

As described in the Marketed Unapproved Drugs CPG, the agency may, at its discretion, identify a period of time during which the agency does not intend to initiate an enforcement action against a currently marketed unapproved drug solely on the ground that it lacks an approved application under section 505 of the act. With respect to unapproved ophthalmic balanced salt solution products, the agency intends to exercise its enforcement discretion for only a limited period of time because ophthalmic balanced salt solution products are drugs with potential safety risks and approved ophthalmic balanced salt solutions for use in surgical procedures of both shorter and longer durations have been available since 1997. Therefore, the agency intends to implement this notice as follows.

For the effective date of this notice, see the **DATES** section of this document. FDA intends to take enforcement action to enforce section 505(a) of the act against any unapproved ophthalmic balanced salt solution product that is not listed with the agency in full compliance with section 510 of the act (21 U.S.C. 360) before September 22, 2008, and is manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after September 23, 2008. FDA also intends to take enforcement action to enforce section 505(a) of the act against any unapproved ophthalmic balanced salt solution that is listed with FDA in full compliance with section 510 of the act but is not being commercially used or sold⁵ in the United States on September 22, 2008 and that is manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after September 23, 2008.

However, for unapproved ophthalmic balanced salt solution products that are commercially used or sold in the United States, have a National Drug Code (NDC) number listed with FDA, and are in full compliance with section 510 of the act before September 22, 2008 ("currently marketed and listed"), the agency intends to exercise its enforcement discretion as follows. FDA intends to initiate enforcement action against any currently marketed and listed unapproved ophthalmic balanced salt solution product that is manufactured

on or after November 24, 2008 or that is shipped on or after January 21, 2009.⁶ Further, FDA intends to take enforcement action against any person who manufactures or ships such products after these dates. Any person who has submitted or submits an application for an ophthalmic balanced salt solution product but has not received approval must comply with this notice.

The agency, however, does not intend to exercise its enforcement discretion as outlined previously if the following apply: (1) A manufacturer or distributor of an unapproved ophthalmic balanced salt solution product covered by this notice is violating other provisions of the act, including but not limited to, violations related to FDA's current good manufacturing practices, adverse drug event reporting, labeling or misbranding requirements or (2) it appears that a firm, in response to this notice, increases its manufacture or interstate shipment of ophthalmic balanced salt solution products above its usual volume during these periods.

Nothing in this notice, including FDA's intent to exercise its enforcement discretion, alters any person's liability or obligations in any other enforcement action, or precludes the agency from initiating or proceeding with enforcement action in connection with any other alleged violation of the act, whether or not related to an unapproved drug product covered by this notice. Similarly, a person who is or becomes enjoined from marketing unapproved drugs may not resume marketing of unapproved ophthalmic balanced salt solution products based on FDA's exercise of enforcement discretion that is set forth in this notice.

Drug manufacturers and distributors should be aware that the agency is exercising its enforcement discretion as described previously only in regard to ophthalmic balanced salt solution products that are marketed under an NDC number listed with the agency in full compliance with section 510 of the act before September 22, 2008. As previously stated, unapproved

ophthalmic balanced salt solution products that are currently marketed but not listed with the agency on the date of this notice must, as of the effective date of this notice, have approved applications prior to their shipment in interstate commerce. Moreover, any person or firm that has submitted or submits an application but has yet to receive approval for such products is still responsible for full compliance with this notice.

C. Discontinued Products

Some firms may have previously discontinued the manufacturing or distribution of products covered by this notice without removing them from the listing of their products under section 510(j) of the act. Other firms may discontinue manufacturing or marketing listed products in response to this notice. Firms that wish to notify the agency of product discontinuation should send a letter, signed by the firm's chief executive officer, fully identifying the discontinued product(s), including NDC number(s), and stating that the product(s) has (have) been discontinued. The letter should be sent to Jennifer Devine (see **ADDRESSES**). Firms should also update the listing of their products under section 510(j) of the act to reflect discontinuation of unapproved ophthalmic balanced salt solution products. FDA plans to rely on its existing records, including drug listing records, or other available information when it targets violations for enforcement action.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (sections 502 and 505 (21 U.S.C. 352)) and under authority delegated to the Deputy Commissioner for Policy under section 1410.10 of the FDA Staff Manual Guide.

Dated: September 8, 2008.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2008-N-0481]

Topical Drug Products Containing Papain; Enforcement Action Dates

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

product, are subject to FDA enforcement action at any time.

⁵ For the purposes of this notice, the term "commercially used or sold" means that the product has been used in a business or activity involving retail or wholesale marketing and/or sale.

⁶ If FDA finds it necessary to take enforcement action against a product covered by this notice, the agency may take action relating to all of the defendant's other violations of the act at the same time. For example, if a firm continues to manufacture or market a product covered by this notice after the applicable enforcement date has passed, to preserve limited agency resources, FDA may take enforcement action relating to all of the firm's unapproved drugs that require applications at the same time (see, e.g., *United States v. Sage Pharmaceuticals*, 210 F.3d 475, 479-480 (5th Cir. 2000) (permitting the agency to combine all violations of the act in one proceeding, rather than taking action against multiple violations of the act in "piecemeal fashion")).

SUMMARY: The Food and Drug Administration (FDA) is announcing its intention to take enforcement action against unapproved topical drug products containing papain and persons¹ who manufacture or cause the manufacture of such products or their shipment in interstate commerce. Topical drug products containing papain are marketed, without approved applications, to debride necrotic tissue and liquefy slough in acute and chronic lesions. Potentially serious adverse events have been reported with topical drug products containing papain. Topical drug products containing papain are new drugs that require approved applications because they are not generally recognized as safe and effective. Currently no firm has an approved application to market a topical drug product containing papain. Manufacturers who wish to market topical drug products containing papain must obtain FDA approval of a new drug application (NDA) or an abbreviated new drug application (ANDA).

DATES: This notice is effective September 23, 2008. For information about enforcement dates, see **SUPPLEMENTARY INFORMATION**, section III.B.

ADDRESSES: All communications in response to this notice should be identified with Docket No. FDA-2008-N-0481 and directed to the appropriate office listed as follows:

Regarding applications under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(b)): Division of Dermatology and Dental Products, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Silver Spring, MD 20993-0002.

All other communications: Jennifer Devine, Center for Drug Evaluation and Research (HFD-310), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51 (rm. 5240), Silver Spring, MD 20993-0002.

FOR FURTHER INFORMATION CONTACT: Jennifer Devine, Office of Compliance, Division of New Drugs and Labeling Compliance, Center for Drug Evaluation and Research (HFD-310), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51 (rm. 5240), Silver Spring, MD 20993-0002, 301-796-3347, e-mail: Jennifer.Devine@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

Papain is a protein-cleaving enzyme derived from papaya fruit (*Carica papaya*) and certain other plants. The latex of the papaya plant and its green fruits contain two proteolytic enzymes, papain and chymopapain. The latter is most abundant, but papain is twice as potent. The presence and effects of proteases in papaya fruit latex have been well known since the 1750s, but it was not until the 1870s that the importance of papaya latex as a source of enzymes was recognized. Although the exact year is unknown, marketing of topical papain drug products in the United States began before 1962.

Topical drug products containing papain are used for the debridement of necrotic tissue and liquefaction of slough in acute and chronic lesions, such as diabetic ulcers, pressure ulcers, varicose ulcers, and miscellaneous traumatic infected wounds. These products generally combine papain with other active ingredients (such as urea, chlorophyllin copper complex, and copper sodium chlorophyllin), which are intended to promote healthy granulation, control local inflammation, reduce wound odors, and rehydrate skin. In addition, papain is marketed in oral formulations for a variety of indications, including as an aid in protein digestion.² It is also used in the food industry as a meat tenderizer.³

Papain-containing drug products in topical form historically have been marketed without approval, and because no firm obtained an application for them prior to passage of the Drug Amendments of 1962, they were not included in the Drug Efficacy Study Implementation (DESI) review.

II. Safety and Efficacy Issues in the Use of Topical Papain Drug Products

Adverse events associated with the use of topical papain products reported to FDA raise serious safety concerns regarding these products. Through January 2008,⁴ FDA has received 37 reports of adverse events associated with topical papain products. In addition to several complaints that the products were ineffective, the reports include cases of potentially life-threatening hypersensitivity reactions. Reactions described include serious cases of anaphylaxis and anaphylactic shock that started within 15 minutes of

topical papain use and resulted in hospitalizations, including admissions to the intensive care unit. Published literature also describes incidents of hypersensitivity to other papain-containing products, including meat tenderizer, contact lens solution, and adhesive removers in the beauty industry. Another concern exists regarding patients with latex sensitivity. Cross-reactivity between latex and papaya has been documented in medical literature, and one of the cases reported to FDA involved anaphylactic shock in a patient with a history of allergy to latex. It is notable that labeling for currently marketed topical papain products does not provide any warnings regarding hypersensitivity reactions and latex cross-reactivity.

FDA is particularly concerned about adverse events associated with the use of papain-containing topical drug products in light of the dearth of published well-controlled studies demonstrating the effectiveness of those products. Given the absence of the kinds of scientific studies routinely conducted by sponsors and submitted for agency review as part of the FDA approval process, it is impossible for the agency to assess either the amount of risk associated with these products or the extent to which their benefits might justify their risks, including severe, systemic, potentially life-threatening hypersensitivity reactions.

III. Legal Status

A. Topical Papain Products Are New Drugs Requiring Approved Applications

Based both on the safety considerations previously described and the absence of published literature documenting that topical drugs containing papain are safe and effective, such drugs are not generally recognized as safe and effective under section 201(p) of the act (21 U.S.C. 321(p)) for any indication, including for the debridement of necrotic tissue and liquefaction of slough in acute and chronic lesions. Therefore, a topical drug product containing papain, alone or in combination with other drugs, is regarded as a new drug as defined in section 201(p) of the act and is subject to the requirements of section 505 of the act. As set forth in this notice, approval of an NDA or an ANDA under section 505 of the act is required as a condition for manufacturing or marketing all topical drug products containing papain. After the dates identified in this notice, FDA intends to take enforcement action as described in this notice against unapproved topical drug products containing papain and persons who

² Lacy, D.F., Armstrong, L.L., Goldman, M.P., Lance, L.L., eds., *Drug Information Handbook*, 2008-2009; 17th edition.

³ See <http://www.foodreference.com/html/fineattentenderizer.html>.

⁴ Data in the current system date back to 1969, when FDA first implemented an adverse event reporting system.

¹ A "person" includes individuals, partnerships, corporations, or associations (21 U.S.C. 321(e)).

cause the manufacture or interstate shipment of such products. Any person who submits an NDA or an ANDA for a topical product containing papain but has not received approval must comply with this notice.

This notice does not affect drugs containing papain in oral dosage forms, which FDA intends to address at a later date.

B. Notice of Enforcement Action

Although not required to do so by the Administrative Procedure Act, the act, or any rules issued under its authority, or for any other legal reason, FDA is providing this notice to persons who are marketing unapproved topical drug products containing papain that the agency intends to take enforcement action against such products and those who manufacture them or cause them to be manufactured or shipped in interstate commerce. Manufacturing or shipping unapproved topical products containing papain can result in enforcement action, including seizure, injunction, or other judicial or administrative proceeding. Consistent with policies described in the agency's guidance entitled "Marketed Unapproved Drugs—Compliance Policy Guide" (the Marketed Unapproved Drugs CPG), the agency does not expect to issue a warning letter or any other further warning to firms prior to taking enforcement action relating to unapproved papain-containing topical drug products. The agency also reminds firms and individuals that, as stated in the Marketed Unapproved Drugs CPG, any unapproved drug marketed without a required approved drug application is subject to agency enforcement action at any time. The issuance of this notice does not in any way obligate the agency to issue similar notices or any notice in the future regarding marketed unapproved drugs.⁵

As described in the Marketed Unapproved Drugs CPG, the agency may, at its discretion, identify a period of time during which the agency does not intend to initiate an enforcement action against a currently marketed unapproved drug on the ground that it lacks an approved application under section 505 of the act in order to, for example, preserve access to medically necessary drugs or ease disruption to affected parties. With respect to

unapproved topical drug products containing papain, the agency intends to exercise its enforcement discretion for only a limited period of time because these are drugs with potential safety risks that lack scientific evidence of effectiveness. Therefore, the agency intends to implement this notice as follows.

For the effective date of this notice, see the **DATES** section of this document. FDA intends to take action to enforce section 505(a) of the act against any unapproved topical drug product containing papain that is not listed with FDA in full compliance with section 510 of the act (21 U.S.C. 360) before September 22, 2008, and that is manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after September 23, 2008. FDA also intends to take action to enforce section 505(a) of the act against any unapproved topical drug containing papain that has a National Drug Code (NDC) number listed with FDA in full compliance with section 510 of the act but is not being commercially used or sold⁶ in the United States on September 22, 2008, and that is manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after September 23, 2008.

However, for unapproved topical drug products containing papain that are commercially used or sold in the United States, have a NDC number listed with FDA, and are in full compliance with section 510 of the act before September 22, 2008 ("currently marketed and listed"), the agency intends to exercise its enforcement discretion as follows. FDA intends to initiate enforcement action against any currently marketed and listed unapproved topical product containing papain that is manufactured on or after November 24, 2008 or that is shipped on or after January 21, 2009.⁷ Further, FDA intends to take

⁶ For the purposes of this notice, the term "commercially used or sold" means that the product has been used in a business or activity involving retail or wholesale marketing and/or sale.

⁷ If FDA finds it necessary to take enforcement action against a product covered by this notice, the agency may take action relating to all of the defendant's other violations of the act at the same time. For example, if a firm continues to manufacture or market a product covered by this notice after the applicable enforcement date has passed, to preserve limited agency resources, FDA may take enforcement action relating to all of the firm's unapproved drugs that require applications at the same time (see, e.g., *United States v. Sage Pharmaceuticals*, 210 F. 3d 475, 479–480 (5th Cir. 2000) (permitting the agency to combine all violations of the act in one proceeding, rather than taking action against multiple violations of the act in "piecemeal fashion")).

enforcement action against any person who manufactures or ships such products after the dates set forth above. Any person who submits a new drug application for a topical drug product containing papain but has not received approval must comply with this notice.

The agency, however, does not intend to exercise its enforcement discretion as outlined previously if the following apply: (1) A manufacturer or distributor of an unapproved topical drug product containing papain covered by this notice is violating other provisions of the act (including but not limited to, violations related to FDA's current good manufacturing practices, adverse drug event reporting, or labeling requirements) or (2) it appears that a firm, in response to this notice, increases its manufacture or interstate shipment of unapproved topical drug products containing papain above its usual volume.

Nothing in this notice, including FDA's intent to exercise its enforcement discretion, alters any person's liability or obligations in any other enforcement action or litigation, or precludes the agency from initiating or proceeding with enforcement action in connection with any other alleged violation of the act, whether or not related to an unapproved drug product covered by this notice. Similarly, a person who is or becomes enjoined from marketing unapproved drugs may not resume marketing of unapproved topical drug products containing papain based on FDA's exercise of enforcement discretion as set forth in this notice.

Drug manufacturers and distributors should be aware that the agency is exercising its enforcement discretion as described previously only in regard to topical papain drug products that are marketed under an NDC number listed with the agency in full compliance with section 510 of the act before September 22, 2008. As previously stated, unapproved topical drug products containing papain that are not currently marketed, or that are currently marketed but not listed with the agency on the date of this notice must have approved applications prior to their shipment in interstate commerce. Moreover, any person or firm that submits an NDA or an ANDA but has yet to receive approval for such products is still responsible for full compliance with this notice.

C. Discontinued Products

Some firms may have previously discontinued the manufacturing or distribution of products covered by this notice without removing them from the listing of their products under section

⁵ The agency's general approach in dealing with these products in an orderly manner is spelled out in the Marketed Unapproved Drugs CPG. That CPG, however, provides notice that any product that is being marketed illegally, and the persons responsible for causing the illegal marketing of the product, are subject to FDA enforcement action at any time.

510(j) of the act. Other firms may discontinue manufacturing or marketing listed products in response to this notice. Firms that wish to notify the agency of product discontinuation should send a letter, signed by the firm's chief executive officer, fully identifying the discontinued product(s), including the product NDC number(s), and stating that the product(s) has (have) been discontinued. The letter should be sent to Jennifer Devine (see **ADDRESSES**). Firms should also update the listing of their products under section 510(j) of the act to reflect discontinuation of unapproved topical papain drug products. Updating of listing information may be advantageous for a firm because FDA plans to rely on its existing records, the results of a subsequent inspection, or other available information when we evaluate whether to initiate enforcement action.

This notice is issued under sections 502 and 505 of the act (21 U.S.C. 352) and under authority delegated to the Deputy Commissioner for Policy under section 1410.10 of the FDA Staff Manual Guide.

Dated: September 8, 2008.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

National Vaccine Injury Compensation Program List of Petitions Received

AGENCY: Health Resources and Services Administration, HHS.

ACTION: Notice.

SUMMARY: The Health Resources and Services Administration (HRSA) is publishing this notice of petitions received under the National Vaccine Injury Compensation Program ("the Program"), as required by Section 2112(b)(2) of the Public Health Service (PHS) Act, as amended. While the Secretary of Health and Human Services is named as the respondent in all proceedings brought by the filing of petitions for compensation under the Program, the United States Court of Federal Claims is charged by statute with responsibility for considering and acting upon the petitions.

FOR FURTHER INFORMATION CONTACT: For information about requirements for filing petitions, and the Program in

general, contact the Clerk, United States Court of Federal Claims, 717 Madison Place, NW., Washington, DC 20005, (202) 357-6400. For information on HRSA's role in the Program, contact the Director, National Vaccine Injury Compensation Program, 5600 Fishers Lane, Room 11C-26, Rockville, MD 20857; (301) 443-6593.

SUPPLEMENTARY INFORMATION: The Program provides a system of no-fault compensation for certain individuals who have been injured by specified childhood vaccines. Subtitle 2 of Title XXI of the PHS Act, 42 U.S.C. 300aa-10 *et seq.*, provides that those seeking compensation are to file a petition with the U.S. Court of Federal Claims and to serve a copy of the petition on the Secretary of Health and Human Services, who is named as the respondent in each proceeding. The Secretary has delegated his responsibility under the Program to HRSA. The Court is directed by statute to appoint special masters who take evidence, conduct hearings as appropriate, and make initial decisions as to eligibility for, and amount of, compensation.

A petition may be filed with respect to injuries, disabilities, illnesses, conditions, and deaths resulting from vaccines described in the Vaccine Injury Table (the Table) set forth at Section 2114 of the PHS Act or as set forth at 42 CFR 100.3, as applicable. This Table lists for each covered childhood vaccine the conditions which may lead to compensation and, for each condition, the time period for occurrence of the first symptom or manifestation of onset or of significant aggravation after vaccine administration. Compensation may also be awarded for conditions not listed in the Table and for conditions that are manifested outside the time periods specified in the Table, but only if the petitioner shows that the condition was caused by one of the listed vaccines.

Section 2112(b)(2) of the PHS Act, 42 U.S.C. 300aa-12(b)(2), requires that the Secretary publish in the **Federal Register** a notice of each petition filed. Set forth below is a list of petitions received by HRSA on April 1, 2007, through December 31, 2007.

Section 2112(b)(2) also provides that the special master "shall afford all interested persons an opportunity to submit relevant, written information" relating to the following:

1. The existence of evidence "that there is not a preponderance of the evidence that the illness, disability, injury, condition, or death described in the petition is due to factors unrelated

to the administration of the vaccine described in the petition," and

2. Any allegation in a petition that the petitioner either:

(a) "Sustained, or had significantly aggravated, any illness, disability, injury, or condition not set forth in the Table but which was caused by" one of the vaccines referred to in the Table, or

(b) "Sustained, or had significantly aggravated, any illness, disability, injury, or condition set forth in the Vaccine Injury Table the first symptom or manifestation of the onset or significant aggravation of which did not occur within the time period set forth in the Table but which was caused by a vaccine" referred to in the Table.

This notice will also serve as the special master's invitation to all interested persons to submit written information relevant to the issues described above in the case of the petitions listed below. Any person choosing to do so should file an original and three (3) copies of the information with the Clerk of the U.S. Court of Federal Claims at the address listed above (under the heading "For Further Information Contact"), with a copy to HRSA addressed to Director, Division of Vaccine Injury Compensation Program, Healthcare Systems Bureau, 5600 Fishers Lane, Room 11C-26, Rockville, MD 20857. The Court's caption (Petitioner's Name v. Secretary of Health and Human Services) and the docket number assigned to the petition should be used as the caption for the written submission. Chapter 35 of title 44, United States Code, related to paperwork reduction, does not apply to information required for purposes of carrying out the Program.

List of Petitions

1. Annie Jackson, Gary, Indiana, Court of Federal Claims Number 07-0217V.

2. Mildred Free Corun, Murphy, North Carolina, Court of Federal Claims Number 07-0219V.

3. Amy and Joel Cochran on behalf of Elbrywn Cochran, Scott Air Force Base, Illinois, Court of Federal Claims Number 07-0221V.

4. Christine Sharlike on behalf of Megan Sharlike, Westerville, Ohio, Court of Federal Claims Number 07-0229V.

5. Kristy Paulsen and Shannon Berhorst on behalf of Landon Michael Lee Berhorst, Deceased, Monticello, Missouri, Court of Federal Claims Number 07-0233V.

6. Nancey Cost on behalf of Jason Cost, Gastonia, North Carolina, Court of Federal Claims Number 07-0234V.

7. Mr. and Mrs. Peter Wynne Wilcox, Jr. on behalf of Marshall Wilcox, Macon,