



Declaration of Gordon Flynn, Ph.D.

I, Gordon Flynn, Ph.D., hereby declare as follows:

1. I have been asked to evaluate the scientific basis for the Citizens' Petition regarding 76-258 submitted on October 21, 2004 by Drs. Brookoff and Voth.
2. 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 September 1, 2001. 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.
3. 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.
4. I received my Bachelors of Science in Pharmacy in 1960 from Rutgers, The State University, and a Ph.D. in Pharmacy in 1965 from the University of Wisconsin at Madison.
5. I have taught physical pharmacy to graduate and undergraduate students for approximately 30 years. I have written approximately 175 publications. 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. My research has included making and testing all manner of these systems, including transdermal delivery systems.

6. The following additional achievements are relevant to my qualifications to comment on this matter. 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 group of 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 am a co-inventor of approximately 12 U.S. patents and patent applications, including six relating to the transdermal delivery technologies. 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.

7. My curriculum vitae, which describes my professional experience and qualifications in greater detail, is attached as Exhibit 1 to this Declaration.
8. I am being compensated for my work in this matter at my usual consulting rates and have no financial interest in the outcome of the agency's decision in this matter.

Mylan's Fentanyl Transdermal System

9. Mylan's fentanyl transdermal system, on file as ANDA 76-258, is a monolithic system. It consists of fentanyl dispersed in a silicone adhesive coated onto a suitable backing film with the delivery surface of the adhesive covered by a release liner.
The fentanyl in Mylan's fentanyl transdermal system is in the form of fentanyl base.
10. The fentanyl in Mylan's fentanyl transdermal system is suspended in the adhesive of the patch. Unlike the gel contained in the Duragesic® reservoir system, the fentanyl in the Mylan fentanyl transdermal system cannot be physically withdrawn from the patch.
11. Mylan's fentanyl transdermal system has been demonstrated to be bioequivalent to the Duragesic® product and was granted final approval by FDA on November 21, 2003.
12. Mylan's fentanyl transdermal systems contain almost exactly the same amount of fentanyl in a system as the Duragesic® products for the same dosage strength, 2.5 mg in the 25 mcg/hr dose. In both products the amount of drug in the increases proportionally with the delivery expectations of the patch.

13. Dr. Mary Southam, Alza's Vice President of Technology Assessment, testified at the patent trial in the United States District Court for the District of Vermont that the concerns expressed by FDA and DEA about the abuse and diversion risks of a fentanyl transdermal system were addressed by reducing the drug loading to the levels seen in Duragesic®. Her testimony is attached at Exhibit 2 hereto.

**Mylan's Fentanyl Transdermal System Does Not Become a Rapid Release
Fentanyl Product If Cut Into Pieces and Placed in the Mouth**

14. The Brookoff/Voth Citizens' Petition posits the scenario in which the Mylan fentanyl transdermal system is cut into pieces and placed in the mouth. The assertion that such use of the Mylan fentanyl transdermal system would convert it into a rapid or immediate release fentanyl product reflects a basic misunderstanding of the science underlying Mylan's system and fentanyl transdermal delivery generally.
15. Even if cut into pieces and placed in the mouth, the Mylan fentanyl transdermal matrix remains a slow-release delivery system and the basic mechanism of delivery of fentanyl does not change. Fentanyl still has to diffuse to the patch's releasing surface before partitioning into the oral fluids, a slow process controlled by fentanyl's solubility in and diffusion coefficient through the patch's adhesive matrix.
16. Unlike Duragesic®, which provides direct access to fentanyl gel when cut open, cutting the Mylan fentanyl transdermal system does not increase the rate at which fentanyl can be delivered from the system. Indeed, because the delivery of fentanyl from a matrix like the Mylan fentanyl transdermal system is always proportional to

its surface area, cutting the system into pieces reduces proportionally the possible delivery of fentanyl from those pieces.

17. Because of its design, the Mylan fentanyl transdermal system is not an efficient way to deliver fentanyl rapidly to and through the oral mucousal surface.
18. To deliver fentanyl efficiently through a membrane (whether a mucousal membrane or the skin), a matrix system needs to be in intimate contact with that membrane. (See Guo, Cremer, Development of Bio-Adhesive Buccal Patches; 541-544. Bio-Adhesive Delivery Systems (Mathiowitz, Chickering III, Lehr. Marcel Dekker. 1999). The Mylan fentanyl transdermal system cannot do so because, due to the hydrophobic nature of its adhesives, it is unable to bind to moist oral tissues (or moist mucosa of any other kind).
19. The Mylan fentanyl transdermal system uses a silicone adhesive. The solubility parameter of polydimethylsiloxane at room temperature is reported to be 7.6. Thus, this adhesive is extremely hydrophobic. Polydimethylsiloxane and related silicone adhesives are hydrophobic and, therefore, will not work to adhere to the oral mucosa.
20. To confirm my belief that the adhesive used in the Mylan fentanyl transdermal system would not adhere to moist oral tissues, I attempted to adhere a placebo patch inside the mouth, to no avail. The scientific theory that such a hydrophobic adhesive would not work in the moist environment of the mouth was borne out in this experiment.
21. This conclusion is supported by the fact that the products on the market that are designed to be adhered to oral surfaces use entirely different types of adhesives, ones

that are extremely hydrophilic, not hydrophobic. (See Kellaway, Ponchel, Duchene. Oral Mucosal Drug Delivery; 360. Modified Release Drug Delivery Technology (Rathbone, Hadgraft, Roberts. Marcel Dekker. 2003; Guo, Cremer. Development of Bio-Adhesive Buccal Patches; 551. Bio-Adhesive Delivery Systems (Mathiowitz, Chickering III, Lehr). Marcel Dekker. 1999).

22. Because the Mylan fentanyl transdermal system would not adhere to the membranes inside the mouth, it would be an inefficient method for delivering fentanyl to the blood stream through that route. If placed in the mouth without adhering to the membranes inside the mouth, the Mylan fentanyl transdermal system would be releasing drug into the saliva rather than into the bloodstream and most of it would be swallowed (washed away). (See Kellaway, Ponchel, Duchene. Oral Mucosal Drug Delivery; 354-355. Modified Release Drug Delivery Technology (Rathbone, Hadgraft, Roberts). Marcel Dekker. 2003).
23. Because of the high first-pass metabolism of fentanyl by the liver, swallowing the small amount of fentanyl released into the mouth will not lead to systemic effects. If a transdermal system does not maintain intimate contact with the buccal mucosa, nearly all of the fentanyl that is released in the oral cavity will be swallowed along with saliva, not absorbed through the local tissue and directly into the bloodstream.
24. I have also reviewed dissolution data on Mylan's fentanyl transdermal system. That data confirms that Mylan's patch would not release fentanyl rapidly in the watery environment of the mouth. When placed in water at physiologic pHs, the Mylan fentanyl transdermal system released only 15 percent of its drug over a half an hour.

25. Mylan's fentanyl transdermal patch contains the base form of fentanyl, a highly water-insoluble component, in a water-insoluble silicone adhesive backed by a water insoluble polymeric film. Most of the fentanyl base contained in Mylan's fentanyl transdermal system is undissolved drug. As a result, although some fentanyl would be released into the mouth, that release would be far from an immediate release of the drug load. In fact, drug release would likely be quite slow because of the slow into water.

Mylan's Fentanyl Transdermal System Is Not Similar To Actiq

26. The Actiq® product, unlike a fentanyl transdermal system, is designed for a rapid release of fentanyl in the mouth for the treatment of cancer breakthrough pain. For that reason, as Drs. Brookoff and Voth acknowledge, it delivers high doses of fentanyl in a very short time (a fraction of an hour) when used as directed.
27. Unlike the Mylan fentanyl transdermal system, Actiq® is specifically designed to deliver fentanyl through the membranous tissues defining the oral cavity. For that reason, Actiq® contains fentanyl in its water soluble citrate form to ensure that it dissolves instantaneously.
28. Every ingredient of the Actiq® formulation save the opacity-inducing dye is water soluble and, therefore, also saliva soluble. When an Actiq® lozenge is placed in the mouth, the whole unit erodes by way of dissolution in saliva and fentanyl is released in citrate (soluble) form as a consequence. By design, Actiq®'s entire drug content

is turned loose in the mouth in a matter of minutes. Indeed, Actiq®'s package insert indicates that it should not last for more than 15 minutes.

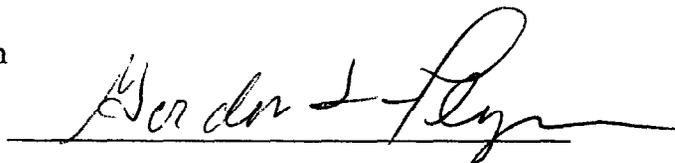
**Janssen Is Marketing a Solid State Monolithic Fentanyl
Transdermal System in Europe**

29. I have also examined materials relating to Janssen's solid state monolith fentanyl transdermal system introduced in Europe. Not only does that product use a solid state matrix design, it also uses twice the amount of fentanyl used in the Mylan fentanyl transdermal system of comparable dose. The assertion by Dr. Coleman found in the Citizens' Petition that Janssen withdrew its monolith product U.S. market because of concerns about abuse and diversion is inconsistent with decision to market that product in Europe.

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 November 11, 2004.

Ann Arbor, Michigan

A handwritten signature in cursive script, appearing to read "Gordon Flynn", is written over a horizontal line.

Gordon Flynn, PhD.