July 12, 2000

Endo Pharmaceuticals, Inc.
Chadds Ford, Pa. 19317

Re: Lidoderm Patch

To Whom It May Concern:

In October 1997 I had cataract surgery and one of the followup medications wa[redacted] After several days of using these drops I developed an allergic reaction (we discovered a cautionery note on the package that this sometimes happens) resulting in a severe case of shingles. My medical doctor prescribed everything for relief from topical to internal but to no avail. As time went on some of the pain lessened but the discomfort did not go away.

In September 1999 my niece read an article in a journal at her job in a hospital which described Lidoderm and lo and behold I have finally found relief (not a cure). At this point, I do not use it daily but when I awake with the recognizable distress, I use this product and within a short time I have relief.

I have thought of writing many times, but finally decided it was time to share my success. Thank you for this product and please pass my thanks on to Dr. Harry Hind whose address I could not find.

[redacted]
Paramus, N.J. 07652

P.S. When I showed my physician the article back in 1999, he had never heard of this product and we had to make several phone calls before finally locating it through AARP Pharmaceutical Dept. I have also mentioned it to several friends troubled as I was.

[redacted] York

A particularly painful case of shingles and resulting postherpetic neuralgia (PHN) pain along her side left [redacted] actically incapacitated. [redacted] 77, spent almost five years searching for some relief before trying the LIDODERM® patch (lidocaine patch 5%) in early 1999. She found the relief she was hoping for in the patch.

Previously [redacted] d tried almost every remedy available for the intense PHN pain she has across her left side. She saw internists, neurologists and anesthesiologists. She tried various pain medications, acupuncture and epidurals. She had an intrathecal pump implanted – it didn't work. She spent four days in New York University hospital trying various treatments. Nothing worked a[redacted] was miserable.

[redacted] says, "no one can ever imagine how bad the pain was." For two years, she says she lay on the couch or in her bed. She couldn't even get dressed or go on any outings. Her husband used to push her outside in a wheelchair just to get some fresh air. She describes her pain as an intense burning sensation, with "shots of electricity" running down her side.

[redacted] nally found Dr. [redacted] rael Pain Center, one of the lead investigators for LIDODERM®. Since starting to use the patch in January 1999, Frieda has gotten some real relief and is again "able to function." She goes on walks and to social engagements and enjoys being active again.

6/99

[redacted] California

When asked to describe the nerve pain he experienced after a case of shingl[redacted] says, "it was devastating, like a hot knife sticking in my back, twisting and turning."

[redacted] now 78 years old, contracted shingles ten years ago and the pain from the damaged nerves across his back – postherpetic neuralgia (PHN) - has remained ever since. [redacted] completely "knocked out" by the pain. Any activity aggravated the nerves, so he ceased all activity. Any touch on his back, including clothes or even bedcovers, caused him such intense pain he would "jump out of (his) skin." When clothes were absolutely necessary, [redacted] uld cut holes out of the back of his shirts so it didn't touch the painful area.

[redacted] retired butcher, tried oral pain medications, cold packs and hot packs. Nothing worked on his pain [redacted] n read in the newspaper about the clinical trials for LIDODERM® (lidocaine patch 5%) that were taking place at the University of California, San Francisco. He says he feels very fortunate that he was accepted into the program, because the patches work "beautifully" to control his pain [redacted] s he doesn't know what he'd do without LIDODERM®.

[redacted] ears a patch every day. He is playing golf again, and is enjoying spending time relatively pain-free with his wife, 4 children, 12 grandchildren and 6 great-grandchildren.

6/99

[redacted]land, Oregon

Whe[redacted]ow age 71, was being treated with chemotherapy for breast cancer in 1985, the last thing on her mind was the shingles virus. However, on top of everything else she was dealing with, [redacted]ntracted a painful case of shingles, a reactivation of the chicken pox virus that most often attacks people whose immune systems are weakened, such as the elderly, AIDS patients or patients undergoing chemotherapy.

The shingles rash broke out across her back on her spine and around her arm. And, unfortunately f[redacted]she experienced permanent nerve damage. She says the shooting pain across her back and arm was "horrible and unbearable."

[redacted]as an x-ray technician who had returned to college in her 50s. She had raised five children and was an avid gardener. When her postherpetic neuralgia (PHN) pain was at its worst[redacted]ould do nothing more than "sit in a chair, hardly moving." She tried oral pain medications, which she said didn't do anything to control her pain. She also tried TENS (transcutaneous electrical nerve stimulation), with no relief.

[redacted]eard from a neighbor about a new PHN study that was to take place in Seattle. She was accepted into the trial and left for Seattle hopeful. The LIDODERM® patch (lidocaine patch 5%) worked to control her pain [redacted]s thrilled.

[redacted]ses three patches a day, every day, combining them with some prescription pain medication when she knows she is going to be particularly active. She does volunteer work at her church, and tutors school children. She is also back to her gardening and is enjoying some extensive traveling with her husband and family.

6/99

[redacted]sco, California

[redacted]ys that he spent months at a time "virtually a prisoner in (his) own house," due to the intense nerve pain he experienced after a case of shingles. [redacted]ngles outbreak in 1992 was across his back and right side. He describes the constant postherpetic neuralgia (PHN) pain that followed as excruciating, saying that even someone blowing on his back or wind could cause him agony. He could not have anything touch his back and didn't wear a shirt for months at a time.

An avid golfer and tennis player [redacted]had to give up the activities he enjoyed. He also couldn't work for a time at his job as a [redacted]

[redacted]ed all available methods to get some pain relief. Strong oral pain medications helped a little, but he says, they caused drowsiness, lethargy, constipation and impaired judgement. And the medications lost their effectiveness over time. [redacted]tried antidepressants, anticonvulsants, injections along the nerves on his back, and acupuncture. Desperate to get his life back, he saw medical doctors, chiropractors and even what he calls a "witch doctor."

Dr. Michael Rowbotham of the University of San Francisco Pain Center enrolle[redacted]n the first set of clinical trials for the LIDODERM® patch (lidocaine patch 5%). [redacted]ys that from the minute he put the patch on, he got true relief from his pain for the first time, without any side effects. He calls the patch a "wonderful, wonderful invention."

[redacted]active again and enjoying life. He is also looking forward to his younger son's upcoming wedding, which he believes he would not even be able to attend without LIDODERM®.

6/99

[redacted]nd, Washington

"If I can just live through December, maybe things will get better," 77-year-old [redacted] remembers thinking in the summer of 1992, when she was stricken by postherpetic neuralgia (PHN) pain after a case of shingles.

[redacted]erve damage is on her upper arm, in her armpit and across her back. The pain is "non-stop, excruciating and indescribable," she says. She was in such pain that she had to give up all the activities she enjoyed, including jazzercize classes and rugbraiding.

Her family doctor diagnosed the PHN and attempted to treat her pain with a variety of products. [redacted]ealls nasty side effects from oral pain medications and antidepressants that didn't work on her pain. She tried bee sting therapy and even had a lidocaine infusion. Nothing helped.

[redacted]en participated in the LIDODERM® (lidocaine patch 5%) study at the University of Washington. The patch, say[redacted] "a howling success." She feels the patches, which she uses every day, have completely changed her life. "It's like night and day," she says. [redacted] husband, two daughters and three grandchildren confer – they are thrilled to have the old [redacted] back.

6/99

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June 29, 1999

BY FACSIMILE/CONFIRMATION COPY BY MAIL

Ms. Laura E.W. Noble
Compliance Officer
Office of Compliance
Chemicals, Clothing, and Household Products Team
U.S. Consumer Product Safety Commission
4330 East-West Highway
Bethesda, Maryland 20814

Dear Ms. Noble:

This confirms and expands on our telephone conversation of June 22, 1999 concerning the Commission's letter of June 14, 1999 to Endo Pharmaceuticals, Inc. ("Endo"). Endo, the marketer of Lidoderm® (lidocaine patch 5%), has asked us to represent the company in this matter.

The Commission's letter refers to the "final rule requiring child-resistant packaging for products containing lidocaine," codified at 16 C.F.R. § 1700.14(a)(23), and promulgated under the authority of the Poison Prevention Packaging Act (PPPA). The Commission's letter also alleges that "if the *Lidoderm* packaging does not comply with the PPPA, it will be a misbranded drug as defined by section 502(p) of the Federal food, Drug, and Cosmetic (FD&C) Act."

Briefly, Endo's position is that the lidocaine standard at 16 C.F.R. § 1700.14(a)(23) does not apply to lidocaine products in patch form ("lidocaine patches"), and that the Commission does not have the statutory authority to enforce the standard against lidocaine patches.

I. FAILURE TO MAKE REQUISITE FINDINGS FOR LIDOCAINE PATCHES

For lidocaine patches, the Commission has not made any of the findings required by the PPPA to impose a standard. As the Commission itself admits in the preamble to the final rule for "products containing lidocaine":

> The . . .PPA . . . authorizes the Commission to establish standards for the "special packaging" of any household substance **if** . . . the special packaging is technically feasible, practicable, and appropriate for such substance. . . .
>
> The findings that the Commission **must make in order to issue a standard** requiring child-resistant . . . packaging for a product are discussed below in Section E. . . .[1]

Section E of the preamble to the final rule repeats that

> the Commission **is required by** section 3(a)(2) of **the PPPA** . . . **to find** that the special packaging is "technically feasible, practicable, and appropriate."[2]

Moreover, the PPPA also requires the commission to find that "the degree or nature of the hazard to children in the availability of such substance, by reason of its packaging, is such that special packaging is required to protect children."[3] It is clear that the Commission

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1 60 Fed. Reg. 17992, 17993 (April 10, 1995) (emphasis added).

2 Id. at 18002 (emphasis added). "Technical feasibility" exists when the technology exists or readily can be developed and implemented by the effective date to produce packaging conforming to the standard. Id. "Practicability" means that special packaging complying with the standard can utilize modern mass production and assembly line techniques. Id. "Appropriateness" exists when packaging complying with the standard will adequately protect the integrity of the substance and not interfere with the intended storage or use. Id.

3 15 U.S.C. § 1472(a)(1) (emphasis added).

cannot make the findings required by the PPPA without considering the dosage forms and the packaging used for products containing the substance.

The notice of proposed rulemaking[4] and the final rule reflect that the Commission made the required findings only with respect to (1) the following dosage forms: "creams, ointments, gels, jellies, viscous solutions, liquids, sprays, aerosols, and injectables," and (2) the following types of packaging: "tube packaging," "squeeze or pump bottles," and "aerosol sprays."[5] The Commission considered also prefilled syringes and a product "in a foil packet containing 1/8 oz of gel."[6]

In order for the standard to legally apply to lidocaine patches, the Commission must make the following findings:

- That the hazard to children in the availability of lidocaine, by reason of its being in a patch, is such that special packaging is required.
- That the technology exists or readily can be developed and implemented by the effective date to produce lidocaine patches packaging conforming to the standard.
- That, for lidocaine patches, special packaging complying with the standard can utilize mass production and assembly techniques.
- That special packaging complying with the standard will adequately protect the integrity of lidocaine in a patch and not interfere with the product's intended storage or use.

For lidocaine in patches, the Commission did not make any of the findings required by the PPPA. Therefore, (1) the standard cannot be interpreted to apply to lidocaine patches; (2) the Commission does not have statutory authority to enforce the standard against lidocaine patches; and (3) Endo's Lidoderm® is not misbranded under section 502(p) of the FD&C Act.

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4 57 Fed. Reg. 34274 (Aug. 4, 1992).

5 See, e.g., 60 Fed. Reg. at 17993-94, 18002-03.

6 Id. at 17994, 18001.

II. NO OPPORTUNITY FOR COMMENT

The Commission may not enforce the standard against lidocaine patches because interested parties were not given notice and an opportunity to comment on it. The PPPA provides that "[p]roceedings to issue, amend, or repeal . . . a standard . . . shall be conducted in accordance with the procedures described by section 553 . . . of Title 5 [i.e., the Administrative Procedure Act (APA)]. . . . [7] The APA provides that a notice of proposed rulemaking shall include "either the terms or substance of the proposed rule or a description of the subjects and issues involved."[8] Furthermore, the APA provides that, "[a]fter notice required by this section, the agency shall give interested persons an opportunity to participate in the rule making through submission of written data, views, or arguments with or without opportunity for oral presentation."[9]

Neither the notice of proposed rulemaking nor the final rule contained any indication that the standard could apply to lidocaine patches. To the contrary, the detailed and specific discussions concerning types of dosage forms and packaging for lidocaine—which fail to make any reference to patches—would reasonably and logically lead the public to conclude that the regulation was not intended to apply to lidocaine patches. Endo and the public were not given notice that the standard might apply to lidocaine patches. Accordingly, there was never a true opportunity to comment on this issue in the rulemaking.

With respect to its applicability to lidocaine patches, the regulation imposing the standard was not promulgated in accordance with the APA. Therefore, the standard is invalid when applied to lidocaine patches.

III. ENDO'S PRIOR COMMUNICATIONS WITH COMMISSION PERSONNEL

In December of 1998, Endo asked us to investigate the applicability of the standard to lidocaine patches. On December 10, 1998, we discussed this issue with Dr. Suzanne Barone, who was represented to us as the Commission's contact for the child-resistant packaging regulations.

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7 15 U.S.C. § 1474(a).

8 5 U.S.C. § 553(b)(3).

9 5 U.S.C. § 553(c).

Dr. Barone informed us that the standard for lidocaine products was not intended to apply to lidocaine patches simply because they were not on the market at the time the standard was proposed and finalized. Dr. Barone added that the Commission was "in the process of formulating its policy on patch products."

Thus, even after consulting with Commission staff, Endo had no reason to believe that the standard would apply to lidocaine patches. To the extent that the letter to Endo means that the Commission has now established a "policy" on lidocaine patches, the prior discussions in this letter make it clear that the Commission may not make a standard applicable to a class of products simply by adopting a "policy." There must be a rulemaking proceeding that affords interested parties the opportunity to comment, and in which the Commission makes the findings required by the PPPA to impose a standard.

IV. APPLYING STANDARD TO LIDODERM® COULD HAVE SEVERE ADVERSE EFFECT ON AVAILABILITY OF AN ORPHAN DRUG

On October 24, 1995, the Food and Drug Administration (FDA) designated Lidoderm® as an "orphan drug" (see Attachment 1).[10] An orphan drug is a drug intended to treat a rare condition that affects fewer than 200,000 persons in the U.S., or affects more than 200,000 persons but for which there is no reasonable expectation that the cost of developing and making available the drug will be recovered from sales.[11] The orphan drug provisions of the FD&C Act are intended to encourage the development and marketing of drugs for rare diseases, through the use of certain economic incentives.[12] Without these economic incentives, the rare condition would go untreated with drugs. See Attachment 3.

To require Endo to now halt the launch of this orphan drug while it attempts to find child-resistant packaging, and determine whether such packaging is "appropriate" for Lidoderm®, would further delay the availability of therapy for persons suffering from this rare condition. In addition, Endo would need to determine whether the increased cost of using child-resistant packaging would make the product so unprofitable as to negate the incentives in the FD&C Act.

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10 Approval to market Lidoderm® was not granted until March 19, 1999 (see Attachment 2).

11 21 U.S.C. § 360bb(a)(2).

12 See, e.g., 21 U.S.C. § 360cc.

Finally, Endo wishes to point out that the envelope in which the Lidoderm® patches are contained bears the following warning: "WARNING: Package not child resistant. Keep used and unused patches out of the reach of children and pets."

V. CONCLUSION

Expanding the scope of the standard for lidocaine products to include lidocaine patches is in violation of the PPPA, the APA, and the Commission's regulations (16 C.F.R. § 1700.3). The Commission has no statutory authority to enforce the standard against lidocaine patches.

In addition to being contrary to the applicable statutes, it would be wholly unfair for the Commission to attempt to enforce the standard against lidocaine patches without first engaging in appropriate rulemaking. If the Commission wishes to make the regulation applicable to lidocaine patches, it should publish a notice of proposed rulemaking. Interested members of the public, including the industry, should be provided an opportunity to comment. We assure the Commission that Endo will participate fully in any new rulemaking.

Please do not hesitate to contact us if you need additional information or wish to discuss this matter.

Sincerely,

HYMAN, PHELPS & McNAMARA, P.C.
Counsel for Endo Pharmaceuticals, Inc.

Samia N. Rodriguez

By Samia N. Rodriguez

SNR/slk

LIST OF ORPHAN PRODUCTS DESIGNATIONS AND APPROVALS

Through December 31, 1998

NAME Generic Name TN=Trade Name	INDICATION DESIGNATED	SPONSOR & ADDRESS DD=Date Designated MA=Marketing Approval
Levocarnitine TN= Carnitor	Treatment of zidovudine-induced mitochondrial myopathy.	Sigma-Tau Pharmaceuticals, Inc. 800 S. Frederick Avenue, Suite 300 Gaithersburg, MD 20877 DD=04/07/1997 MA= / /
Levomethadyl acetate hydrochloride TN= Orlaam	Treatment of heroin addicts suitable for maintenance on opiate agonists.	Biodevelopment Corporation 8180 Greensboro Drive, Suite 1000 McLean, VA 22102 DD=01/24/1984 MA=07/09/1993
Lidocaine patch 5% TN= Lidoderm Patch	For relief of allodynia (painful hypersensitivity), and chronic pain in post-herpetic neuralgia.	Hind Health Care, Inc. 3707 Williams Rd., Suite 101 San Jose, CA 95117 DD=10/24/1995 MA= / /
Liothyronine sodium injection TN= Triostat	Treatment of myxedema coma/precoma.	SmithKline Beecham Pharmaceuticals One Franklin Plaza P.O. Box 7929 Philadelphia, PA 19101 DD=07/30/1990 MA=12/31/1991
Lipid/DNA human cystic fibrosis gene TN=	Treatment of cystic fibrosis.	Genzyme Corporation P.O. Box 9322 One Mountain Road Framingham, MA 01701 DD=04/08/1996 MA= / /
Liposomal Cyclosporin A TN= Cyclospire	For aerosolized administration in the prevention and treatment of lung allograft rejection and pulmonary rejection events associated with bone marrow transplantation.	Vernon Knight, M.D. Baylor College of Medicine, Dept. of Molecular Physiology One Baylor Plaza Houston, TX 77030 DD=04/30/1998 MA= / /
Liposomal N-Acetylglucosminyl-N-Acetyl muramly-L-Ala-D-isoGln-L-Al a -gylcerolidpalmitoyl TN= ImmTher	Treatment of osteosarcoma.	Endorex Corp. 900 North Shore Drive Lake Bluff, IL 60044 DD=06/10/1998 MA= / /
Liposomal N-Acetylglucosminyl-N-Acetyl muramly-L-Ala-D-isoGln-L-Al a -gylcerolidpalmitoyl TN= ImmTher	Treatment of Ewing's sarcoma.	Endorex Corp. 900 North Shore Drive Lake Bluff, IL 60044 DD=06/10/1998 MA= / /
Liposomal amphotericin B TN= AmBisome	Treatment of cryptococcal meningitis.	Fujisawa USA, Inc. 3 Parkway North Center Deerfield, IL 60015 DD=12/10/1996 MA=08/11/1997

ATTACHMENT 2
LETTER, JUNE 29, 1999

LAMIVUDINE

SOLUTION; ORAL
EPIVIR-HBV
+ GLAXO WELLCOME — 5MG/ML — N21004 001 — DEC 08, 1998
+ — 5MG/ML — N20596 002 — DEC 08, 1998

TABLET; ORAL
EPIVIR-HBV
+ GLAXO WELLCOME — 100MG — N21003 001 — DEC 08, 1998
+ — 100MG — N20564 002 — DEC 08, 1998

LEUCOVORIN CALCIUM

INJECTABLE; INJECTION
LEUCOVORIN CALCIUM
AP + ABBOTT — EQ 10MG BASE/ML — N40147 001 — JUN 25, 1997
AP + BEDFORD — EQ 200MG BASE/VIAL — N40056 001 — MAY 23, 1995

LEUCOVORIN CALCIUM PRESERVATIVE FREE
AP + ABBOTT — EQ 10MG BASE/ML — N40147 001 — JUN 25, 1997
AP + BEDFORD — EQ 200MG BASE/VIAL — N40056 001 — MAY 23, 1995
AP BIGMAR — EQ 10MG BASE/ML — N40286 001 — FEB 26, 1999
AP — EQ 200MG BASE/VIAL — N40258 001 — FEB 26, 1999

TABLET; ORAL
LEUCOVORIN CALCIUM
> ADD > AB INVAMED — EQ 15MG BASE — N75327 001 — MAR 24, 1999
> ADD >

> ADD > LEVALBUTEROL HYDROCHLORIDE

> ADD > SOLUTION; INHALATION
> ADD > XOPENEX
> ADD > + SEPRACOR — EQ 0.021% BASE — N20837 001 — MAR 25, 1999
> ADD > + — EQ 0.042% BASE — N20837 002 — MAR 25, 1999
> ADD >

> ADD > > ADD > > ADD > > ADD >

LIDOCAINE

FILM, EXTENDED RELEASE; TRANSDERMAL
LIDODERM
+ HIND HLTHCARE — 700MG/12HR — N20612 001 — MAR 19, 1999

LIDOCAINE; PRILOCAINE

AEROSOL; TOPICAL
EMLA
+ ASTRA PHARMS — 2.5%;2.5% — N20962 001 — FEB 04, 1999

DISC; TOPICAL
EMLA
+ ASTRA PHARMS — 2.5%;2.5% — N20962 001 — FEB 04, 1999

LISINOPRIL

TABLET; ORAL
ZESTRIL
ZENECA — 30MG — N19777 00 — JAN 26, 199

LITHIUM CARBONATE

CAPSULE; ORAL
LITHONATE
AB SOLVAY — 300MG — N16782 00
— 300MG — N16782 00

TABLET; ORAL
LITHIUM CARBONATE
AB PFIZER — 300MG — N16834 00
AB + — 300MG — N16834 00
LITHOTABS
AB + SOLVAY — 300MG — N16980 00
— 300MG — N16980 00

MEPERIDINE HYDROCHLORIDE

INJECTABLE; INJECTION
DEMEROL
AP + ABBOTT — 25MG/ML — N05010 00

ATTACHMENT 2
LETTER, JUNE 29, 1999

LAMIVUDINE

SOLUTION; ORAL
EPIVIR-HBV
+ GLAXO WELLCOME 5MG/ML N21004 001 DEC 08, 1998
+ 5MG/ML N20596 002 DEC 08, 1998

TABLET; ORAL
EPIVIR-HBV
+ GLAXO WELLCOME 100MG N21003 001 DEC 08, 1998
+ 100MG N20564 002 DEC 08, 1998

LEUCOVORIN CALCIUM

INJECTABLE; INJECTION
LEUCOVORIN CALCIUM
AP + ABBOTT EQ 10MG BASE/ML N40147 001 JUN 25, 1997
AP + BEDFORD EQ 200MG BASE/VIAL N40056 001 MAY 23, 1995

LEUCOVORIN CALCIUM PRESERVATIVE FREE
AP + ABBOTT EQ 10MG BASE/ML N40147 001 JUN 25, 1997
AP + BEDFORD EQ 200MG BASE/VIAL N40056 001 MAY 23, 1995
AP BIGMAR EQ 10MG BASE/ML N40286 001 FEB 26, 1999
AP EQ 200MG BASE/VIAL N40258 001 FEB 26, 1999

TABLET; ORAL
LEUCOVORIN CALCIUM
> ADD > AB INVAMED EQ 15MG BASE N75327 001 MAR 24, 1999

> ADD > LEVALBUTEROL HYDROCHLORIDE

> ADD > SOLUTION; INHALATION
> ADD > XOPENEX
> ADD > + SEPRACOR EQ 0.021% BASE N20837 001 MAR 25, 1999
> ADD > + EQ 0.042% BASE N20837 002 MAR 25, 1999

> ADD > LIDOCAINE

> ADD > FILM, EXTENDED RELEASE; TRANSDERMAL
> ADD > LIDODERM
> ADD > + HIND HLTHCARE 700MG/12HR N20612 001 MAR 19, 1999

LIDOCAINE; PRILOCAINE

AEROSOL; TOPICAL
EMLA
+ ASTRA PHARMS 2.5%;2.5% N20962 001 FEB 04, 1998

DISC; TOPICAL
EMLA
+ ASTRA PHARMS 2.5%;2.5% N20962 001 FEB 04, 1998

LISINOPRIL

TABLET; ORAL
ZESTRIL
ZENECA 30MG N19777 00[illegible] JAN 26, 199[illegible]

LITHIUM CARBONATE

CAPSULE; ORAL
LITHONATE
AB SOLVAY 300MG N16782 00
300MG N16782 00

TABLET; ORAL
LITHIUM CARBONATE
AB PFIZER 300MG N16834 00
AB + 300MG N16834 00
LITHOTABS
AB + SOLVAY 300MG N16980 00
300MG N16980 00

MEPERIDINE HYDROCHLORIDE

INJECTABLE; INJECTION
DEMEROL
AP + ABBOTT 25MG/ML N05010 0[illegible]

information regardless of the size of the proposed target patient population. A product may still be designated as an orphan by demonstrating that the financial criteria of the law are applicable, regardless of the number of patients affected.

P.L. 100-290 amended the Orphan Drug Act on April 18, 1988, and requires that the application for designation be made prior to the submission of an application for marketing approval, New Drug Application (NDA) or Product License Application (PLA). Prior to this amendment, the designation request could be filed at any time prior to FDA's approval to market the product.

Section 1205 of P.L. 104-188 reinstated the tax credits for clinical testing expenses of orphan drugs for the period July 1, 1996 to May 31, 1997 and allows these credits to be carried forward/back like some other business tax credits.

The Orphan Drug Final Regulations were published in the Federal Register on December 29, 1992, and became effective thirty days thereafter.

Orphan Drug Designation

In order for a sponsor to obtain orphan designation for a drug or biological product, an application must be submitted to OOPD, and the designation approved. The approval of an application for orphan designation is based upon the information submitted by the sponsor. A drug that has obtained orphan designation is said to have "orphan status." Each designation request must stand on its own merit. Sponsors requesting designation of the same drug for the same indication as a previously designated product must submit their own data in support of their designation request. The approval of an orphan designation request does not alter the standard regulatory requirements and process for obtaining marketing approval. Safety and efficacy of a compound must be established through adequate and well-controlled studies.

Incentives of the Orphan Drug Act

The Orphan Drug Act (P.L. 97-414, as amended) includes various incentives that have stimulated a considerable amount of interest in the development of orphan drug and biological products. These incentives include tax credits for clinical research undertaken by a sponsor to generate required data for marketing approval, and seven years of marketing exclusivity for a designated drug or biological product approved by the FDA.

Section 527 of the Orphan Drug Act provides a seven-year period of exclusive marketing to the first sponsor who obtains marketing approval for a designated orphan drug or biological product. Exclusivity begins on the date that the marketing application is approved by FDA for the designated orphan drug, and applies only to the indication for which the drug has been designated and approved. A second application for the same drug for a different use could be approved by FDA.

Final regulations on the tax credits were published in the Federal Register on October 3, 1988 (53 FR 38708), and the current version of these regulations are in Title 26, Code of Federal Regulations, Section 45c. The Internal Revenue Service administers the tax credit provisions, and specific questions about the interpretation of the law or regulations affecting the applicability of the tax credit provision of the Act should be directed to IRS. If more information on tax credits is needed, contact Pass Through and Special Industries Division, Office of the Chief Counsel, Internal Revenue Service, 1111 Constitution Avenue, NW, Washington, DC 20224; telephone is (202) 622-3120.

Protocol Assistance

Section 525 of the Orphan Drug Act provides for formal protocol assistance when requested by the sponsors of drugs for rare diseases or conditions. The formal review of a request for protocol assistance is the direct responsibility of the Center for Drug Evaluation and Research (CDER) or the Center for Biologic Evaluation and Research (CBER), depending on which Center has authority for review of the product. The Office of Orphan Products Development (OOPD) is responsible for insuring that the request qualifies for consideration under section 525 of the FFDCA. This includes determining "whether there is reason to believe the sponsor's drug is a drug for a disease or condition that is rare in the United States." A sponsor need not have obtained orphan drug designation to receive protocol assistance.

Once OOPD determines that the proposed compound is for a disease or condition that is rare in the U.S., the request will be forwarded to the responsible reviewing division for formal review and direct response. OOPD monitors the review process within the respective CDER/CBER reviewing division and, where possible, assists in resolving specific issues that may arise during the review process. It should be understood that protocol assistance provided under the Act does not waive the necessity for the submission of an Investigational New Drug Application (IND) by sponsors planning to conduct clinical trials with the product.

Research Grants

The FDA, through OOPD, funds the development of orphan products through its grants program for clinical studies. The Request for Applications (RFA) announcing availability of funds is published in the Federal Register each year - usually in June. Eligibility for grant funding is extended to medical devices and medical foods for which there is no reasonable expectation of development without such assistance. Applications are reviewed by panels of outside experts and are funded by priority score.

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September 7, 1999

BY FACSIMILE/CONFIRMATION COPY BY HAND

Ms. Laura E.W. Noble
Compliance Officer
Office of Compliance
Chemicals, Clothing, and Household Products Team
U.S. Consumer Product Safety Commission
4330 East-West Highway
Bethesda, Maryland 20814

Dear Ms. Noble:

This responds to the Commission's letter of August 19, 1999, concerning Lidoderm®, a prescription orphan drug in patch form to be marketed by Endo Pharmaceuticals, Inc. ("Endo").

The Commission's August 19th letter only confirms the importance of the requirement of the Poison Prevention Packaging Act (PPPA) that the Commission issue a special packaging standard (a) "by regulation," (b) after "it finds that ... the special packaging to be required by such standard is technically feasible, practicable, and appropriate," (c) after considering its reasonableness, available scientific, medical, and engineering data concerning the special packaging, the manufacturing practices of the industries affected, and the nature and use of the household substance, and (d) if it "publishes" its findings and reasons therefor. 15 U.S.C. § 1472(a)-(c). See also 16 C.F.R. § 1700.3.

Endo reiterates that, with respect to its applicability to lidocaine patches, and Endo's product in particular, the standard at 16 C.F.R. § 1700.14(a)(23) was not promulgated in compliance with the requirements of the PPPA, the Administrative Procedure Act (APA), and the agency's own regulations. Therefore, the Commission does not have the statutory authority to enforce the standard against Endo's lidocaine patch.

First Point in Letter

The first point in the August 19th letter is that "there was ample opportunity for all interested parties to comment upon this proposed rule."

Endo is not asserting that there was no "ample opportunity" to comment. Endo's position is that there was no opportunity for lidocaine patch marketers to comment because they were not "interested parties." Notice "must provide sufficient factual detail and rationale for the rule to permit interested parties to comment meaningfully." Florida Power & Light Co. v. United States, 846 F. 2d 765, 771 (D.C. Cir. 1988) (emphasis added); see also American Medical Ass'n v. Reno, 57 F.3d 1129, 1132 (D.C. Cir. 1995). The only lidocaine "patches" approved by the Food and Drug Administration (FDA) for marketing are Endo's patch and the Emla disc (see Attachment 2 to our letter of June 29, 1999). These products were not being marketed at the time the standard was promulgated. The Emla disc was not approved for marketing until February 4, 1998. Id. Endo's product was approved for marketing on March 19, 1999. Id. FDA did not even designate Lidoderm® as an orphan drug (this does not authorize marketing) until October 24, 1995, more than six months after the Commission published the final rule. See Attachment 1 to our letter of June 29, 1999.

Thus, today's marketers of lidocaine "patches," including Endo, were not "interested parties" when the standard was promulgated. If they were not "interested parties," they cannot be deemed to have received notice and an opportunity to comment meaningfully. Indeed, they had no opportunity at all to comment.

The APA provides that a reviewing court may "hold unlawful and set aside agency action ... found to be ... without observance of procedure required by law." 5 U.S.C. § 706(2)(D). An agency's failure to use notice-and-comment rulemaking is subject to "strict scrutiny" by a reviewing court. Environmental Defense Fund, Inc. v. Gorsuch, 713 F.2d 802, 816-17 (D.C. Cir. 1983) ("Any claim of exemption from APA rulemaking requirements 'will be narrowly construed and only reluctantly countenanced.'"); Natural Resources Defense Council, Inc. v. EPA, 683 F.2d 752, 760 (3d Cir. 1982) ("'[R]eview of an agency's procedural compliance with statutory norms is an exacting one.' *NRDC v. SEC*, 606 F.2d 1031, 1048 (D.C. Cir. 1979). The exacting standard applicable in

determining whether an agency has failed to comply with the procedural requirements for its action contrasts with the deferential standard applicable to substantive challenges to agency action.").

The Commission's regulations set forth the PPPA's requirements for establishing a special packaging standard, and confirm that such agency action "shall be in accordance with section 5 of the [PPPA] as to procedure." 16 C.F.R. § 1700.3. Section 5 of the PPPA, 15 U.S.C. § 1474(a), requires the Commission to use the notice-and-comment procedure of section 553 of the APA, 5 U.S.C. § 553(b)(3). It is a well-established principle that agencies must follow their own regulations. Vitarelli v. Seaton, 369 U.S. 535, 545 (1959); Service v. Dulles, 354 U.S. 363, 388 (1957); Saddler v. Department of Army, 68 F.3d 1357, 1358 (Fed. Cir. 1995).

Where an agency fails to abide by its own regulations, a reviewing court should set the resulting agency action aside. Kelly v. Railroad Retirement Bd., 625 F.2d 486, 492 (3d Cir. 1980) ("[f]ailure to comply with its regulations renders the agency's act null"); Union of Concerned Scientists v. Atomic Energy Comm'n, 499 F.2d 1069, 1082 (D.C. Cir. 1974) ("an agency's failure to follow its own regulations is fatal to the deviant action"); Doyle v. Brock, 632 F. Supp. 256, 263 (D.D.C. 1986) ("[a]gency action inconsistent with the regulations must be overturned"), aff'd, 821 F.2d 778 (D.C. Cir. 1987). The D.C. Circuit has said it very eloquently:

> [I]t is elementary that an agency must adhere to its own rules and regulations. *Ad hoc* departures from those rules, even to achieve laudable aims, cannot be sanctioned ... for therein lie the seeds of destruction of the orderliness and predictability which are the hallmarks of lawful administrative action.

Reuters Ltd. v. FCC, 781 F.2d 946, 950-51 (D.C. Cir. 1986).

Second Point in Letter

The second point in the August 19th letter is that the regulation "is quite clear" because it mentions "products containing ... lidocaine" without any qualification other than the amount of lidocaine.

This agency statement ignores the context in which the regulation was promulgated and dismisses the fact-finding requirements of the PPPA. Regardless of the "clarity" of a regulation, it will not be valid if it is not consistent with the statute under which it was promulgated. See, e.g., United States v. Larionoff, 97 S. Ct. 2150, 2156 (1977); Webb v. Hodel, 878 F.2d 1252, 1255 (10th Cir. 1989).

Third Point in Letter

The third point in the August 19th letter is that "it is apparent that the Commission intended to include all delivery systems ... including lidocaine-containing patches." The support given for this allegation is that comments were filed seeking exclusion of some dosage forms but the Commission "expressly determined that the rule should not exempt certain products because [of] the potential for injury."

First, this simply shows that the Commission did not refuse to exempt lidocaine patches because no comments mentioning lidocaine patches were filed or could have been filed. Second, a "potential for injury" is only one of the findings the Commission is required to make. Thus, even assuming, for the sake of argument, that the Commission made a finding that lidocaine patches had a "potential for injury," that would not make the standard legally applicable to such products because the other required findings were not made for lidocaine patches. Moreover, the degree or nature of the hazard of a substance to children must be assessed "by reason of its packaging." 15 U.S.C. § 1472(a)(1) (emphasis added). The Commission did not consider lidocaine-patch "packaging," as required by the PPPA and its own regulations.

The "all delivery systems" that the commission "intended to include" were the delivery systems being marketed at that time. To the extent that the Commission believes that it may apply a special packaging standard to any and all new delivery systems that come into the market after the standard is promulgated, the provisions of the PPPA do not support that position. The PPPA requires the Commission to make special packaging findings based on the "packaging" for the product.

Finally, it simply flies in the face of logic to contend that the Commission "intended" to include a delivery system that did not exist at the time the regulation was promulgated. One cannot "intend" to do that about which one has no knowledge.

Fourth Point in Letter

The fourth point in the August 19th letter is that because "there are lidocaine ... patches ... currently ... in child-resistant packaging," it "is evident that it is technically feasible, practicable, and appropriate for lidocaine patches to be in child-resistant packaging." The letter also states that "lidocaine's action occurs through topical application to the affected area."

First, the PPPA does not allow the Commission to establish a standard simply by stating in a letter to one company that "it is evident" that the special packaging is technically feasible, practicable, and appropriate. The law requires the Commission to

make this and other specific findings by notice-and-comment rulemaking. The PPPA and APA's requirements are intended to ensure agency compliance with the Due Process Clause of the Constitution of the United States. Surely the Commission is not asserting that the Constitution has no bearing on its activities.

Second, Endo's product is not a topical product—it is a transdermal, extended release patch that does not function as a topical product. The FDA-approved package insert for Lidoderm® (copy attached) states:

> The penetration of lidocaine into intact skin after application of LIDODERM® is sufficient to produce an analgesic effect, but less than the amount necessary to produce a complete sensory block.

Unlike other lidocaine products, Lidoderm® does not work by having a topical anesthetic effect—Lidoderm® has a transdermal, analgesic, localized effect, for the relief of pain associated with post-herpetic neuralgia, which is a rare condition in the U.S. As a result, what might be feasible, practicable, and appropriate for other lidocaine products is not necessarily feasible, practicable, and appropriate for Endo's lidocaine patch. This agency statement is evidence of the perils involved when an agency takes regulatory action without following the required due process requirements imposed by Congress and the Constitution.

For an agency regulation to survive an "arbitrary and capricious" analysis, the agency must, at a minimum, "examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'" Motor Vehicle Manufacturers Ass'n of the United States v. State Farm Mutual Automobile Insurance Co., 463 U.S., 29, 43 (1983) (emphasis added) (quoting Burlington Truck Lines, Inc. v. United States, 371 U.S. 156, 158 (1962)). In this case, the Commission cannot say that application of the standard to Endo's product is not arbitrary and capricious. It is impossible for the Commission to assert that there is a "rational connection between the facts found and the choice made" because the Commission has made no findings at all for lidocaine patches such as Endo's product.

Also, "[i]n addition to requiring a reasoned basis for agency action, the 'arbitrary or capricious' standard requires an agency's action to be supported by the facts in the record." Olenhouse v. Commodity Credit Corp., 42 F.3d 1560, 1575 (10th Cir. 1994) (emphasis added). Here, with the possible exception of the findings relating to lidocaine's toxicity (which is only one of the issues the Commission is required to address), there are no findings in the rulemaking record that support the Commission's position that the standard applies to Endo's product.

imposed on a product simply because the marketer is aware that there are toxicity hazards. Even assuming that such awareness is relevant when the Commission makes a hazard determination, it would not be sufficient to cover all of the findings that the PPPA requires the Commission to make. The PPPA requires that the Commission make the toxicity hazard finding by notice-and-comment rulemaking and considering the packaging for the product. This the Commission has failed to do for lidocaine patches.

Second, Endo is not using the warning to comply with the standard because the standard does not apply to Endo's product.

Conclusion

The Commission's regulation for lidocaine products, as applied to lidocaine patches such as Endo's, was not promulgated in accordance with the requirements of the PPPA, the APA, and the Commission's regulations. Because lidocaine patches were not considered by the Commission at the time the rule was issued, and could not have been considered because they were not being marketed at that time, Endo's product is not subject to the standard for lidocaine products.

Final Remarks

We are appalled at the Commission's nonchalant dismissal of the requirements of the PPPA. The Commission's response to our June 29, 1999 letter completely ignores Endo's legal arguments. Briefly summarized, the Commission's position is that the standard applies to Endo's product because (1) the Commission promulgated a standard for "products containing ... lidocaine," and (2) although lidocaine patches did not exist at the time the standard was promulgated, it is desirable to apply the standard to such products because they may present a safety hazard to children. The agency has chosen to ignore that, under the principles of administrative law, the standard may not be legally applied to lidocaine patches simply because the agency considers it a laudable thing to do. No reviewing court will countenance an agency's failure to comply with the procedural and substantive requirements imposed upon it, however convenient and efficient such failure might be.

Endo will vigorously defend its product against any attempts to enforce the standard against it. Any such enforcement attempt would not be lawful because it would be based on an invalid/misinterpreted regulation. See, e.g., Aerolineas Argentinas v. United States, 77 F.3d 1564, 1574-76, 1578 (Fed. Cir. 1996).

Endo's failure to make the product available could result in its losing orphan drug marketing exclusivity under the Federal Food, Drug, and Cosmetic Act (FDC Act). During

the seven years following marketing approval, orphan drug marketers must "assure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug" was approved. 21 U.S.C. § 360cc(b)(1). Also, since the product was approved in March, Endo has received well over 3,000 calls from sufferers of post-herpetic neuralgia asking when the only FDA-approved drug for their condition will be available to ease their pain and suffering. In order to meet the requirements of the FDC Act and the serious needs of these patients, Endo cannot delay the launch of the product.

Sincerely,

HYMAN, PHELPS & McNAMARA, P.C.
Counsel for Endo Pharmaceuticals, Inc.

By Samia N. Rodriguez

SNR/tee

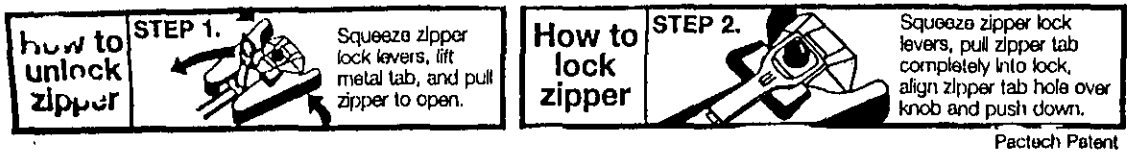
Attachment

ATTACHMENT 1
LETTER, SEPTEMBER 7, 1999

LIST OF ORPHAN PRODUCTS DESIGNATIONS AND APPROVALS

Through December 31, 1998

NAME Generic Name TN=Trade Name	INDICATION DESIGNATED	SPONSOR & ADDRESS DD=Date Designated MA=Marketing Approval
Levocarnitine TN= Carnitor	Treatment of zidovudine-induced mitochondrial myopathy.	Sigma-Tau Pharmaceuticals, Inc. 800 S. Frederick Avenue, Suite 300 Gaithersburg, MD 20877 DD=04/07/1997 MA= / /
Levomethadyl acetate hydrochloride TN= Orlaam	Treatment of heroin addicts suitable for maintenance on opiate agonists.	Biodevelopment Corporation 8180 Greensboro Drive, Suite 1000 McLean, VA 22102 DD=01/24/1984 MA=07/09/1993
Lidocaine patch 5% TN= Lidoderm Patch	For relief of allodynia (painful hypersensitivity), and chronic pain in post-herpetic neuralgia.	Hind Health Care, Inc. 3707 Williams Rd., Suite 101 San Jose, CA 95117 DD=10/24/1995 MA= / /
Liothyronine sodium injection TN= Triostat	Treatment of myxedema coma/precoma.	SmithKline Beecham Pharmaceuticals One Franklin Plaza P.O. Box 7929 Philadelphia, PA 19101 DD=07/30/1990 MA=12/31/1991
Lipid/DNA human cystic fibrosis gene TN=	Treatment of cystic fibrosis.	Genzyme Corporation P.O. Box 9322 One Mountain Road Framingham, MA 01701 DD=04/08/1996 MA= / /
Liposomal Cyclosporin A TN= Cyclospire	For aerosolized administration in the prevention and treatment of lung allograft rejection and pulmonary rejection events associated with bone marrow transplantation.	Vernon Knight, M.D. Baylor College of Medicine, Dept. of Molecular Physiology One Baylor Plaza Houston, TX 77030 DD=04/30/1998 MA= / /
Liposomal N-Acetylglucosminyl-N-Acetyl muramly-L-Ala-D-isoGln-L-Al a -gylcerolidpalmitoyl TN= ImmTher	Treatment of osteosarcoma.	Endorex Corp. 900 North Shore Drive Lake Bluff, IL 60044 DD=06/10/1998 MA= / /
Liposomal N-Acetylglucosminyl-N-Acetyl muramly-L-Ala-D-isoGln-L-Al a -gylcerolidpalmitoyl TN= ImmTher	Treatment of Ewing's sarcoma.	Endorex Corp. 900 North Shore Drive Lake Bluff, IL 60044 DD=06/10/1998 MA= / /
Liposomal amphotericin B TN= AmBisome	Treatment of cryptococcal meningitis.	Fujisawa USA, Inc. 3 Parkway North Center Deerfield, IL 60015 DD=12/10/1996 MA=08/11/1997



To Pharmacist:

This product **MUST** be dispensed in this child-resistant pouch.
Please place all envelopes and the package insert in this child-resistant pouch prior to dispensing and discard the carton.

CHILD-RESISTANT POUCH
9 x 12in

Endo®

Endo Laboratories

July 21, 2000

Re: Lidoderm® (lidocaine patch 5%) Packaging Change

Dear Pharmacist,

The U.S. Consumer Product Safety Commission (CPSC) has taken the position that Lidoderm® is subject to the Poison Prevention Packaging Act regulations. The purpose of this letter is to advise you of a new procedure to follow in dispensing Lidoderm® at the request of the CPSC.

Endo Laboratories is developing a new, child-resistant, commercial package for Lidoderm®. Until the new packaging is available, we are providing separate child-resistant pouches for use when dispensing Lidoderm®. We are notifying you of this development at this time and ask for your cooperation during the transition.

Effective August 1, 2000, this child-resistant pouch will be inside each carton of Lidoderm® shipped to our customers. Please call 1-800-462-3636 to receive a complimentary supply of child-resistant pouches to be used to dispense the supply of Lidoderm® that is currently on your shelves.

Until the new package is available, you must dispense Lidoderm® in the child-resistant pouch included in each box of Lidoderm®, unless the customer requests otherwise. Each box of Lidoderm® contains six envelopes. Whether the prescription calls for one or more envelopes (each envelope contains five individual patches), please place the prescribed amount in the child-resistant pouch and make sure that the pouch is properly closed when you dispense the prescription. For your convenience, we are including instructions for operation of the child-resistant mechanism on the top of each pouch. In addition, labels with dispensing instructions have been applied to the lid of each box of Lidoderm®. Once the box is empty, please discard it. Additional pouches are available by calling the number listed above.

Thank you for your assistance and cooperation. We will keep you informed as we progress in the development of the new packaging for Lidoderm®. If you have any questions or concerns, please call Endo at 1-800-462-3636.

Sincerely,

Matthew Davis, MD, RPh
Director – Medical Affairs

Enclosure: Lidoderm® Package Insert

223 WILMINGTON WEST CHESTER PIKE CHADDS FORD, PENNSYLVANIA 19317 Tel: 610-558-9800

ATTENTION PHARMACIST:
Child-Resistant Pouch Inside Carton
This product **MUST** be dispensed in the enclosed child-resistant pouch. Please place all envelopes and the package insert in the enclosed child-resistant pouch prior to dispensing and discard the carton.

70615/PF

TAB B

DRAFT 5/4 Billing Code 6355-01

CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

POISON PREVENTION PACKAGING;

NOTICE OF STAY OF ENFORCEMENT FOR LIDODERM® PATCH

AGENCY: Consumer Product Safety Commission.

ACTION: Stay of Enforcement.

SUMMARY: This notice announces the Commission's decision to stay enforcement of special packaging requirements for the orphan drug, Lidoderm®. The Commission will stay enforcement as long as the following conditions continue: (1) the individual Lidoderm® patches continue to be marketed in an outer package that is child-resistant ("CR"); (2) the outer CR pouches bear a label warning of the toxicity of lidocaine and the importance of storing unused patches in the CR pouch; (3) Lidoderm® remains an orphan drug for the treatment of post-herpetic neuralgia ("PHN"); (4) Lidoderm® continues to be manufactured at its present location under the operating conditions described in Endo Pharmaceutical's ("Endo") petition; and (5) Endo monitors poisoning data and immediately notifies the Commission of any incidents.

DATE: The stay will be effective on _____ **[insert date of publication in the Federal Register]**

FOR FURTHER INFORMATION CONTACT: Gerri Smith, Office of Compliance, Consumer Product Safety Commission, Washington, D.C. 20207; telephone (301) 504-0608, extension 1160.

SUPPLEMENTARY INFORMATION:

A. Background

Under the Poison Prevention Packaging Act ("PPPA"), the Commission has the authority to require special packaging for drugs (as well as certain other household products) if it finds that child resistant ("CR") packaging is necessary to protect children from serious personal injury or illness from handling using or ingesting the drug and that CR packaging is technically feasible, practicable and appropriate. 15 U.S.C. 1472(a). In 1995, the Commission issued a rule requiring CR packaging for lidocaine products with more than 5 milligrams (mg) of lidocaine in a single package. 16 CFR 1700.14 (10).

Lidoderm® is a dermal patch that contains lidocaine. Each Lidoderm® patch contains 700 mg lidocaine. Lidoderm® is marketed in the form of five patches inside a non-CR resealable foil envelope to maintain the integrity of the product. One non-CR carton of Lidoderm® contains six envelopes (each envelope contains five patches) for a total of 30 patches per carton.

In May 1999, Commission staff discovered that Lidoderm® was being packaged in non-CR packaging and notified the distributor, Endo Pharmaceuticals Inc. ("Endo") of the special packaging requirement for lidocaine products. To comply with the PPPA, the immediate container for a product that requires special packaging must be CR. Thus, for Lidoderm® patches, each patch must be packaged in an individual CR pouch or a single resealable CR pouch must contain all of the patches (i.e., no carton and no

foil envelope, only a resealable CR pouch). At Endo's request, the Commission granted Endo a temporary stay of enforcement on May 15, 2000, on the condition that Endo provide pharmacists with an outer CR package to dispense the product while it was developing a plan and timeline to package each patch in a CR pouch.

On August 14, 2000, Endo petitioned the Commission for a partial exemption for Lidoderm® from special packaging requirements stating that "it is not practicable to market each Lidoderm® patch in a child-resistant envelope." The petitioner argues that to do so is cost prohibitive and would force it to discontinue production of Lidoderm®. Endo asks for an exemption so that it may replace the non-CR carton with the CR pouch so that the six envelopes (5 patches per envelope) are marketed in the CR pouch, not in the non-CR carton.

B. The Product

Lidoderm® is a lidocaine-containing dermal patch available only by prescription. It is manufactured by Teikoku Seiyaku, Co., Ltd., a Japanese company, and the only manufacturer the Food and Drug Administration ("FDA") has approved to manufacture Lidoderm®. Endo is the only distributor the FDA has approved for Lidoderm®. The FDA designated Lidoderm® as an orphan drug on October 24, 1995 and approved it for marketing on March 19, 1999. Endo started marketing Lidoderm® on September 15, 1999. Orphan drugs are intended for rare diseases affecting less than 200,000 people or affecting more than 200,000, but for which there is no

expectation that the costs of drug development will be recovered from sales. The Orphan Drug Act encourages the development of orphan drugs, through economic incentives such as tax credits for clinical research and seven years of marketing exclusivity.

Lidoderm® is prescribed to treat post-herpetic neuralgia ("PHN"), a rare, chronic condition that results from nerve injury caused by shingles. Shingles occurs following reactivation of the herpes zoster virus (the same virus responsible for chickenpox) and is characterized by painful fluid-filled skin blisters. PHN is more common in the elderly. Approximately 10% of all patients with shingles develop PHN. Endo estimates that about 200,000 Americans have PHN. There is no cure for PHN, and treatment is aimed at controlling the pain by various methods including drug therapy (e.g., analgesics, antidepressants, topical anesthetics, and anticonvulsants), acupuncture, and nerve block.

Each carton of Lidoderm® contains 30 patches packaged in six resealable foil envelopes with five patches per envelope. Neither the carton nor the individual envelopes are CR. Currently, Endo is including a CR reclosable pouch large enough for the six envelopes in each carton. Each Lidoderm® patch is 22 square inches (10 cm x 14 cm) and contains 700 mg of lidocaine. The amount of lidocaine systemically absorbed from Lidoderm® depends on both the duration of exposure and the surface area of skin covered. The recommended dose is up to three patches at one time only once for up to 12 hours in a 24-hour period. Patches

may be cut into smaller sizes prior to removal of the release liner. The petitioner did not provide data related to the stability of the lidocaine in a cut or used patch, but instructions on the product envelope advise that the patch adhesive contains water and will dry out if the package is left open.

According to the petition, Lidoderm® is unlike other patch systems in that the lidocaine in Lidoderm® is not contained in a reservoir, but is embedded in the patch adhesive. Therefore, the patch releases a low level of lidocaine into the skin over a long time period ensuring that it produces analgesia (pain reduction) rather than anesthesia (numbness). Since only a small percentage (3% ± 2%) of lidocaine is absorbed dermally from the Lidoderm® patch when used therapeutically, about 95% of the lidocaine will remain in a used patch. Endo states that the lidocaine is less accessible from this patch system than from other formulations (such as, creams and liquids) and that a child would need to chew or suck on the patch for some time before any lidocaine would be absorbed through the mouth or swallowed. However, there are no oral absorption data indicating the extent of oral exposure necessary for a child to absorb a toxic dose. Endo provides a warning with the product to store and dispose of Lidoderm® out of the reach of children and pets.

C. Endo's Request

In its petition, Endo asks essentially that the temporary stay of enforcement granted by the Commission on May 15, 2000, be

made a permanent exemption from special packaging requirements. Endo argues that full compliance with the PPPA, which requires that the immediate container of a lidocaine-containing drug be CR, would be cost-prohibitive. Endo maintains that the costs of new equipment, plant re-engineering, and testing for FDA approval are prohibitive and would force them to discontinue marketing Lidoderm®. Teikoku estimates a total cost of [redacted] for the changes required to place each patch in a CR pouch. This includes the cost of: 1) four new envelope processing machines; 2) producing three FDA submission batches; 3) extended specification compliance testing on all three batches; 4) accelerated stability testing; and 5) real-time stability testing. The petitioner maintains that "manufacturing and packaging one patch per envelope would result in [redacted] in the cost of manufacturing Lidoderm® because there would be significant increases in the amount of labor and materials."

Endo also argues that it would take five times longer than the current packaging method to produce an equivalent amount of Lidoderm® in individual CR pouches. Endo states that this change in the production schedule for Lidoderm® is an "undue burden" for Teikoku because it would affect Teikoku's production of other products. Teikoku is unwilling to allow another manufacturer to take over production because the manufacturing process for Lidoderm® is proprietary. CPSC has not been able to verify the accuracy of Endo's cost estimates. However, Endo maintains that it will discontinue production of

Lidoderm® if forced to place each patch in CR packaging. If that were to happen, Lidoderm® would no longer be a therapeutic option for PHN patients.

D. PPPA Requirements for an Exemption

The Commission's regulations provide for a company or other interested persons to submit a petition requesting an exemption from PPPA requirements. 16 CFR Part 1702. Those rules require a petitioner to provide a justification for the exemption based on one or more of the following grounds: (1) special packaging is not necessary to protect children from serious injury or illness from the substance; (2) special packaging is not technologically feasible, practicable, or appropriate for the substance; and/or (3) special packaging is incompatible with the substance. 16 CFR 1702.7. Similarly, the Commission's rules provide that if the Commission finds that a petitioner has presented "reasonable grounds" for an exemption, it shall publish a proposed amendment exempting that substance from special packaging requirements. "Reasonable grounds" are:

> information and data sufficient to support the conclusion that:
> (a) The degree or nature of the hazard to children in the availability of the substance, by reason of its packaging, is such that special packaging is not required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting the substance, or
> (b) Special packaging is not technically feasible, practicable, or appropriate for the substance, or
> (c) Special packaging is incompatible with the particular substance.

16 CFR 1702.17.

In its petition, Endo states as its justification that "it

is not practicable to market each Lidoderm® patch in a child-resistant envelope." Endo argues that the high cost and practicable difficulties, discussed above, packaging each individual Lidoderm® patch in a CR container justify an exemption.

Endo states that there have been no reports of adverse events or accidental exposures of Lidoderm® to children. Although Endo states that Lidoderm® does not present the same degree of poisoning risk to children as other lidocaine products, Endo does not argue and does not provide any data indicating that the lidocaine in Lidoderm® patches is not toxic to children. Thus, Endo does not seem to be relying on lack of toxicity to children as a justification for an exemption.

Legislative history of the PPPA indicates that the term "practicability" means that "special packaging meeting the standard would be susceptible to modern mass-production and assembly-line techniques." S. Rep. 845 91st Cong., 2d Sess 10 (1970). Endo does not argue that Lidoderm® cannot be produced with CR packaging that complies with the PPPA. Rather, Endo asserts that such packaging would be so costly that it could not continue to market Lidoderm®. Thus, the Commission cannot make the requisite finding that CR packaging would not be practicable for Lidoderm® that would justify an exemption under the Commission's regulations.

E. Stay of Enforcement

Endo has, however, presented information indicating the need

for the orphan drug Lidoderm®, the prohibitive cost involved in CR packaging for each Lidoderm® patch, the limited market for the product, and the protection for children that would be provided by packaging Lidoderm® patches in an outer CR package. The Commission finds that these circumstances justify the stay of enforcement. The stay will be issued with the following conditions:

1. The individual Lidoderm® patches must continue to be marketed in an outer CR pouch that contains six envelopes with five patches in each envelope;

2. The outer CR pouches must bear a label warning of the toxicity of lidocaine and the importance of storing unused patches inside the CR pouch to protect children from accidental exposure;

3. Lidoderm® must remain an orphan drug for the treatment of post-herpetic neuralgia ("PHN");

4. Lidoderm® must continue to be manufactured at its present location at Teikoku under operating conditions described in Endo's petition; and

5. Endo must monitor poisoning data and immediately notify the Commission of any incidents.

Dated: _____

_____
Sadye E. Dunn, Secretary
Consumer Product Safety Commission