



**Department of Veterans Affairs
Medical Center
4150 Clement Street
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DECLARATION OF PETER M. ELIAS, M.D. ^{In Reply Refer To:}

I, Peter M. Elias M.D., hereby declare as follows, under penalty of perjury of the laws of the United States:

1. I am a practicing physician specializing and Board certified in both fields of dermatology and dermatopathology. I also am Professor of Dermatology at the University of California at San Francisco and the Veterans Affairs Medical Center, San Francisco. I have an active research program that is heavily focused on the physiology and biology of the skin, particularly relating to the *stratum corneum* and its barrier properties, skin irritation phenomena and its evaluation, and a wide variety of skin diseases and their pathophysiology. I have authored more than four hundred publications and have received numerous honors and awards in the field of dermatology. My educational and professional background and a list of my publications are set forth in greater detail in my *curriculum vitae*, a copy of which accompanies this declaration.

2. I have been asked by Mylan Technologies Inc. ("Mylan") to provide my analysis and opinions in connection with a Citizens Petition submitted to the Food and Drug Administration by Steven L. Shafer, M.D., Docket No. 2004P-0340. Neither I nor any member of my family is or has been employed by Mylan or any of its affiliated companies, nor do I or any member of my family own any stock in Mylan or any of its affiliated companies. I have occasionally consulted with Mylan, and over the past 3 years, I have received less than \$5,000 in consulting fees from the company.

3. Because of its broad implications for the field of patch-assisted transdermal drug delivery, I have carefully analyzed and considered the Citizens Petition and the accompanying documentation. For the reasons set forth below, I disagree with Dr. Shafer's opinion that testing on "stripped" skin is necessary for establishing bioequivalence of a generic fentanyl transdermal system to the approved Duragesic® product.

4. As an initial matter, I have no reason to question Dr. Shafer's expertise in the areas of anesthesiology and associated pharmacokinetics; however, the comments and positions set forth in the Citizens Petition reflect a serious lack of understanding of the structure and physiology of skin as they relate to the penetration of active drug molecules, and the interrelationship of such structure and physiology to both drug delivery and irritation phenomena. Dr. Shafer's characterization of the *stratum corneum* as "... a layer of dead, desiccated skin cells on the outermost surface of the skin" (Citizens Petition at 1) simply stated is 30 years out of date and is not accurate. Nor is it accurate to state that "[t]he *stratum corneum* is readily removed by such simple maneuvers as applying tape to the skin and peeling [sic] the tape off." *Id.* at 1-2. His statements evince a lack of current knowledge of the relevant literature that forms the underpinnings of the understanding of drug delivery across this dynamic interface.

5. The central thesis proposed by Dr. Shafer is that the skin barrier might unknowingly be compromised by stripping prior to application of a fentanyl transdermal system, thereby resulting in a significant risk to the patient from dangerously high fentanyl plasma levels. This thesis is scientifically untenable. Simply put, damage to the

skin barrier to an extent sufficient to significantly increase drug penetration, does not occur by the routine application and removal of surgical tapes and bandages. In fact, greater than 20 sequential strippings of truncal or forearm skin are required before significant changes in permeability can be detected. Moreover, if such damage were to occur, contrary to Dr. Shafer's assertion that such changes would be invisible, it would be readily apparent to even the most casual observer that abrogation had occurred, i.e. the stripped surface would appear shiny and erythema would be evident. Thus, pursuant to label instructions, healthcare providers and patients would be able to avoid placement of a patch on such damaged areas.

6. The *stratum corneum* consists of two layers: the *stratum disconjunctum* (the outermost layer) and the *stratum compactum* (the innermost layer). Dr. Hans Schaeffer and others (reference 1) have demonstrated that while the outermost layers of the *stratum disconjunctum* can be removed with successive applications of adhesive materials, this layer plays no significant role in providing the skin's barrier properties. It is the innermost layer, the *stratum compactum*, which provides both the permeability barrier properties of the skin and the limiting membrane to transdermal drug delivery. Many early researchers similar to Dr. Schaeffer, such as Drs. Irvin Blank and Harvey Blank (references 2, 3) have confirmed this structure-function relationship. In addition, our group has shown in multiple studies that over 10 strippings with adhesive materials are required to increase the permeability to water and drug substances (reference 4). This conclusion, too, has been reached by many different researchers, using a variety of measures of the barrier function, and all have drawn the same conclusion (references 5,

6). Thus, the Citizens Petition is based on an incorrect premise that routine single applications of bandages, tapes, electrocardiogram patches and their removal will damage the skin sufficiently to lower its barrier properties. Much more aggressive sequential and repetitive stripping would be required to produce such an effect.

7. As noted above, damage sufficient to compromise the barrier properties of the skin, produces not only visible changes in the skin structure but also irritation. While the skin is a robust barrier to the penetration of foreign molecules, it is simultaneously an exquisite indicator of events that abrogate its integrity which initially causes irritation. Very low levels of damage caused by chemicals, surfactants, or mechanical manipulation are readily observed by an increasing cascade of skin reddening and inflammation, indicative initially of mast cell degranulation and later of initiation of cytokine cascade (reference 7). Indeed this sensitivity and easily observed cascade of reactions forms the basis for product safety evaluations, allergy patch testing, and other diagnostic test procedures. This high degree of sensitivity means that stripping of the outer layers of the *stratum corneum*, when sufficient to degrade the barrier is readily observable and that this observation is easily made without expertise in dermatology.

8. In summary, it is my opinion that before sufficient stripping of the skin has occurred to compromise its barrier properties and to significantly affect the transport of an active drug molecule, such as fentanyl, accompanying physical changes and irritation will be readily noticeable. Given the cautions against multiple applications of patches to the same application site and against patch application on irritated skin, which have been standard precautions for Duragesic® and virtually all transdermal patch labeling, it is highly unlikely that a medical professional, care giver, or patient would apply such a

product unknowingly to damaged skin. In my view the risk of high blood levels from such product usage is nothing more than speculation and has no scientific basis.

Signed this 18 day of August, 2004 in San Francisco, California.



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