THE UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION

February 15, 2005

Citizen Petition to Request Risk Assessment of SJS and TEN; and Investigation of Withholding of Safety Information regarding Risks of Stevens Johnson Syndrome and Toxic Epidermal Necrolysis Associated with Ibuprofen products; and the Addition of Critical Safety Information Relating to Serious Skin Reactions Associated with the Use of Ibuprofen to All Prescription and OTC Labeling;	**Docket No.** 2005P-0072

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CITIZEN PETITION

I. Introduction and Action Requested

Roger E. Salisbury, M.D., Michael "Rusty" Nicar, Ph.D., Randall Tackett, Ph.D., Steven Pliskow, M.D., Darlene and Andrew Kiss, and other parents of victims of SJS and TEN caused by ibuprofen products submit this petition to request action by the Food and Drug Administration (FDA) relating to the drug product, ibuprofen (Motrin, Advil, etc.). Further, petitioners are requesting that a full risk assessment of SJS and TEN associated with ibuprofen be conducted by the FDA. Petitioners are further seeking the FDA to conduct an investigation into the withholding of critical safety information regarding the risks of SJS and TEN associated with ibuprofen by McNeil Pharmaceuticals, manufacturer of Motrin products, and Wyeth Consumer Healthcare, manufacturer of Advil products, both from the FDA and the American public. Additionally, the petitioners request that FDA require the manufacturers of ibuprofen to amplify their prescription and OTC labeling to adequately warn prescribers, health care professionals and consumers of the increased risk of Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) associated with ibuprofen that has been established in the scientific literature since 1978 through the present. Further, petitioners request that additional warnings and instructions be provided in the Warnings and Precautions section of any prescription labeling for all ibuprofen products sold in

the U.S. to include a specific warning about the risk of serious skin reactions like SJS and TEN, and to disclose to physicians and consumers instructions to discontinue any/all ibuprofen product(s) at the first sign of a rash, mucosal blisters or sores in the mouth, eyes, throat, or genitalia, and any unexplained or persistent fever.

The proposed actions include the addition of a bolded Black Box Warning in the prescription labeling to comply with 21 CFR 201.57, and the dissemination of "Dear Doctor" and "Dear Healthcare Professional" letters to alert prescribers, pharmacists, medical associations, burn centers, and hospitals to this critically important information. The Petition also requests amplification of multiple sections of the OTC label for ibuprofen products, including placement of critical information regarding the risks of SJS and TEN associated with ibuprofen in the "Warnings" and "Stop Use" sections on all ibuprofen products sold in the U.S. (21 CFR 201.66)

This Petition is submitted pursuant to 21 CFR 10.30, and relates to Sections 201(n), 502 (a), 502 (f)(1) and 505 of the Federal Food, Drug and Cosmetic Act; and 21 CFR 201.57 and 21 CFR 201.66.

II. Statement of Factual Grounds

A. The Current Ibuprofen Labeling Fails to Comply with FDA Labeling Requirements

The Federal Food, Drug and Cosmetic Act and the Code of Federal Regulations provide specific requirements for the content and format of labeling materials relating to prescription drug products. Pursuant to 21 CFR 201.57, the **Warnings** section must describe all serious adverse reactions and potential safety hazards, limitations in use imposed by them, and actions to be taken if these events should occur. Events leading to serious injury or death may be placed in the Warnings section in a prominently displayed box for added emphasis.

FDA regulations note that pharmaceutical product labeling must be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug. A causal relationship need not have been provided. In order to alert prescribers to new warnings as soon as possible, FDA also permits manufacturers to add new warnings to their labeling without first securing FDA approval (21 CFR 314.70).

The current labeling for prescription ibuprofen products does not provide any information relating to SJS and TEN in the Warnings (or even the Precautions) section of the insert. These sections are required to include the most critical information relating to product safety and the steps to be taken to ensure safe product use. Obviously, these sections of the package insert for prescription ibuprofen products should describe the increased risk of SJS and TEN associated with ibuprofen that has been established in the scientific literature, and in conjunction with the rising numbers of serious skin reactions associated with

ibuprofen use and precautionary procedures to halt progression of these events. Based on available literature and adverse event data, this information should have been added to the Warnings section of the labeling several years ago. Because toxic epidermal necrolysis has a 30% mortality rate and has been reported to be as high as 80% in certain populations, it is important to provide warnings and instructions in the prescription package inserts for ibuprofen products to alert the prescriber to these risks and steps to reduce the harm from these life-threatening and fatal reactions.

Other prescription package inserts have such warnings and precautions, even though their risks of SJS and TEN are lower than ibuprofen. For example, Zithromax (azithromycin) carries a SJS and TEN warning, but the scientific literature reports that it has a lower relative risk for SJS and TEN than ibuprofen. Moreover, the FDA has approved a black box warning for the COX-II NSAID Bextra to specifically warn about the risk of SJS and TEN associated with Bextra, and we believe that the same warning should be placed on prescription ibuprofen products based on the scientific evidence that is available in the spontaneous adverse event databases and the scientific literature.

SJS and TEN are adverse events that are noted in the package insert for prescription ibuprofen products in the in the Adverse Reactions section. However, there is no discussion or information relating to the magnitude and severity of these events in the Warnings section, or any discussion about the increased risks of SJS

and TEN that as been established in the scientific literature, as well as the rise in case reports in the scientific evidence observed over the last several years. The precautions to be taken to halt the progression of early symptoms of SJS and TEN are also not specifically described in any ibuprofen labeling, whether prescription or OTC.

FDA laws and regulations also specify the format and content of OTC product labeling pursuant to 21 CFR 201.66. Because medical intervention does not usually accompany OTC use, specific sections are available in OTC labeling to assist patients with recognition of potentially serious adverse events and to understand those situations in which drug use should be stopped and medical attention should be sought.

Unfortunately, the current U.S. OTC labeling for ibuprofen products does not provide any description or information relating to EM, SJS, or TEN. As such, patients are not alerted to the severity of these skin reactions and are not instructed to discontinue all ibuprofen use if/when any of the early symptoms of SJS and TEN occur.

Ibuprofen manufacturers cannot reasonably argue that the current Allergy Alert in the OTC label is in any way related to SJS and TEN. A review of the New Drug Applications submitted by these manufacturers confirms that the FDA considered the allergy alert to be intended for anaphylaxis related events which occur in aspirin sensitive patients. The allergy alert statements on the ibuprofen

labeling are not directed to SJS/TEN events. However, if aspirin sensitivity is deemed to necessitate a Warning statement, then the ibuprofen-related SJS/TEN events certainly warrant similar labeling attention. After all, there are significantly more skin-related events than allergic reactions associated with ibuprofen use.

Both the prescription and OTC labels employed in the U.S. fail to comply with the labeling requirements needed to ensure patient safety. Paragraph C provides an analysis of the international labeling employed with ibuprofen products. It will be seen that U.S. prescribers and patients are provided with substantially less information relating to SJS and TEN than patients receiving ibuprofen outside the United States. Furthermore, to our knowledge, McNeil Pharmaceuticals and Wyeth Consumer Healthcare have not filed this foreign labeling with the FDA in their Annual reports for their respective pediatric ibuprofen products to alert the FDA that they employ different labeling in foreign countries.

B. The Medical and Scientific Literature Confirm Causal Relationship between SJS and TEN associated with Ibuprofen, as well as increasing risks of Serious Skin Reactions Associated with Ibuprofen Use.

Ibuprofen is an effective drug that is generally well tolerated in adults and children. It is effective for pain and inflammation in adults and for fever in children. FDA has rejected the applications for the pain indication for pediatric ibuprofen suspension submitted by McNeil and Wyeth in the past. However, using a new federal regulation instituted in 1994, both applications were approved by the

Agency based on extrapolation of data from adult studies of ibuprofen, and the pediatric formulation of ibuprofen was approved for prescription and OTC use for pain and fever. Under the supervision of a physician, the use of ibuprofen in treating fever should be reserved for those children with high or long-lasting fever. Under a physician's care, early signs of severe morbidity (eg., renal failure, toxic skin reactions) could be monitored for, and when they occur, the drug could be rapidly withdrawn and treatment commenced. OTC status for treatment of common fever in children, especially otherwise healthy children, affords a different benefit-risk balance. This benefit-risk would be quite favorable, even given the discretionary nature of mild – moderate fever pharmacotherapy, if it were not for two rare, but very severe adverse drug reactions, SJS and TEN.

Based on the review of NDAs, scientific literature and other relevant materials, we believe that substantial evidence for the causal relationship between ibuprofen and SJS and TEN existed when the first prescription pediatric formulations Pediaprofen and Children's Advil were approved in 1989. Substantial confirmation of that causal relationship has continued to accumulate over the ensuing years both in the scientific literature and in pharmacoepidemiology studies.

The casual relationship between NSAIDS and rare but severe skin reactions (SJS, TEN) is well-documented and recognized by the leaders of the dermatology community. Though the reactions rates are suspected to vary by sub-type of

NSAID, all have been implicated, including ibuprofen. Those facts have already been recognized by the FDA, McNeil and Wyeth so that the product labeling for prescription Children's Motrin and Children's Advil contains the following:

> *Incidence less than 1% (Probable causal relationship)*
>
> *"Skin and appendages" Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson's Syndrome, alopecia, exfoliative dermatitis, Lyell's syndrome (toxic epidermal necrolysis), photosensitivity reactions.*

Evidence in support of this causal relationship between ibuprofen and SJS and TEN are from clinical case reports that have been reported since the late 70's until present in adults and children. After 1995, substantial additional evidence of this relationship has been accumulated, much of it specific to ibuprofen. In addition to the case reports of ibuprofen induced SJS and TEN since 1995, the SCAR study group consisting of very well respected dermatologists and epidemiologists in the scientific community conducted a international case-control study that demonstrated a statistically significant causal relationship between ibuprofen and SJS and TEN with a RR of 5.3, 95% CI 1.2-25. (Mockenhaupt, et. al. 2003)

McNeil and Wyeth sponsored studies such as the Boston University Fever Study (BUFS) and the Children's Analgesic Medicine Project (CAMP) which were used in support of their applications for the Rx. to OTC switch, which were

approved in 1995 and 1996, respectively. While these studies were informative about the common safety profile of ibuprofen in the pediatric population, they were uninformative toward the assessment of the risk for rare and severe reactions such as SJS or TEN. Despite the request from the FDA to the sponsors to design these postmarketing safety studies (BUFS & CAMP) to evaluate the rare, but serious adverse events associated with pediatric ibuprofen, we further believe that these issues were not adequately studied. Moreover, McNeil and Wyeth have failed to provide the FDA full information regarding the safety issues surrounding serious skin reactions, including SJS/TEN that were not presented in their applications for their OTC pediatric formulations.

Evidence of causal relationship and increased risks were in existence prior to OTC switch of the pediatric formulation in 1995-1996 and thru the present

There was considerable experience with ibuprofen beginning with its U.S. approval for arthritis in adults in 1974. It rapidly became the most widely prescribed NSAID. Its common safety profile was excellent. There was, however, developing evidence for a number of rare but severe adverse outcomes associated with its' use. Most notably they are; severe skin reactions and kidney failure. The cumulative evidence base on SJS and TEN are presented in Tables 1-5. Regulatory milestones are noted on the relevant tables.

It is clear that the labeling change in 1982 that added SJS as "probably related" was based on a substantial set of accumulated evidence. The addition of TEN as being "probably related" in 1994 was based on both a better understanding the SJS-TEN continuum and further accumulated evidence.

Table 1: Accumulation of Knowledge of Risk of SJS/TEN in Adults associated with NSAIDs (1978 thru 1989)

WHAT	WHEN	HOW	How Strong	References
NSAIDS (Adults) & SJS/TEN	1983	Case reports of SJS/TEN	Suggestive (Signal)	FDA review (Judith Jones, 1983) - FDA-FOI, WHO, CSM - Skin ADEs (1974-1989) McNeil & Wyeth databases
NSAIDs (Adults) & SJS/TEN	1984-1987	Published case reports of SJS/TEN in literature	Supportive	(1)Stern R., et al., JAMA, Vol. 252, No. 11, pp. 1433-7, (1984); (2) Stern R., et al., Jour of Amer Acad Derma, Vol. 12, No. 5, Part 1, pp. 866-75, (1985); (3)Stern, RS, et al., Current Perspectives in Immunodermatology, Chapter 6, pp. 75-97 (1984); (4) O'Brien, WM, et. al., J Rheumatology, 12: pp. 13-20 (1985) (5) Roujeau J., Scand J Rheumatology, Suppl. 65, pp. 131-4, (1987); (6) Roujeau J., et al., Arch Dermatol, Vol. 123, pp. 1166-70, (1987); (7) Stern R., et al., Arch Dermatol, pp. 3-17, (1987)
NSAIDs (Adults) & SJS/TEN	1989	Published or sponsored studies	Supportive	(1) Stern R., et al., J Am Academy of Dermatology, Vol. 21, No. 2, Part 1, pp. 317-22, (1989);(2) Bigby, M, et. al., Primary Care, Vol. 16, No. 3, pp. 713-727 (1989)
Ibuprofen (Adults) & SJS/TEN	1983	Case reports of SJS/TEN	Supportive	- McNeil and Wyeth internal reports (1983); -UK CSM Roster of Skin

				ADEs (1969-1983) -FDA-FOI, WHO, CSM - Skin ADEs (1974-1989) Wyeth databases
Ibuprofen (Adults) & SJS/TEN	1978-1989	Published case reports	Supportive	**(1)** Sternlieb P., et al., NY State Jour of Med, pp. 1239-43, **(1978); (2)** Stern R., et al., JAMA, Vol. 252, No. 11, pp. 1433-7 **(1984); (3)** Stern R., et al., Jour of Amer Acad Derma, Vol. 12, No. 5, Part 1, pp. 866-76, **(1985); (4)** O'Brien, WM, et. al., J Rheumatology, 12: pp. 13-20 **(1985); (5)** Laing, et. al. J Am Acad Derm, 19: pp. 91-94 **(1988).**
"Probable Causal Relationship" for SJS in Adult RX Label for Motrin/Advil	1982	All of the above	Probable rate less than 1%	Addition to FPL for Motrin/Advil dated 1982

"Incidence less than 1% (Probable causal relationship)
"Skin and appendages" Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson's Syndrome, alopecia."

Table #2 :Accumulation of Knowledge of Risk of SJS/TEN in adults (1990 thru 1996)

WHAT	WHEN	HOW	HOW STRONG	REFERENCES
NSAIDS (Adults) & SJS/TEN	1990-1996	Case reports of SJS/TEN	Supportive	FDA-FOI, WHO, CSM - Skin ADEs (1990-1996) Wyeth databases
NSAIDS (Adults) & SJS/TEN	1990-1996	Published case reports in Literature	Moderate	**(1)** Roujeau, JC, J Am Acad Derm, 23:pp.1039-58 **(1990); (2)** Roujeau, JC, Arch Dermatol, Vol. 126, pp. 37-42 **(1990); (3)** Strom, BL et. al., Statistics in Medicine, vol. 10, pp. 565-576 **(1991); (4)** Stern, RS, et al., Immunology and Allergy

				Clinics of North America, Vol. 11, no. 3, pp. 493-507 **(1991);(5)** Schopf, et. al., Arch Dermatol, Vol. 127, pp. 839-842, **(1991); (6)** Roujeau, JC, et. al., Dermatology, 186:pp. 32-37 **(1993); (7)** Roujeau, JC, et. al. NEJM, Vol. 331, pp. 1272-1285 **(1994); (8)** Roujeau, JC, J Amer Acad Dermatol. Vol. 31, pp. 301-302 **(1994)**
NSAIDS (Adults) & SJS/TEN	1995	Published or sponsored studies	Strong	Roujeau, JC, et. al., NEJM, Vol. 333, pp.1600-1607 **(1995).**
Ibuprofen (Adults) & SJS/TEN	1990-1996	Case Reports	Supportive	FDA-FOI, WHO, CSM - Skin ADEs (1990-1996) McNeil & Wyeth databases
Ibuprofen (Adults) & SJS/TEN		Published case reports in Literature	Supportive	**(1)** Roujeau, JC, Arch Dermatol, Vol. 126, pp. 37-42 **(1990); (2)** Strom, BL et. al., Statistics in Medicine, vol. 10, pp. 565-576 **(1991); (3)** Strom, BL et. al., Arch Dermatol, Vol. 127, pp. 831-838 **(1991)**; **(4)** Halpern, SM, et.al., Adverse Drug React. Toxicol Rev., 12 (2): pp. 107-128 **(1993); (5)** Roujeau, JC, et. al. NEJM, Vol. 331, pp. 1272-1285 **(1994); (6)** Halpern, SM, et.al., Arch Dermatol., vol. 130, pp. 259-60 **(1994)**
Ibuprofen (Adults) & SJS/TEN		Published or sponsored studies	Moderate	Roujeau, JC, et. al., NEJM, Vol. 333, pp.1600-1607 **(1995).**
"Probable Causal Relationship" for TEN in Adult RX Label for	1994	All of the above	Probable rate less than 1%	Addition to FPL for Motrin/Advil dated 1994

Motrin/Advil				
"Probable Causal Relationship" for TEN in Pediatric RX Label for Motrin/Advil	1994	All of the above	Probable rate less than 1%	Addition to FPL for Pediatric Motrin/Advil dated 1994
Pediatric OTC prep marketed	1996	N/A	N/A	N/A

Incidence less than 1% (Probable causal relationship)
"Skin and appendages" Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson's Syndrome, alopecia, exfoliative dermatitis, Lyell's syndrome (toxic epidermal necrolysis), photosensitivity reactions. (1994 FPL)

Table 3: Accumulation of Knowledge of Risk of SJS/TEN in Adults associated with NSAIDs (1997 thru 6/2002)

WHAT	WHEN`	HOW	How Strong	References
NSAIDS (Adults) & SJS/TEN	1997-2002	Case reports of SJS/TEN	Supportive	FDA-FOI & WHO databases McNeil & Wyeth databases
NSAIDs (Adults) & SJS/TEN	1998-2002	Published case reports/reviews of SJS/TEN in literature	Moderate	**(1)** Paul, CN, et al., J Burn Care & Rehab., Vol. 19, pp. 321-33 **(1998); (2)** Bell, MJ, et. al., J Rheumatol, 25:pp. 2026-2028 **(1998); (3)** Carucci, JA, et. al., Int. J Dermatol, Vol. 38, pp. 228-239 **(1999); (4)** Fritsch, PO, et. al., Fitzpatrick's Dermatology in General Medicine, 5th. Ed., Vol. 1, Chap. 59, pp. 644-654 **(1999); (5)** Garcia-Doval;, I, et. al., Arch Dermatol., Vol. 136, pp. 323-327 **(2000); (6)** Wolkenstein, P, et. al., Dermatologic Clinics, Vol. 18, no. 3, pp. 485-495 **(2000); (7)** Svennson, CK, et. al., Pharmacol Rev., 53: pp. 357-379 **(2000)**
NSAIDs (Adults) &		Published or sponsored		

SJS/TEN		studies		
Ibuprofen (Adults) & SJS/TEN	1997-2002	Case reports of SJS/TEN	Supportive	FDA-FOI, WHO, McNeil & Wyeth databases
Ibuprofen (Adults) & SJS/TEN	1997-2002	Published case reports/reviews of SJS/TEN caused by ibuprofen	Moderate	**(1)** Salomon, D, et. al., Annals of Dermatology, 124 (Suppl.):S216-217 **(1997); (2)** Viard, I, et. al. , Journal of Science, Vol. 282, pp. 490-93 **(1998); (3)** Becker, D, Lancet, Vol. 351, pg. 1417, **(1998); (4)** Fritsch, PO, et. al., Fitzpatrick's Dermatology in General Medicine, 5th. Ed., Vol. 1, Chap. 59, pp. 644-654 **(1999); (5)** Garcia-Doval;, I, et. al., Arch Dermatol., Vol. 136, pp. 323-327 **(2000); (6)** Wolkenstein, P, et. al., Dermatologic Clinics, Vol. 18, no. 3, pp. 485-495 **(2000)**
Ibuprofen (Adults) & SJS/TEN	2002	Published studies		
Significant subsequent evidence			Strong	Mockenhaupt, et. al., J Rheumatol, Vol. 30, pp. 2234-40 **(2003)**

Table #4 - Accumulation of Knowledge of Risk of SJS/TEN from NSAIDS/Ibuprofen in Pediatrics

WHAT	WHEN	HOW	HOW STRONG	REFERENCES
Higher risk of severe rash in pediatrics	1994	Literature on Lamotrigine & other anti-convulsants	3 fold higher than adults	Dooley, 1994 Roujeau 1995 Besag, 1997 Guberman, 1999
Ibuprofen (Children) & SJS/TEN	1984 - 2002	Case reports	Supportive	FDA-FOI, WHO, McNeil & Wyeth databases
Ibuprofen (Children) & SJS/TEN	1984 - 2002	Published case reports in Literature	Strong (1999)	**(1));** Roujeau, JC, J Am Acad Derm., Vol. 23, pp. 1039-58 **(1990); (2)** Roujeau, JC, et. al., NEJM, Vol. 331, pp. 1272-1285

				(1994); (3) Power,et. al., Ophthalmology, Vol. 102, pp. 1669-1676 **(1995); (4)** Srivastava, M, et. al., Gastroenterology, Vol. 115, pp. 743-746 **(1998); (5)** Sheridan, RL, et. al., J Burn Care Rehab., Vol. 20, pp. 497-500 **(1999) (6)** Fritsch, PO, et. al., Fitzpatrick's Dermatology in General Medicine, 5th. Ed., Vol. 1, Chap. 59, pp. 644-654 **(1999); (7)** Wolkenstein, P, et. al., Dermatologic Clinics, Vol. 18, no. 3, pp. 485-495 **(2000); (8)** Sheridan, RL, et. al., Pediatrics, Vol. 109, pp. 74-78 **(Jan. 2000); (9)** Spies, M, et. al., Pediatrics, Vol. 108, pp. 1162-1168 **(2001)**
Ibuprofen (Children) & SJS/TEN		Published or sponsored studies	Non-informative	BUFS (Lesko, 1995) CAMP (submitted in NDA supplement only)
Probable Causal Relationship to SJS in label Children's Rx Advil	1987	N/A	N/A	Addition to FPL for Pediatric Motrin/Advil dated 1987
Pediatric OTC prep marketed	1994	N/A	N/A	No SJS/TEN warning, nor any 'cease and seek MD" advice
Probable Causal Relationship to TEN in Rx /NDA label Children's Advil	1994			Addition to FPL for Pediatric Motrin/Advil dated 1994
Constant risk on continued exposure	2000		Strong	Garcia-Doval, 2000 Stern, 2000

Recent evidence on Ibuprofen & SJS/TEN (pediatrics)	1999 & 2001	Published case-series	Extremely Strong	Sheridan, 1999 & 2001
	2004			Taghian, M, J Pediatrics, Vol. 145, pp. 273-276 **(2004)**

The Severe Cutaneous Adverse Reaction (SCAR) study

The SCAR study was a huge multinational effort to determine the etiology and risk factors for the most severe of the cutaneous reactions. The methodology was published by Kelly et.al, (1995), with the results published by Roujeau et.al. (1995), Auquier-Dunant et.al. (2002), and Mockenhaupt et.al.,(2003). The Roujeau study identified cases then assessed exposure to all drugs. They found oxicam NSAIDS highly statistically significant but the proprionic acid NSAIDS, though having an increased point estimate, fell short of statistical significance. The point estimate for ibuprofen was 4.5 (2/245 or 0.0082 over 2/1147 or 0.0017) though statistical significance was not reached. This was clearly a signal in the adult population. Note that isoxicam was removed from the French marketplace after being associated with 13 cases of TEN (Roujeau JC, 1990). That followed the removal of benoxaprofen from the U.S. market in 1982 for toxicity that included cases of TEN (Stern 1984).

Mockenhaupt et.al. (2003) reported on a component of the SCAR study, a population-based registry in Germany and on data from the US spontaneous reporting system. There were 373 diagnostically validated cases in the multi-

national case-control component and 950 in the German registry. The same questionnaire and definitions were used in both of these component studies.

In the case-control component 112 of 373 were exposed to an NSAID (excluding aspirin). The oxicams (RR 34, 95% CI: 11-105) were strongly associated with the greatest increase in risk for SJS and TEN. Of the non-oxicam NSAIDs with sufficient numbers of exposed cases, only diclofenac and ibuprofen has significantly increased risks of SJS and TEN. The relative risk for ibuprofen was 5.3 (95% CI: 1.2-25). For the propionic acid NSAIDS (including ibuprofen), they estimated the excess risk to be less than one case in a million exposures. . Given the number of children exposed to the pediatric formulations of OTC ibuprofen, the expected number of ibuprofen associated cases worldwide , even at 3 cases per million, could be sizable and of public health import.

The SCAR study (Roujeau et.al., 1995, and Mockenhaupt et.al., 2003) clearly implicates all NSAIDS, in varied intensity, in a causal relationship with SJS/TEN. Based solely on the SCAR studies, Roujeau, et. al.'s paper signaled ibuprofens' causal relationship, and Mockenhaupt, et. al.'s paper validated its statistical significance.

C. The International Labeling/Proposed Labeling For Ibuprofen Provide More Warnings Relating To Serious Skin Reactions and The Need For Immediate Patient Care.

The Therapeutics Products Directorate commissioned an expert panel to draft an updated Guidance Document: **Guidance for Industry – Basic Product Monograph Information for Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in 2003.**

Health Canada/TPD have proposed that all prescription NSAID manufacturers, including manufacturers of prescription ibuprofen products, would have to provide a specific warning about SJS and TEN in their respective package inserts. Comments were provided to Health Canada until September 9, 2003. Final implementation of this document is expected shortly. A copy of this Notice is attached hereto, and incorporated herein fully by reference as **Attachment 1.**

Labeling of foreign OTC ibuprofen products provides additional warnings that are not present on the domestic ibuprofen products. For example, McNeil/Johnson & Johnson market a product called Dolormin Ibuprofen Juice which is a non-prescription ibuprofen product sold in Germany. This product has a package insert that warns German consumers of side effects associated with this OTC product of rare but serious skin reactions, such as reddening and blister formation (e.g. erythema multiforme exudativum multiforme) which is bullous EM/SJS. Wyeth markets ibuprofen products known as Spalta in Germany that contain similar information to the public as well.

Further, Wyeth markets ibuprofen products in European countries, including the Netherlands that specifically mention SJS and TEN on the OTC labeling.

American consumers deserve to be provided with appropriate warnings about serious life-threatening side effects as provided to foreign consumers. This foreign labeling was revealed in lawsuits that have been filed against the makers of Children's Motrin and Advil, however, the makers have insisted that these documents remain confidential and are not to be disclosed to anyone, except those persons associated with the law firms or their staff.

Petitioners are requesting that the FDA obtain such foreign labels and that they be translated into English and disseminated to the public without delay so that such information can be viewed by the American public.

D. Incidence and Frequency of all SJS and TEN events and for Ibuprofen are More Frequent and have a Higher Mortality Rate than Reye Syndrome

The Aspirin and Reye Syndrome experience taught us that a low frequency event which is also life-threatening is critically important when a large and otherwise healthy population is exposed to a discretionary drug product. For decades, "Baby aspirin" was very important for treatment of childhood fevers. When a safer alternative that was just as effective, acetaminophen (APAP), was marketed, "Baby aspirin" became discretionary though still widely used. When the association with Reye Syndrome was discovered and confirmed, it made the benefit-risk balance unacceptable. That situation is almost exactly like this ibuprofen-SJS/TEN situation.

It is widely recognized that at therapeutic doses, APAP and Ibuprofen are equigesic. Many pediatric specialists use ibuprofen and APAP together or in alternating regimens to break high fever. Some specialists consider ibuprofen superior in these cases of high fever.

Analgesic-induced Reye syndrome is an exceedingly rare phenomenon and occurs more rarely than ibuprofen-induced SJS and TEN. The frequency of SJS has been estimated to be as high as 49-60/per million. (Strom, et. al., Statistics in Medicine, 1991) Moreover, a recent scientific paper has estimated that there are 5000 hospitalizations for patients with SJS and TEN that occur annually in the U.S. (Stern, RS, Pharmacoepidemiology and Drug Safety, 2005)

The absolute risk of Reye Syndrome has been estimated to be 6.2 per 100,000 (Cecil's Textbook of Medicine, 19th ed.) , while the absolute risk for SJS associated with ibuprofen exposure was reported from The Boston University Fever Study to be 7.2 per 100,000. Obviously, when comparing the absolute risk between Reye Syndrome and SJS caused by ibuprofen in the pediatric population, one must also consider the difference between the mortality rates between these two diseases. Reye Syndrome has an estimated mortality rate of 10%, while SJS and TEN range from 5%-30%, and up to 80% for TEN. A child exposed to ibuprofen that develops SJS and TEN has s greater likelihood of developing SJS and TEN, and is more likely to die from it than a child that develops Reye Syndrome from aspirin.

Yet, despite the lower risk of developing the disease and lower mortality rates, the FDA has required that all manufacturers of aspirin products contain a specific warning about Reye Syndrome, but they have not required any such warnings about SJS and TEN. The FDA must act now on these issues in order to serve the public's health in protecting American adults and children from the substantial risk of harm posed by SJS and TEN associated with ibuprofen and NSAIDs, not to mention the extraordinary healthcare costs associated with treating these diseases and the economic impact it has on causing permanent disability to American people afflicted with SJS and TEN.

E. Conclusion and Remedies Sought by Petitioners

The Kiss family is petitioning the FDA after their three year-old daughter Heather Kiss, died from toxic epidermal necrolysis caused by Children's Advil on March 17, 2003. Other parents of children who suffered permanent injuries from SJS and TEN associated with Children's Motrin and Advil are also joining the Kiss family in support of this petition. Additionally, scientists who are familiar with the regulatory history of McNeil Pharmaceutical and Wyeth Consumer healthcare's pediatric ibuprofen products, and the scientific literature regarding SJS and TEN, believe that there is major public health problem at issue with SJS and TEN associated with ibuprofen products that needs to be addressed immediately to protect the American public from the harm posed in the use of ibuprofen products

without an adequate warning and instructions regarding the risk of SJS and TEN associated with ibuprofen.

Unlike labeling employed outside the U.S., the U.S. labeling does not provide even minimal information relating to the increased risks described in the scientific literature, or the continued escalation in the numbers of adverse event reports describing serious skin reactions in adults and children receiving ibuprofen.

These reactions may quickly progress from a drug eruption and/or fever to the severe, life-threatening and fatal events associated with Stevens Johnson Syndrome and Toxic Epidermal Necrolysis. Toxic Epidermal Necrolysis has a reported mortality rate of 30%-80%. However, recognition of the early symptoms and the discontinuation of all ibuprofen products can prevent progression to SJS and TEN. Morbidity and mortality can be significantly reduced with early recognition and treatment (Wolkenstein and Revuz, Dermatologic Clinics, 2000). Garcia-Doval et al., in the Archives of Dermatology (2000) calculated an odds ratio for a better prognosis of 0.69 for each day the drug was withdrawn with drugs with a short half-life. This is particularly relevant for ibuprofen since it has a half-life of approximately 2 hrs under normal metabolic and pharmacokinetic conditions. SJS and TEN usually begin with non-specific flu-like symptoms (e.g. fever, sore throat, burning eyes) with the emergence of skin and mucous membrane lesions within one day to a week. The dermatological symptoms usually present as a rash, itching skin and blisters that progress to more severe cutaneous lesions such

as SJS and TEN, and systemic involvement if not recognized and the drug withdrawn.

It is therefore imperative that the U.S. product labeling alert physicians, patients, and consumers to the signs and symptoms relating to ibuprofen-induced SJS and TEN and provide instructions to prevent progression of these symptoms.

The petitioners request that the FDA Commissioner act immediately to require the labeling additions noted below. This action is especially critical because of ibuprofen's wide use in children and as OTC preparations.

- **Bolded Black Box Warning for Prescription Products:**

> **Serious Skin Reactions**
> **Serious skin reactions including Erythema Multiforme. Stevens Johnson Syndrome and Toxic Epidermal Necrolysis have been associated with the use of NSAIDs, including ibuprofen. These events occur rarely and have been identified in U.S. and worldwide postmarketing safety surveillance programs and the scientific literature. These reactions are potentially life-threatening and fatal, but may be reversible if ibuprofen is discontinued immediately at the first sign of a rash, mucosal lesion or blisters (sores in mouth, throat, eyes, or genitalia), or if an unexplained or persistent fever occurs while taking ibuprofen. Patients should be advised to stop taking ibuprofen, if any of these symptoms occur and contact their physician immediately.**

- **Dear Doctor and Dear Healthcare Professional Letters**

The Petitioners believe the gravity of the reported dermatologic events dictate health care providers be alerted to this information as soon as possible.

These letters should be provided to all U.S. prescribers because of the high use of ibuprofen in all age populations and as prescription and OTC products. Letters should also be sent to pharmacists, medical associations, hospitals (including critical care and burn centers) to allow the most rapid and most extensive dissemination of this critical safety information. These letters should provide specific guidance to prescribers and patients for the detection of these events and the medical intervention necessary to halt their critical progression.

- **Reconsideration of the OTC status of the pediatric formulation or, at minimum, changing the Labeling for OTC Ibuprofen Products**

The FDA should either reconsider removing the pediatric or adult ibuprofen products from the market as over-the-counter- medications to prescription products under the supervision of a physician with amplified warnings and precautions in the revised package insert to warn about risks of SJS and TEN, or alternatively provide the following labeling changes to the OTC labeling for ibuprofen products:

Warnings **(to follow "Allergy alert")**

Serious Skin Reactions: Ibuprofen may cause serious skin reactions that begin as rashes and blisters on the skin, and in the areas of the eyes, mouth and genitalia. These early symptoms may progress to more serious and potentially life-threatening diseases, including Erythema Multiforme, Stevens Johnson Syndrome

and Toxic Epidermal Necrolysis. Seek immediate medical attention if any of these symptoms develop while taking ibuprofen.

Stop use and ask a doctor if

- a skin rash or blisters on the eyes, mouth or genitalia occur because these symptoms may be an early sign of rare and life-threatening reactions including Erythema Multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis.

III. Environmental Impact Statement

The Petitioners believe the actions requested in this Petition provide no significant environmental impact. The requested actions will not introduce any substance into the environment and is categorically excluded pursuant to 21 CFR 25.30.

IV. Economic Impact Statement

This information is only to be submitted when requested by the Commissioner following a review of this petition.

V. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

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Darlene and Andrew Kiss, Aberdeen, NJ
Three-year old daughter, Heather, died after taking Children's Advil
(Ibuprofen) from Toxic Epidermal Necrolysis

Christy and Steven Esnard, Houston, Texas
5 year-old daughter suffered permanent injuries after taking Children's Motrin
(Ibuprofen) from Stevens Johnson Syndrome

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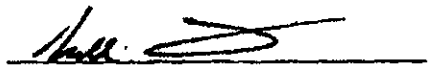

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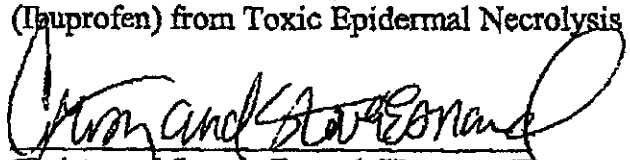

Christy and Steven Esnard, Houston, Texas
5 year-old daughter suffered permanent injuries after taking Children's Motrin (Ibuprofen) from Stevens Johnson Syndrome

LaSandra and Levell Madden, Dallas, Texas
8 year-old daughter suffered permanent injuries after taking Children's Advil (Ibuprofen) from Toxic Epidermal Necrolysis

LaSandra + Levell Madden

LaSandra and Levell Madden, Dallas, Texas
8 year-old daughter suffered permanent injuries after taking Children's Advil (Ibuprofen) from Toxic Epidermal Necrolysis