailbiting and thumbsucking deterrent drug products in part 310 follows FDA's established policy for regulations in which there are no monograph conditions. (See, e.g., §§ 310.510, 310.519, 310.525, 310.526, 310.532, 310.533, and 310.534.) If, in the future, any ingredient is determined to be generally recognized as safe and effective for use in an OTC nailbiting and thumbsucking deterrent drug product, the agency will promulgate an appropriate regulation at that time.

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 does not use the terms "Category I" (generally recognized as safe and