

October 13, 2005

To Whom It May Concern:
Division of Dockets Management
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

0228 5 07 10 07

CITIZEN PETITION

(see last page for complete author address information)

As a result of my work and research in conjunction with preparing a past declaration in response to certain citizens' petitions submitted to the FDA relating to fentanyl transdermal systems, I became aware of the significant dangers associated with the use of reservoir systems for transdermal delivery. That information has led me to the conclusion that, due to improvements in transdermal technology and, in particular, the development of transdermal matrix delivery systems that clinically perform as well as their predecessor reservoir systems, there is no justification for continued acceptance and use of transdermal patches operating with far less safe reservoir technologies.

ACTIONS REQUESTED

I, Gordon L. Flynn, request that the FDA take the following actions:

- a) not approve further liquid reservoir transdermal systems unless and until the potential manufacturers of such systems provide convincing evidence that the seals of the form-fill-seal patches they wish to introduce are failsafe with regard to leakage,
- b) review the manufacturing procedures and controls now in place for the production of presently marketed liquid reservoir transdermal systems to make sure that these are failsafe with regard to leakage,
- c) review the overall safety of use of liquid reservoir patches now on the market from standpoint of risk of harm to patients using such patches appropriately and also from the standpoint of their relative ease of drug abuse.

Gordon L. Flynn, Ph.D.
Emeritus Professor and Private Citizen

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2005P-0441

CFI

PERSONAL CREDENTIALS FOR MAKING THIS FILING

I am an Emeritus Professor of Pharmaceutics (Physical Chemistry applied to pharmaceutical problems) at the University of Michigan's College of Pharmacy, having retired on 9/1/2001. Though officially retired, I remain professionally active. I have been a faculty member at the University of Michigan since 1972 and a full Professor since 1977. I also was an Adjunct Professor of Pharmaceutical Chemistry at the University of San Francisco from November 1988 to December 1989 while on leave from the University of Michigan.

I was employed as a Chemist at Abbott Laboratories (N. Chicago, Illinois, 1961), as a Research Associate at The Upjohn Company (Kalamazoo, Michigan, 1965-70), and as a Senior Research Scientist at The Upjohn Company (1971-72). I also served as the Vice President, Basic Research, at Cygnus Research Corporation from September 1988 to October 1989 while on leave from the University of Michigan.

I received my Bachelors of Science in Pharmacy in 1960 from Rutgers, The State University, and a Ph.D. in Physical Pharmacy in 1965 from the University of Wisconsin at Madison. I have taught physical pharmacy (pharmaceutics) to graduate and undergraduate students for over 30 years and have published approximately 175 scientific articles, this number including primary research articles, review articles and book chapters. These publications relate to, among other topics, the physical properties and behaviors of local and systemic dermal dosage forms, the former including cosmetic and pharmaceutical semisolids (lotions, creams, gels and ointments) and the latter including transdermal patches. I am a co-inventor on approximately 12 U.S. patents and patent applications, including six relating to transdermal delivery technologies. I have been recruited by ('commissioned by') the American Pharmaceutical Association (APhA) to write, with a singular co-author, a textbook on pharmaceutics. This book is presently tentatively titled: *Physical and Biophysical Bases of Pharmacy Practice – Decisions in Drug Delivery*. Work on the book is well underway.

My research has included making and testing all manner of topical delivery systems, including transdermal delivery systems. The following additional achievements are relevant to my qualifications as an expert in the matters at hand. I served for five years as a member of the Pharmacology Study Section of the

National Institutes of Health, three of the years as a standing (regular) member of this elite committee of medical scientists. In my capacity as a member of this study section, I was frequently called upon to judge the merits of research proposals involving transdermal delivery strategies. I performed comparable service on other occasions for the NICHD (National Institute of Child Health and Human Development) and for other NIH subdivision ad hoc study sections that were formed to evaluate SBIR (Small Business Innovative Research) Grants. I have been elected and served as Chairman of the Gordon Research Conferences on Barrier Function of Mammalian Skin. I have long been a member of the planning committee of the PPP Conference (Perspectives in Percutaneous Penetration Conference) held in Europe every other year. I have also long served as a consultant to the FDA (Food and Drug Administration) on matters of topical and transdermal delivery and have lectured in about a half dozen AAPS-FDA workshops on matters relevant to FDA Guidances then under development for topical and transdermal delivery systems. I have long consulted with Mylan Technologies relative to their transdermal systems. I have an ongoing contract with the company to explore new drugs and approaches for transdermal delivery. This business relationship was begun in the mid-1990's.

A *curriculum vitae* that describes my professional experience and qualifications in greater detail is attached to this Petition as Exhibit 1.

Of considerable importance, despite my ongoing business relationship with Mylan Technologies, I am acting on my own in preparing this petition and am receiving no compensation for my efforts from this company or any other company or agency. In this regard, my personal view is that it takes a lifetime to build credibility and only one weak moment in life to destroy it. No amount of money could induce me to write something that I don't believe. The petition action I'm taking is my idea alone. I take it because I believe it will save innocent lives.

STATEMENT OF GROUNDS

A thorough review of the transdermal literature teaches one that patches containing highly potent drugs are wonderful drug delivery vehicles if properly prescribed and properly used. However, like dosage forms used by every other route of drug administration, particularly including injections, tablets and capsules containing psychoactive and narcotic drugs, some level of misuse and abuse of the dosage

forms appears inevitable given human shortcomings.^a Furthermore, even in the light of close and careful FDA monitoring, manufacturing errors and defects are also possible with any dosage form. And even properly manufactured products tend to have inherent weaknesses that make them fallible.

Misuse of drugs at times involves incorrect practitioner prescribing of them and at other times pharmacist errors in directing patients and nurses on the use of them. Of course, nurses and patients themselves inadvertently commit errors in using them too. For example, with the drug fentanyl, there are instances of use that have led to fatal outcomes that are on record where physicians have prescribed fentanyl patches for narcotic-naïve patients. The literature distributed with fentanyl patches (label copy) and all official fentanyl monographs make it clear that such use is dangerous and outside of acceptable practice with fentanyl patches. There have also been instances where pharmacists have given erroneous directions for applying patches, with patients then being found dead in their beds wearing more than a single patch. And patients themselves become confused about the use of their medications. Oftentimes they reason that if one dose (patch) of a drug isn't getting the 'job done' (e.g., providing pain relief in the case of fentanyl), second and further doses of the drug in question (patches) should be taken (applied). Where fentanyl is the drug, this too can lead to macabre consequences. All of the above misuses stem from errors of judgment, from misunderstandings of drugs and their delivery systems, from practitioner carelessness or, at times, from simple patient and practitioner ignorance. Given human failings, ill-fated outcomes with transdermal products as these will never be completely abolished by providing better information to prescribers and patients or through more stringent regulation.

Improper manufacture of dosing platforms and the manufacture and distribution of dosage forms with inherent physical weaknesses contribute to the failings of transdermal systems. Again I turn to fentanyl for relevant examples. Duragesic®, the first marketed fentanyl patch and J&J's currently marketed patch in the United States, provides a case in point. In February of 2004 Janssen Pharmaceutica (Johnson & Johnson) put out an "urgent product recall" on a lot of Duragesic® because "a small percentage of these patches which were distributed in the U.S.

^a In preparing this petition, I've chosen to use references only to the extent that they serve as examples from the greater literature that illustrate the points being made. I have an extensive file of primary and newspaper references, as I'm sure the FDA has too, to draw the example references from. I've carefully studied them all. Should the FDA wish, on FDA request I will provide the agency with copies of every one of the references that I have on file.

may leak medication along one edge.”^b The company estimated that something less than 19,000 patches out of a lot total of 440,000, on the order of 5% of the lot, were defective. Written this way, it’s not so obvious that this so-called “small percentage” had the potential to take the lives of roughly one out of every twenty legitimate users of this lot of the fentanyl product! And though the issue will obviously be argued in court, several deaths very likely did result from the manufacturing defect.^c In viewing these unfortunate and clearly unintended events, it’s important to realize that the fentanyl that is in this patch is almost entirely found in its liquid reservoir. This reservoir has to be sealed off tightly so that the patch doesn’t leak its contents while in storage or after it’s been placed on the skin. Quite obviously, reservoir leakage sets up a truly dangerous situation. Leakage in the course of its clinical use causes the hydroalcoholic fentanyl gel in the reservoir to spread out over the skin, increasing the surface area of fentanyl’s delivery and also accelerating the evaporation of the alcohol and water that are the main solvents of the gel, the evaporative process itself then driving fentanyl into the skin. As a consequence, the amount of fentanyl that is absorbed soon after applying a leaky patch can rise to a hazardous, even lethal level, and, as suggested, some deaths do seem to have resulted from this manufacturing flaw. Stringent quality assurance procedures and good manufacturing practices minimize but don’t fully eliminate the potential for problems as these happening with reservoir systems. Thus, the possibility of this type of problem taking place will never fully disappear as long as reservoir patches remain in use. This is true for all reservoir patches containing highly potent, potentially lethal drugs. It certainly is true for the present day USA Duragesic® and it would be just as true for any new fentanyl product that emulates Duragesic’s® form-fill-seal patch design. It’s true for the present day clonidine reservoir patch (Catapres®) and any future successor clonidine reservoir patches as well.

Abuse of patches is yet another serious problem, most particularly with fentanyl (Duragesic®) but also with other medicated reservoir patches. Duragesic’s® abuse, in particular, has taken many forms: a) contents of the reservoir have been drawn up into a syringe and injected, b) patches have been drained by syringe or

^b Urgent product recall. Janssen Pharmaceutica. lot number 0327192. 75 µg/hr Duragesic® patches, dated February 16 and 17, 2004.

^c A law suit involving a likely death due to the manufacturing defect in Queen Anne’s County, MD reported on WBOC TV 16 web site on January 26th, 2005; a second death in Illinois known to this author from private sources. And on Friday, July 15, 2005, the FDA issued a public health advisory warning to physicians regarding the safe use of transdermal fentanyl patches, indicating at the time the agency is investigating 120 deaths associated with the use of Duragesic® dating back to the moment of commercial introduction of the product in 1990.

simply cut open and manually drained, in either instance with the gel contained within them then being swallowed, c) the gel has been applied rectally in the manner of a suppository, d) the gel has been placed under the tongue (sublingually) to effect fentanyl's absorption, e) the gel has been removed and heated, with fentanyl vapors then drawn into the lungs, and f) the gel itself has been inhaled. All of these abuses are facilitated by the easy access that drug abusers (in the case of fentanyl, narcotic addicts) have to the gel in this still marketed reservoir product. Many of the abuses would simply not be possible at all if the fentanyl were contained in a matrix (monolithic) transdermal product. Of greatest importance, no deaths would be associated with the proper use of fentanyl patches that were properly prescribed, with proper administration directions given, and properly used by the patients who need them were all the fentanyl patches in use matrix (monolithic) systems.^d Though speculative, it's reasonable to assume that more than half of the over 100 deaths attributed to Duragesic's® abuse by pitiable souls with drug habits wouldn't have occurred either, though admittedly this presumption could well underestimate the determination and sagacity of street drug addicts. Consideration of the features of form-fill-seal and matrix transdermal designs will make all these matters clear.

A. Form-fill-seal (Reservoir) Transdermal Patches

The so-called reservoir design of form-fill-seal transdermal systems typically has a reservoir holding a fluidized concentrate of drug and, also typically, contains a permeation enhancer or two. The contents of the reservoirs of these systems, therefore, have no rate-controlling features of themselves. In fact, due to the presence of permeation enhancers, the reservoir contents are actually rate accelerating. In other words, the contents of present-day patch reservoirs would deliver their drugs at higher rates cm^2 by cm^2 than solutions of the same drugs in the absence of enhancers.

Because the substance of the reservoirs found in reservoir systems themselves do not have mechanisms to control the rate of delivery of the drugs they contain, reservoir transdermal systems, whether holding fentanyl or another drug, are dependent on the integrity of the seals around their reservoirs and the membranes that lie in front and at the back of the reservoirs placed there to prevent dangerous, uncontrolled release of the drugs from the reservoirs. As has already been pointed

^d Underlining of the text for emphasis

out, problems with the inadvertent release of fentanyl from Duragesic's® reservoir have led to a recent recall of one lot of USA Duragesic® and may be behind the recall of several more lots of Duragesic® manufactured in Europe. The USA recall was instituted after it was determined that a particular lot of patches “might leak medication along one edge.” As Janssen itself explained, “exposure to the leaked medication could result in increased absorption of the opiate component, fentanyl, leading to increased drug effect, including nausea, sedation, drowsiness, or potentially life-threatening complications.”^e

The reservoir design also puts those patients at risk who might inadvertently misuse reservoir products. Again using Duragesic® as the example, the literature reports at least two instances in which patients or physicians cut Duragesic® systems into smaller pieces in efforts to reduce the delivered dose.^f One patient cut a Duragesic® patch in half, resulting in the spillage of its reservoir contents over a wider area of skin, with resultant increased absorption. Thus, because of the reservoir design of this product, this sectioning of the patch allowed the drug-containing gel to escape and overdose the patient.

Reservoir systems like Duragesic® are entirely dependent on the proper functioning of their so-called rate controlling membranes. Originally, the rate-controlling membranes were touted as actually controlling the absorption of the drugs in the reservoir systems. When clinical data accumulated and made it clear that the stratum corneum of the skin was the real rate-controlling element in percutaneous absorption processes with respect to all but scopolamine patches, the rate-controlling membranes were then claimed to prevent dose-dumping of drugs from the reservoirs if and when patches might be applied to barrier-defective skin surfaces (a circumstance seemingly ruled out though product application directions). Nonetheless, to some extent, they can play this role. Regardless, these membranes are fragile and, therefore, are susceptible to tear, rupture, puncture and then leakage if they are improperly manufactured, damaged in use, or just plain tampered with. Consequently, despite the deliberately cultivated position (and successfully induced perception) that rate-controlling membranes are assets in the development of safe transdermal systems, the reality is that these membranes and their seals can fail in use and are easily overcome. The rate-controlling membrane story seems even to have fostered a false sense of security relative to reservoir

^e Loc. cit.

^f R. J. Roberge et al., *Transdermal Drug Delivery System Exposure Outcomes*, **J. Emergency Med.**, 18:147-51, 2000

transdermal systems in the clinical community. The reality is that the rate control inherent to matrix systems is a more reliable way to prevent dose dumping and is far less susceptible to any efforts to intentionally defeat a given patch's rate-control features.

As has been stressed here, due to the natures of the media contained in reservoir systems, potential leakage or rupture is worryingly dangerous. Again, with Duragesic® as the example, the alcohol used as a permeation enhancer in this specific product means that any fentanyl-laden gel that leaks onto the skin due to a rupture or leak in the reservoir will cause the drug to pass into and through the skin uncommonly quickly. Because the delivery of drugs through the skin is directly proportional to the surface area of the skin that a drug delivery vehicle makes contact with, the leakage of a drug like fentanyl outside the parameters of a patch can dramatically increase the amount of drug delivered to a patient. The bottom line is that, because of the inherent vulnerability to damage and/or manufacturing problems (and ease of abuse) that reservoir designs have, reservoir systems universally pose a significant risk to patients (and, for other reasons, to the drug-abusing community) that isn't shared with matrix transdermal designs.

The main emphasis of my stated concern relates to the protection of legitimate patients using transdermal dosage forms that were legitimately prescribed, properly dispensed, and properly applied, though we must also do what we can to limit the proclivities addicts have for self harm. In this regard, back in 1997 the question was asked concerning Oralet, an oral transmucosal delivery system for fentanyl that was under FDA review: "Can the risk of accidental or iatrogenic toxicity be reduced to a level where the benefits to the intended users outweigh the risk to the rest of the patients and the public?"⁸ In the instances of highly potent, potentially lethal drugs in reservoir transdermal systems, the answer is yes! Matrix transdermal dosage forms aren't encumbered with anywhere near the same amount of risk that reservoir patches carry.

On the drug abuse side of the question, the scientific literature reflects that the reservoir design of currently available reservoir transdermal systems, most especially fentanyl and clonidine reservoir transdermal systems, lends itself to drug abuse. For example, the medical literature includes many reports of abuse of fentanyl transdermal systems by intravenous injection of the contents of this

⁸ from the HTML version of the file: <http://www.fda.gov/ohrms/dockets/ac/97/transcript/33271t1.rtf>

reservoir system.^h In addition to abuse by injection, the contents of reservoirs in fentanyl transdermal systems have been subjected to abuse by inhalation.ⁱ There is significant evidence in the literature that transdermal systems having reservoir designs are abused by placing the systems in the mouth and chewing or cutting them to cause the drug-laden contents of their reservoirs to be squirted into the mouth.^j All the references cited below involve fentanyl's abuse, but there are comparable literature articles, though far fewer in number, on the abuse of the clonidine found in Catapres®. All of these forms of abuse are facilitated by the reservoir design of the mentioned transdermal systems. This design, of itself, makes it easy for drug abusers to extract, withdraw, express and otherwise remove most of the drug from the systems. By virtue of their design, matrix systems are nowhere near as susceptible to abuses by these very same means. Therefore, based on my review of the literature relative to these issues, it is my heartfelt view that the FDA should not approve additional reservoir systems for the transdermal administration of all potent drugs, but most especially, at this time, the FDA should not approve further reservoir transdermal systems containing fentanyl and its narcotic kind.

B. Matrix Transdermal Systems

Matrix transdermal systems, sometimes called monolithic systems, have the drugs they contain incorporated in their adhesive layers or in other polymeric layers placed in a stack behind their adhesive layers. In one sense, they are solid-state devices. In most cases they simply have drug-containing adhesive layers that are coated onto a suitable backing film, with the delivery surface of the adhesive covered by a release liner. With the drug in these latter transdermal systems in solution or in suspension in the adhesive or other polymeric layer of a patch, drug cannot be physically withdrawn from the patch by syringe nor does it ooze out of such patches when the integrity of one of them is breached via cutting. In short, it takes someone with considerable, real analytical expertise to get drug out of one of

^h J.M. DeSio et al., *Intravenous Abuse of transdermal fentanyl*, **Anesthesiology**, 79:1139, 1993; M.D. Reeves and C.J. Giniifer. *Fatal intravenous misuse of transdermal fentanyl*, **MJA**, 177: 552, 2002; A M. Tharp et al., *Fatal intravenous fentanyl abuse four cases involving the extraction of fentanyl from transdermal patches*, **Am. J. Forensic Med. Pathol.**, 25:178-81, 2004; etcetera.

ⁱ _Anonymous, *Inhalation abuse of fentanyl* [comment], *The Medical Letter on Drugs and Therapeutics*, 33: 8, 1991; K.A. Marquardt and R.S. Tharratt, *Inhalation abuse of fentanyl patch*, **Clin. Toxicol.**, 32: 75, 1994

^j M.L. Arvanitis and R.C. Satonic, *Transdermal fentanyl use and abuse*, **Am. J. Emergency Med.**, 20: 58, 2002; I.A. Liappas, et al., *Oral transmucosal abuse of transdermal fentanyl*, **J. Psychopharmacol.**, 18: 277, 2004; Parucker, M., Swann, W: *Potential for Duragesic patch abuse*, **Ann Emerg Med** 2000; 35:244; A. Poklis, *Fentanyl A Review for Clinical and Analytical Toxicologists, Clinical Toxicology*, **J. Toxicol.-Clin. Toxicol.**, 33:439-447, 1995

these patches. Given the emphasis on fentanyl in this petition, it seems appropriate to mention that the recently approved, generic fentanyl transdermal system offers the very safety and risk-limiting benefits of matrix systems that are alluded to here.

The recently approved generic fentanyl transdermal system also contains close to the same total amount of fentanyl that Duragesic® contains at each given delivery strength. For example, at the dosing strength of 25 mcg/hr, the respective patches each contain 2.5 mg of total drug. The amount of drug in each of the systems increases proportionally with the delivery areas of the respective patches and thus in proportion to the stated delivery expectations of the respective patches.

Consequently, when used properly and when functioning correctly, the presently marketed fentanyl systems are equally efficient in delivering their total drug loads over the intended course of their clinical wear. They are as good in this regard as seems possible for transdermal systems to be (well over 50% and up to 80% of the fentanyl contained in these systems is clinically delivered). This attribute of the systems is quite important too, especially where drugs of abuse are concerned, as spent patches have even been taken off cadavers in morgues and been recovered from wastebaskets by individuals intending to abuse the drug in them. The smaller the quantity of drug left in each properly used, spent patch, the less of a problem this type of 'drug recovery' can possibly turn out to be.

There are some other positive attributes of matrix transdermal designs that should be mentioned. Unlike patches with liquid or semi-liquid reservoirs, most matrix patches can be sectioned to form smaller adhesive pieces that proportionally cut down the dosing rate. The contact adhesives used in transdermal delivery systems (variously, acrylate polymers, PIB's and silicone polymers) are all hydrophobic. Consequently, the drugs they contain aren't easily extracted into saliva or other aqueous media. In part, this is also because transdermal drugs themselves tend to be hydrophobic, for low polarity is an asset for partitioning of the drugs into the interstitial lipids that provide for diffusion through this conduit phase of the human stratum corneum. This means that abusers can chew them or swallow them with far less effect than if they were chewing or swallowing a damaged reservoir system. The hydrophobicity of the contact adhesives used transdermally prevents transdermal patches of all kinds from adhering to moist mucosal surfaces as well.

CONCLUSION

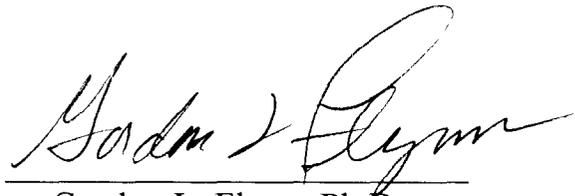
Transdermal patches containing potent drugs in liquid or semi-liquid reservoirs are intrinsically far less safe clinical systems than matrix transdermal patches that deliver the same drugs. Reservoir transdermal designs also facilitate abuse of the drugs contained in the patches. The FDA can protect the general public by holding manufactures to a higher standard of manufacturing practice that guarantees the seals in such patches are failsafe. The FDA can even better serve the public's interest by refusing to accept reservoir transdermal designs when comparably performing, comparably efficient matrix transdermal patches are available.

ENVIRONMENTAL IMPACT

It's my belief that this petition is exempt under 21 C.F.R. § 25.31 from the requirement for an environmental assessment.

I declare under the penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on October 17th, 2005.
Ann Arbor, Michigan



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FACSIMILE MESSAGE

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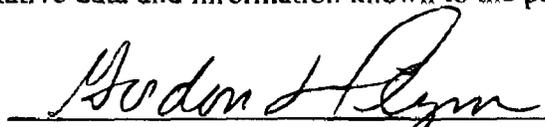
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NUMBER OF PAGES INCLUDING COVER PAGE: 1

Dear Mr. Jaffe,

In reference to the Citizen Petition that I forwarded to the FDA a little over a week ago that you contacted me about, I, the undersigned, certify, that, to my best knowledge and belief, my submitted petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.


Gordon L. Flynn

10 / 28 / 2005
date

Date and time composed: October 28, 2005 @ 4:46 PM

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FACSIMILE MESSAGE

ATTENTION: Lyle Jaffe
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DESTINATION FAX NUMBER: 301 827-6870

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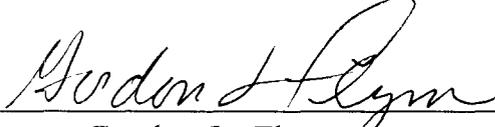
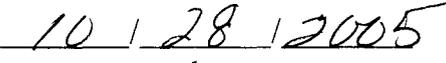
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Date and time composed: October 28, 2005 @ 4:46 PM