



MYLAN TECHNOLOGIES INC.

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August 27, 2004

VIA FEDERAL EXPRESS

Division of Dockets Management (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

RE: Comments of Mylan Technologies Inc. on Docket No. 2004P-0340:
Action on Regulation of Generic Transdermal Fentanyl Delivery System,
and New Product Approvals for Transdermal Fentanyl

Dear Sir or Madam:

Mylan Technologies Inc. ("Mylan"), submits these comments in response to the above-referenced Citizen Petition filed by Steven L. Shafer, M.D. ("Dr. Shafer" or "Petitioner") on July 28, 2004 (the "Petition").

Mylan has an interest in the Petition, because Mylan has submitted an abbreviated new drug application ("ANDA") for a generic fentanyl transdermal system ("FTS"), and the Petitioner has recommended to the Food and Drug Administration ("FDA" or "Agency") that it not approve any generic FTS or new FTS formulation in the absence of a demonstration of bioequivalence to the approved Duragesic® transdermal system ("Duragesic®") on both intact skin and so-called "stripped" skin.

I. INTRODUCTION

Based purely on speculation and faulty scientific premises, Dr. Shafer requests that generic FTS applicants be required to demonstrate bioequivalence to Duragesic® not only when the patch is applied to normal skin according to label directions, but also when it is applied to "stripped" skin contrary to those label directions. Dr. Shafer incorrectly concludes that patients may be exposed to toxic levels of fentanyl in the absence of such a showing on stripped skin.

Dr. Shafer bases his recommendations on studies that have been known to him for nearly ten years, yet his concerns are raised just months before generic FTS will be introduced to the public and after one generic FTS has been fully examined and

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determined by the FDA to be safe and efficacious. Inexplicably, Dr. Shafer has kept his alleged concerns to himself while companies like Mylan have developed, together with the FDA, bioequivalency protocols and standards for transdermal fentanyl systems, and the Agency has examined at least one ANDA and has determined that it meets all approval requirements. As will be demonstrated herein, Dr. Shafer, who is an anesthesiologist and not an expert in dermatology or transdermal drug delivery, has based his recommendations on a misunderstanding of the physiology and barrier properties of the skin and a misinterpretation of the studies upon which he relies.

Mylan respectfully requests that the Agency deny the Petition for at least the following reasons. *First*, while it has been well known for decades that stripped skin is more permeable than intact skin, Dr. Shafer has failed to understand that the extent of stripping that is required to compromise the barrier properties of the skin cannot occur with simple application and removal of surgical tapes and bandages. *Second*, Dr. Shafer apparently has failed to appreciate that when skin stripping has occurred to an extent sufficient to compromise its barrier properties, it exhibits visible damage and irritation. Existing label instructions direct that patches not be applied to damaged or irritated skin. *See Final Printed Labeling for Duragesic®* (Approved May 20, 2003). *Third*, the studies upon which Dr. Shafer relies do not support his conclusion that application of generic FTS on stripped skin may result in toxic levels of fentanyl. *Last*, the data upon which Dr. Shafer relies is derived from a study involving an experimental and unapproved fentanyl patch and not a generic FTS that was designed to be bioequivalent to Duragesic®.

II. THE CITIZEN PETITION DOES NOT DEMONSTRATE ANY NECESSITY TO MODIFY THE LONGSTANDING REQUIREMENTS AND STANDARDS FOR DEMONSTRATING BIOEQUIVALENCE TO DURAGESIC®

A. Dr. Shafer's observation that stripped skin is more permeable than intact skin is not a new phenomenon.

Dr. Shafer's observation that stripped skin is more permeable than intact skin is not new, only misconstrued. It is a phenomenon that has been described in the dermatology literature for over five decades and certainly was well known to the Agency's medical experts when bioequivalence protocols and standards for transdermal fentanyl systems were being developed. In fact, Agency records will reveal that the FDA was actively involved with Mylan in designing the bioequivalency test protocols and standards for its generic FTS. If at any time, Agency's experts (or Mylan's) had concluded that further bioequivalency testing was necessary, they would have developed test protocols (both for Duragesic® and for other products) to insure that the application of the patches to stripped skin would be safe. The fact is that such safety problems simply do not exist.

Furthermore, the Petitioner offers no data to support the assertion that the skin barrier is easily compromised by a single removal of an adhesive medical device such as a band-aid or ECG patch. Neither reference cited by Dr. Shafer supports this assertion.

Dr. Shafer's assertions are purely speculative, and as explained in the accompanying declaration of Dr. Peter M. Elias, scientifically baseless. ("Elias Decl.") As Dr. Elias explains, numerous reports in this area conclude that at a minimum ten or more tape removals are necessary to compromise the skin barrier function significantly. Elias Decl. ¶ 5. These reports confirm that repeated tape applications and removals are necessary for significant diminution of the barrier properties. They also conclude that the location of the skin barrier function is within the lower layer of the *stratum corneum*, known as the *stratum compactum*. Elias Decl. ¶ 6. As Dr. Elias explains, Dr. Shafer's description of the *stratum corneum* as a layer of dead, desiccated cells is overly simplistic and incorrect. *Id.* The upper layer of the *stratum corneum*, known as the *stratum disconjunctum*, is a loosely held layer of dead cells. However, that layer does not provide the barrier function of the skin. *Id.* Instead, the tightly held *stratum compactum* provides that barrier function, and that layer is removed only with multiple strippings that will not occur in typical hospital or clinical settings.

B. Dr. Shafer has misunderstood and drawn incorrect conclusions from the Fiset *et al.* and Varvel *et al.* publications.

Dr. Shafer bases his conclusions largely on remarks contained in the "discussion" section of the Fiset *et al.* publication. Those remarks merely speculate that compromised skin barrier function might explain the variable performance of the experimental product evaluated in the reported study. Neither study upon which Dr. Shafer relies was a controlled study to assess the effect of skin stripping on the delivery of fentanyl from either Duragesic® or the Cygnus transdermal system.

A critical underpinning of Dr. Shafer's conclusions is based on a misunderstanding of the Fiset *et al.* paper. Dr. Shafer first erroneously contends that the results of the Fiset *et al.* study demonstrate variable performance for the Cygnus transdermal system. From this misconception, Dr. Shafer concludes that this variability and relatively high (but non-toxic) fentanyl blood levels in one subject resulted from the application of the Cygnus patch to the skin that was highly permeable, because it had been stripped of the *stratum corneum*. Petition at 2. As explained in the accompanying declaration of Dr. Mario Gonzalez, the Petitioner's contentions are based on a misunderstanding of the Fiset *et al.* results.

Dr. Gonzalez, a noted expert in the fields of transdermal drug delivery and pharmacokinetics, has analyzed the data reported in both the Fiset *et al.* and Varvel *et al.* publications and demonstrates that the data reported in the two studies have comparable variability (coefficients of variation). Gonzalez Decl. ¶¶ 5,7. Dr. Gonzalez explains that this degree of variability is typical for studies of transdermal systems, and therefore, do not support Dr. Shafer's contention that high blood levels were attributable to the application of the patch to highly permeable, stripped skin. Gonzalez Decl. ¶ 10. Additionally, a comparison of the so-called high doses absorbed by individual subjects to the mean absorbed dose for the respective products reveals that there is no significant

difference¹, thus demonstrating no excess variability in the performance of the Cygnus product as compared to Duragesic®.

Indeed, there are many possible explanations for the occasional high blood levels observed in the Fiset *et al.* study. First, occasional high blood levels often are observed in these types of studies and are attributable to patient-to-patient variations and to alterations of drug metabolism and/or clearance. Gonzalez Decl. ¶ 8. Second, the Cygnus patch used in that study was not a generic equivalent of Duragesic®. Duragesic® is intended to deliver fentanyl over a 72-hour period and provides a peak plasma concentration in the 46-60 hour time frame. In contrast, the Cygnus patch is specifically designed to deliver fentanyl over a 24-hour period and at a much higher rate during that period. This specific difference in the intended product performance was to achieve a product that could be used for the treatment of post-operative pain, an indication for which Duragesic® is not approved. Dr. Shafer's contention that excessive variation and high blood levels of fentanyl resulted from the application of the Cygnus patch to stripped skin is unjustified.

C. Dr. Shafer's request is predicated on an erroneous premise that patches will be applied in contraindication to the labeling on undetectably injured skin.

Dr. Shaffer's contention that skin stripping that is sufficient to compromise skin barrier function is not visible is scientifically unsupported. Elias Decl. ¶ 7-8. The *stratum corneum* must be repetitively stripped before a significant alteration of fentanyl flux is observed. Elias Decl. ¶ 6. If this extent of skin stripping were to occur in vivo, the skin would manifest visible damage and would rapidly become irritated. Elias Decl. ¶ 7. The application of FTS to damaged or irritated skin is contraindicated for Duragesic® and its generic equivalents (and for virtually all transdermal drug delivery systems). Accordingly, the label directions for Duragesic® and generic FTS instruct the user that the patch should not be applied to irritated, damaged skin and that a new skin site should be used for repeated patch application. See *FPL for Duragesic®*.

The Petitioner is apparently unaware that the number of skin strippings necessary to adversely affect the skin's barrier function can be readily observed. As explained by Dr. Elias, these changes would be readily apparent to even the most casual observer. Elias Decl. ¶ 5, 7. (discussing the Pinkus publication). Pinkus has specifically studied the visual manifestations of skin stripping by adhesive tapes and notes that the effects of as few as four strippings are visually observable. Pinkus, H., *Examination of the Epidermis by the Strip Method of Removing Horny Layers I. Observations on Thickness of the Horny Layer, and Mitotic Activity After Stripping*, J. Invest. Derm. 16:383 (1951). As a practicing and research dermatologist, and Professor of Dermatology, Dr. Elias has extensive experience in observing normal and diseased/damaged skin, and he has specific experience with evaluating skin barrier function resulting from such damage. As Dr. Elias explains, by the time enough damage has occurred to skin that its barrier function

¹ The ratio of the high doses absorbed by individual subjects to mean absorbed dose for Duragesic® was 139% (4.75/3.41) as compared to 131% (6.53/4.96) for Cygnus.

has been compromised with regard to drug penetration, such damage is obvious even to the untrained observer. Dr. Shafer's assertion that the casual removal of adhesive medical devices is likely to cause undetectable damage to the barrier function of skin is unfounded.

III. CONCLUSION

For all of the foregoing reasons, the Citizen Petition should be denied.

Respectfully submitted,



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