DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
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Re: Docket Nos. 2004P-0506/CP1, 2004P-0472/CP1 & SUP1, 2004P-0540/CP1, and 2004P-0340/CP1

Dear Petitioners:

This letter is a consolidated response to four citizen petitions in the dockets referred to above[1] and comments submitted on the petitions. Although each of the petitions has a slightly different focus and raises distinct concerns regarding the approval of generic versions of fentanyl transdermal systems under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), each has requested that the Food and Drug Administration (FDA) take specific actions before approving pending or future abbreviated new drug applications (ANDAs) for fentanyl transdermal systems. For the reasons stated below, the petitions are denied. Although we are denying the petitions, we intend to continue to monitor incidents of abuse, misuse, and diversion associated with all fentanyl transdermal systems. Based on this evaluation, we may also consider whether to request a voluntary risk management plan (RMP) for both the innovator and generic fentanyl transdermal systems and encourage manufacturers to consider the advisability of developing and implementing an RMP for these products.

[1] 2004P-0506/CP1 "Alza Petition," 2004P-0472/CP1 & SUP1 "Brookoff Petition," 2004P-0540/CP1 "Mead Petition," and 2004P-0340/CP1 "Shafer Petition."

I. BACKGROUND

The fentanyl transdermal system is a potent opioid analgesic classified in Schedule II under the Controlled Substances Act.[2] The fentanyl transdermal system is indicated for the management of chronic pain in patients who require continuous opioid analgesia. Alza Corporation (Alza) is the sponsor of Duragesic, a fentanyl transdermal system (NDA 19-813).[3] Duragesic, approved by FDA in 1990, is a transdermal patch designed to provide continuous release of fentanyl through the skin over a period of time. Four strengths of Duragesic are currently approved: sizes of 10 cm^2, 20 cm^2, 30 cm^2, and 40 cm^2, delivering nominal doses of 25, 50, 75, and 100 μg of fentanyl per hour, respectively.

The petitions generally raise issues arising from two different designs of fentanyl transdermal systems, known as reservoir and matrix systems. The Duragesic transdermal system is a reservoir system, consisting of four functional layers and a protective liner. The functional layers consist of:

(1) a backing layer of polyester film;
(2) a drug reservoir of fentanyl and alcohol gelled with hydroxyethyl cellulose;
(3) an ethylene-vinyl acetate copolymer membrane that is claimed to control the rate of fentanyl delivery to the skin surface (rate-controlling membrane); and
(4) a silicone adhesive containing fentanyl.

A matrix system has been proposed in at least one pending ANDA for a generic version of Duragesic. In a matrix system, the drug is uniformly distributed in the adhesive layer (i.e., the reservoir of the drug is in the adhesive layer). A matrix system will generally contain no rate-controlling layer because it relies on the chemical composition of the product to control the rate of drug release. Although the mechanism to control the rate of absorption is different, a matrix system can deliver the drug in a predictable and controlled fashion.

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Act, which established the current ANDA approval process. To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective. To rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the listed drug it references (21 U.S.C. 355(j)(2)(A)(iv)). In addition, a drug product described in an ANDA must contain the same active ingredients, indications for use, route of administration, dosage form, strength, and labeling as the listed drug it references (21 U.S.C. 355(j)(2)(A) and 355(j)(4)). The basic assumption underlying the Hatch-

[2] 21 U.S.C. 812.
[3] Duragesic is manufactured by Alza Corporation and distributed by Janssen Pharmaceutica Products, L.P. both subsidiaries of Johnson & Johnson.

Waxman Amendments is that bioequivalent drug products that contain the same active ingredients, indications for use, route of administration, dosage form, strength, and labeling are therapeutically equivalent and may be substituted for each other.

II. DISCUSSION

The petitions request that FDA refuse to approve any new or pending ANDA or 505(b)(2) application for fentanyl transdermal systems that uses a matrix delivery system because of potential safety and regulatory concerns associated with use of a matrix system.

A. Dosage Form

Alza's petition claims that differences between the reservoir and matrix transdermal systems require FDA to classify the two systems as different dosage forms that are not pharmaceutical equivalents (Alza Petition at 1,7). The petition states that the differences in potential abuse, drug delivery, and performance characteristics on stripped or heated skin warrant classifying matrix and reservoir systems as different dosage forms. The petition alleges that fentanyl transdermal systems that differ in release mechanism from Duragesic may perform differently from Duragesic under the conditions of actual use, and should not be considered pharmaceutical equivalents to the innovator product (Alza Petition at 8-9).

In our view, the fentanyl transdermal matrix system should not be classified as a different dosage form from the fentanyl transdermal reservoir system of Duragesic. The term "dosage form" is not separately defined in the Act or in FDA's regulations. The term, however, is used in the definition of a "drug product," which is defined as "a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance . . ." (21 CFR 314.3(b)). As this definition illustrates, a dosage form is the way of identifying the drug by its physical form, which is linked both to the physical appearance of the drug product and to the way it is administered.[4] See also Pfizer Inc. v. Shalala, 1 F. Supp. 2d 38, 46 aff'd in part and rev'd in part, 182 F. 3d 975 (D.C. Cir. 1999) ("a drug's dosage form is not based on its release mechanism but on its appearance and the way the drug was administered").

FDA has published a list of dosage forms in Appendix C of *Approved Products with Therapeutic Equivalence Evaluations*, commonly referred to as the Orange Book. Although this list is not binding, it provides guidance for industry on what constitutes the "same" or "identical" dosage form. In general, the "same dosage form" requirement is met if the dosage form of the proposed generic drug product falls within the same dosage form category in the Orange Book as the RLD. All transdermal products are listed in the Orange Book under "film, extended-release." A review of the dosage form

[4] As noted above, the Act requires a generic drug product to have the same dosage form as the RLD (21 U.S.C. 355(j)(2)(A)(iii)). Approved generic drug products that have the same dosage form as the RLD, among other characteristics, are "pharmaceutical equivalents" (21 CFR 320.1(c)) and may be rated therapeutically equivalent in the Orange Book.

classifications in the Orange Book demonstrates that the Agency has consistently chosen not to base its dosage form descriptions on release mechanisms.[5] In the regulation detailing reasons to refuse to approve an application, the Agency implicitly acknowledges that the "release mechanism" is a part of the composition or formulation of the drug rather than the "dosage form" of the drug. See 21 CFR 314.127(a)(8)(ii)(A) ("FDA will consider the inactive ingredients or composition of a drug product unsafe and refuse to approve an abbreviated new drug application . . . Examples of changes that may raise serious questions of safety or efficacy include, but are not limited to the following: . . . The use of a delivery or a modified release mechanism never before approved for the drug.").[6]

There are at least three different types of release mechanisms covered by the dosage form "extended-release films," the dosage form category that includes the fentanyl products at issue. These extended-release films may vary in several ways, including the way the drug is contained in the system, the amount of active ingredient in the system, the way the drug is released from the system, and the size of the system. Despite these differences in release technologies, the drugs are all considered by FDA to have the same dosage form.[7]

Once it is established that the reservoir and matrix systems are the same dosage form, it follows that matrix and reservoir transdermal products can be pharmaceutical equivalents. FDA's regulations recognize that extended-release products that deliver the identical amounts of the active ingredient over the same dosing period can be pharmaceutical equivalents even if residual (i.e. undelivered) volumes differ. They define pharmaceutical equivalents as "drug products in identical dosage forms that contain identical amounts of the identical active ingredient . . . or in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredients over the identical dosing period . . ." (21 CFR 320.1(c)).

FDA has considered numerous products with different release mechanisms to be pharmaceutically equivalent.[8] Furthermore, as FDA has noted previously, there is "no

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[5] The release mechanism is not specifically considered in evaluating whether two drug products have the same dosage form; however, the Agency could refuse to approve an ANDA if it found that a difference in release mechanism caused the composition of the proposed drug product to be unsafe (21 CFR 314.127(a)(8)(i)(B)), or if it caused the proposed drug product to not be bioequivalent to the reference listed drug.

[6] See also, Preamble to Final Rule Implementing Hatch-Waxman Amendments, (57 FR 17950, 17969, April 28, 1992) (equating change in release mechanism with other changes in inactive ingredients, not changes in dosage form).

[7] Similarly, drug products classified under the dosage form "spray" may vary in the type of container closure system used, the actuator, or the nozzle, yet FDA considers all sprays to be the same dosage form in spite of differences in release technologies. In addition, the release mechanisms for extended-release tablets may differ (e.g., matrix, osmotic pump), but the products are considered to be the same dosage form.

[8] Examples of FDA approved drug products with different release mechanisms that FDA has found to be therapeutically equivalent (pharmaceutically equivalent and bioequivalent) include:

scientific basis for distinguishing dosage forms on the basis of release mechanisms." Moreover, "bioequivalency standards assure the therapeutic equivalence of any pharmaceutically equivalent extended-release product."[9]

As discussed in section B below, several petitions suggest that matrix systems have a greater abuse potential than reservoir systems and some suggest that the difference in abuse potential precludes a finding of pharmaceutical equivalence. The petitioners argue that the matrix system may be subject to more abuse than the reservoir system because the fentanyl can be more easily extracted from the matrix system and that this difference distinguishes the two types of products as different dosage forms. However, these concerns go to the safety of the formulation, not the sameness of the dosage form or the pharmaceutical equivalence of the products. Moreover, as explained below, we believe that both the reservoir and matrix fentanyl transdermal systems have the potential to be abused, and petitioners have not presented data sufficient to persuade us that matrix products have a greater abuse liability potential than reservoir ones. We find that theoretical differences in potential abuse liability are not sufficient to reclassify a transdermal system with a different release mechanism as a novel dosage form. FDA considers both the reservoir and matrix type of transdermal products to be the same dosage form, and we deny your request to classify the matrix system for fentanyl transdermal products as a different dosage form.

B. Risk Management Plan

Two petitions request that FDA require an RMP for fentanyl transdermal systems using a matrix system because they allege that the fentanyl transdermal matrix systems may be diverted and abused with greater ease than fentanyl reservoir systems (Alza Petition at 6; Brookoff Petition at 14).[10] The petitioners argue that because the generic version uses a matrix system that can be cut into small pieces, and fentanyl is more easily extracted from a matrix system than from a reservoir system, matrix systems present a different and larger potential for abuse compared with Duragesic (Alza Petition at 2,4; Brookoff Petition at 9,10).

(a) ANDA 75-269, Nifedipine Extended-release Tablets, Biovail Laboratories Inc., which has an extended-release coating, was designated therapeutically equivalent to NDA 19-684, Procardia XL (Nifedipine) Extended-release Tablets, Pfizer Inc., which has an osmotic extended-release mechanism.
(b) ANDA 76-467, Glipizide Extended-release Tablets, Watson Laboratories, which has an extended-release coating, was designated therapeutically equivalent to NDA 20-329, Glucotrol XL (Glipizide) Extended-release Tablets, Pfizer Inc., which has an osmotic extended-release mechanism.
(c) NDA 20-704, Claritin Reditabs (Loratidine Orally Disintegrating Tablets), Schering Plough Corp., over-the-counter drug product utilizing a certain orally-disintegrating tablet technology was designated therapeutically equivalent to multiple ANDAs that use different orally-disintegrating tablet technology. *See also, Pfizer Inc., v. Shalala*, 1 F. Supp. 2d 38, (D.D.C. 1998); 182 F.3d 975 (D.C. Cir. 1999) (regarding nifedipine); *Warner-Lambert Co. v. Shalala*, 202 F.3d 326 (D.C. Cir. 2000) (regarding phenytoin). In both cases, the court upheld FDA's approval of an ANDA product where the generic capsule/tablet version was considered the same dosage form as the RLD's capsule version.
[9] FDA Response to Citizen Petition by Pfizer, Inc., Docket No. 93P-0421 at 5,11 (August 12, 1997).
[10] We note that neither petition identifies legal authority under which FDA could require a risk management plan for fentanyl transdermal products as a condition of approval.

Alza notes that it commissioned a study to compare the relative attractiveness of prescription opioids to potential abusers (Alza Petition at 5). The study found that of the 14 products included in the research, OxyContin was considered the most attractive (1st) and Duragesic was the least (14th). According to Alza, the fentanyl-in-matrix formulation was considered 11th in relative attractiveness (Alza Petition at 5-6), thus indicating that it has a higher abuse liability potential than Duragesic.

Alza acknowledges that it markets a fentanyl transdermal matrix system in some European markets, and has replaced the reservoir system with the matrix system in those markets (Alza Petition at 3). Alza states, however, that before a matrix system is introduced into a market, it conducts an assessment of the local abuse potential of the matrix system (Alza Petition at 3). Alza claims that although it has determined that its matrix system has an acceptable risk-benefit profile for European markets, opioid abuse is more of a problem in the United States than in Europe and, thus, the risk-benefit profile of a matrix product in the United States is less favorable (Alza Petition at 3). Alza further argues that studies showed that the fentanyl in Alza's own matrix formulation marketed in Europe was readily extractable with common household solvents and provided a higher yield than soaking the gel-in-reservoir system in the same solvents.

The information provided by the petitioners is not sufficient to lead us to conclude that a matrix system has a higher abuse potential than the reservoir system of Duragesic. As commenters to the Alza petition note, Alza's study was flawed because, among other things, "the researchers note that nearly a quarter of [persons sampled] claimed experience with the fentanyl matrix patch, which was not available" (Noven Pharmaceuticals, Inc., December 23, 2004, comment to Alza petition at 9). The fact that such a high percentage of persons sampled claimed experience with a product that had never been produced or marketed undercuts the reliability of the survey results. In addition, Alza has provided the Agency with no raw data to support its conclusions. Finally, the statistical validity of the "Opioid Attractiveness Scale" and of the sample size used for Alza's study has not been demonstrated by Alza.

We conclude that both matrix and reservoir formulations may be subject to abuse, although the methods of abuse and/or misuse may differ (e.g., although the matrix formulation could be cut into multiple pieces for sharing among a group of people, the gel from the gel-in-reservoir system may be frozen and then broken into small fragments for sharing, or alternatively aliquots of the gel may be injected into multiple people). The fentanyl in a matrix system may be extractable by using common household solvents, but this method of extraction takes time and may require that the adhesive be removed from the extracted mixture. The fentanyl-containing gel of the reservoir system may be extracted directly from the reservoir, bypassing the wait time of 45 minutes or more associated with soaking the matrix formulation. Moreover, both formulations have a substantial amount of fentanyl remaining after the prescribed 72 hours of use.

Thus, although we are concerned that fentanyl abuse may be a growing problem in the United States market, the matrix system does not raise product-specific abuse concerns. We intend to continue to monitor reports of abuse; RMPs may be considered in the future

to address any concerns. We would support and assist any efforts by a manufacturer to develop an RMP. If FDA concludes that voluntary RMPs are appropriate for fentanyl transdermal systems, the innovator as well as the generic versions will be requested to implement such plans.

C. Bioequivalence and Clinical Studies

The Act generally requires an ANDA applicant to provide, among other things, information to show that the generic drug is bioequivalent to the RLD (21 U.S.C. 355 (j)(2)(A)(iv)). Section 355(j)(8)(B) provides that a generic drug shall be considered to be bioequivalent to the listed drug if:

> "(i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or (ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug."

The standard bioequivalence (pharmacokinetic) study is conducted using a two-treatment crossover study design in a small number of volunteers, usually 24-36 healthy normal adults. Single doses of the test and reference drug products are administered to each of these volunteers, and the blood, plasma, or serum levels of the drug are measured over time. The pharmacokinetic parameters characterizing the rate and extent of absorption are examined by statistical procedures. The pharmacokinetic parameters of interest are the area under the plasma concentration vs. time curve (AUC) calculated to the last measured concentration time (AUC_{0-t}); AUC extrapolated to infinity ($AUC\infty$), which represents the extent of absorption of the drug; and the maximum or peak drug concentration (C_{max}). C_{max} is affected by the rate of absorption and is considered to be a surrogate for the rate of absorption.

The statistical methodology for analyzing these bioequivalence studies is called the two one-sided test procedure. Two situations are tested with this statistical methodology. The first of the two one-sided tests determines whether a test (generic) product, when substituted for a reference (brand-name) product, is significantly less bioavailable. The second of the two one-sided tests determines whether the reference product, when substituted for the test product, is significantly less bioavailable. Based on the opinions of FDA medical experts, a difference of greater than 20 percent for each of the above tests has been determined to be significant and, therefore, undesirable. Numerically, this

is expressed as a limit of test-product average/reference-product average of 80 percent for the first statistical test and a limit of reference-product average/test-product average of 80 percent for the second statistical test. By convention, all data are expressed as a ratio of the average response (AUC and C_{max}) for test and reference, so the limit expressed in the second statistical test is 125 percent (reciprocal of 80 percent).

For statistical reasons, all data are log-transformed prior to statistical testing. In practice, these statistical tests are carried out using an analysis of variance procedure (ANOVA) and calculating a 90 percent confidence interval for both C_{max} and AUC. The confidence interval for both AUC and C_{max} should be entirely within the 80 percent to 125 percent boundaries described above. Because the mean of the study data lies in the center of the 90 percent confidence interval, the mean of the data is usually close to 100 percent (a test/reference ratio of 1).

The pharmacokinetic parameter T_{max} is defined as the time to peak plasma drug concentration following dosing. T_{max} is also used as a general index of the rate of drug absorption. T_{max} can be statistically analyzed by nonparametric methods but, due to the highly variable nature of T_{max} data, this parameter cannot be analyzed by the same ANOVA methodology used to construct the 90 percent confidence intervals. Thus, statistical criteria are not applied to T_{max}. FDA considers T_{max} as supportive data in determining whether two products are bioequivalent.

The Mead petition argues that because fentanyl is a Schedule II opioid analgesic with an overdose potential, the Agency should require more restrictive bioequivalence criteria even when an ANDA has the same rate-controlling membrane layer as the RLD (Mead Petition at 3). The petitioner requests that the Agency use the following criteria for such fentanyl transdermal systems:

> (1) The partial AUC up to median T_{max} of the brand as an estimate of the absorption phase of the test formulation should be equivalent (90% Confidence Interval (CI) to be within 80%-125%) to that of the RLD in order to ensure that the rate of absorption of this potent opioid is not a safety concern.
> (2) The bioequivalence limits for C_{max} and AUC should be contained within 90%-111% for 90% CI or contained within 80%-125% for 95% CI. This restrictive bioequivalence requirement is necessary because of the potency of fentanyl (any significant change in plasma levels may have serious or life-threatening clinical consequences).

We disagree that ANDAs for fentanyl transdermal systems should be subject to more restrictive bioequivalence criteria than we apply to other ANDAs.

Before a generic transdermal patch can be approved, it must be shown to be bioequivalent to the reference listed drug. This requirement ensures that the plasma/serum profiles of the two products are sufficiently similar so that a similar efficacy and safety profile can be expected. Although, as noted above, bioequivalence is generally evaluated by comparing AUC and C_{max} for the test and reference products, if a

product described in an ANDA differed significantly from the RLD in plasma concentration profile during early time points or after the removal of the patch, we would not judge the two products to be therapeutically equivalent. In short, we will not approve an ANDA for a fentanyl transdermal system that uses the matrix system unless we believe it will perform the same as the RLD (which may contain a rate-controlling layer).

Moreover, the petitioners have not provided any data to show that the current FDA criteria for bioequivalence are inappropriate for these drug products. Fentanyl is not a narrow therapeutic index drug and, in the past, the Agency has applied the standard bioequivalence limits of 80-125% on the confidence interval of the mean C_{max} and AUC test/reference ratio in its review of supplemental changes in other fentanyl products (e.g., Duragesic and Actiq), as well as other high potency drug products (such as the approval of generic oxycodone products), with no increased risk to patient safety, as determined by post-marketing surveillance. Adding the parameter of partial AUC (0-T_{max}) to the bioequivalence comparison would not provide additional information in a case where a generic product with a release mechanism different from the RLD produces a similar time-concentration profile as the RLD. With respect to requiring partial AUC, the petitioner has not provided any information to support its contention that its use would identify potential safety or effectiveness problems that would not be identified through traditional bioequivalence measures. Consequently, we deny Mead's request to require more restrictive bioequivalence criteria for generic fentanyl transdermal systems.

FDA's bioavailability and bioequivalence guidance recommends that applicants seeking approval of systemically available generic products statistically compare only AUCt, AUC∞ and C_{max}, unless another approach is more appropriate for valid scientific reasons. It is our current position that there is no valid scientific reason justifying the use of partial AUC (AUCpR). With specific regard to transdermal products, FDA recommends using only AUCt, AUC∞ and C_{max}. See the guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*. This guidance recommends using AUCpR only for orally administered immediate-release drug products in limited situations - those in which appropriate clinical efficacy and safety trials and pharmacokinetic/pharmacodynamic (PK/PD) studies call for better control of drug absorption into the systemic circulation.

The limited situations described in the guidance do not pertain to Duragesic because it is not orally administered, no sufficient clinical data or PK/PD data support the value of AUCpR in bioequivalence studies of Duragesic, and fentanyl elimination from Duragesic contributes substantially to AUCpR, thereby limiting this metric's use in evaluating the rate of fentanyl absorption. Moreover, available scientific data do not support the routine use of AUCpR in bioequivalence studies because this approach has been tested only in simulated pharmacokinetic studies and has not been validated by in vivo data. Finally, FDA's approval of a variety of parenteral, oral, and transdermal dosage forms that release fentanyl at different rates suggests that strict control of the rate of fentanyl absorption is not a critical safety concern justifying the use of AUCpR. It is our conclusion, therefore, that the statistical comparison of C_{max}, AUCt, and AUC∞ is sufficient to determine whether a proposed generic product is bioequivalent to Duragesic.

The Mead petition also asks the Agency to require clinical safety and efficacy studies for any generic transdermal fentanyl systems that do not contain a rate-controlling membrane layer (Mead Petition at 3). Fentanyl is the active moiety in the drug product, and it can be readily quantitated in the plasma with accuracy and precision. Therefore, the preferred method for bioequivalence testing is an in vivo test in humans in which the concentration of the active ingredient in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time (21 CFR 320.24). Clinical safety and efficacy studies are significantly less sensitive than pharmacokinetic studies at detecting potential differences in bioequivalence. Therefore, we deny Mead's request to require clinical safety and efficacy studies, because they are not appropriate in this case.

D. Skin Testing

The Shafer petition explains that Duragesic has a rate-limiting membrane that is intended to provide approximately the same resistance to skin penetration as intact skin. Shafer claims that other transdermal systems lack any intrinsic control of the rate of transdermal drug delivery and that these systems rely on intact stratum corneum[11] to control the rate of fentanyl delivery (Shafer Petition at 2). The petitioner argues that such systems have demonstrated huge variability in fentanyl delivery rate and concentration, potentially exposing patients to toxic levels of fentanyl (Shafer Petition at 2). As a result, the petitioner asks that the Agency require ANDA applicants for fentanyl transdermal systems to demonstrate bioavailability/bioequivalence against Duragesic on both intact skin and on stripped skin (i.e., skin in which the stratum corneum has been intentionally removed with adhesive tape) (Shafer Petition at 1). The petitioner also requests the Agency to require a demonstration of safety on stripped skin for any new fentanyl formulation (Shafer Petition at 1). The petitioner claims that because the Duragesic transdermal system has a rate-controlling membrane layer that provides an upper limit on the rate at which fentanyl can be released from the reservoir into the skin, the membrane acts as a safety mechanism for preventing delivery of fentanyl at too high a rate (Shafer Petition at 2). Finally, the petitioner states that FDA should issue a guidance for generic approval of transdermal opioids stating that appropriate bioequivalence studies should be performed on both intact skin and stripped skin. If a generic product demonstrates bioequivalence in both settings, then it can reasonably be expected to be as safe as the innovator (Shafer Petition at 3).

We do not agree that bioequivalence testing on stripped skin is necessary. Although we might consider such testing pre-clinically to derive scientific data, we have not required clinical testing on stripped skin for Duragesic or for any other transdermal products. Bioequivalence testing for an ANDA should generally be consistent with the *Dosage and Administration* directions in the product labeling of the RLD, especially when subject safety is a concern. The *Dosage and Administration* section for the fentanyl transdermal system RLD specifically states that Duragesic "should be applied to non-irritated and non-irradiated skin . . ." and new systems "should be applied to a different skin site after removal of the previous transdermal system." The drug labeling for approved ANDAs

[11] The stratum corneum is the layer of dead, desiccated skin cells on the outermost surface of the skin.

for fentanyl transdermal systems will contain the same dosage and administration instructions.[12] Bioequivalence evaluation using skin in which the stratum corneum has been intentionally removed would be contrary to the labeled use of the RLD and may raise an unacceptable safety concern for study subjects.

Although we agree that the stratum corneum can impede the flux of transdermal fentanyl, and its removal may result in faster transfer of fentanyl across the skin (over a dosing interval), resulting in higher systemic availability, the release of fentanyl from any fentanyl transdermal system (including the Duragesic patch) is a dynamic process influenced by many factors. In the Duragesic patch, the ethylene-vinyl acetate co-polymer layer (rate-controlling membrane) constitutes one factor that contributes to the rate of release. This layer functions separately from and in addition to the impact of different skin types among individuals, and differences in body sites within the same individual, on drug absorption. There are insufficient data to determine precisely the role the rate-controlling membrane plays in decreasing variability, or in preventing overdosing when the patch is applied to a body site where the stratum corneum has been removed. The petitioner suggests that if a transdermal system lacked a rate-controlling membrane, then the system relies exclusively on intact stratum corneum for drug (fentanyl) delivery. This is incorrect. Matrix patches, where the drug is uniformly distributed in the adhesive layer, may contain no rate-controlling layer, but use a chemical control to limit the rate of fentanyl infusion. To obtain approval, a matrix system, like a reservoir system, must show that it can deliver the drug in a predictable and controlled fashion. The makeup of the formulation (type of excipients), independent of a rate-controlling membrane, can significantly affect the release of drug from a transdermal system and its transfer across the skin.

We agree that there may be some variability in skin permeability among individuals that can affect the rate of absorption from a fentanyl transdermal system, but the petitioner has not provided any data to show that a transdermal system with a physical control (such as the rate-controlling membrane found in Duragesic) is superior to a matrix transdermal system, which lacks the rate-controlling membrane but relies, instead, on a chemical control. The petitioner claims that the rate-controlling membrane provides an upper limit on the rate at which fentanyl can be released into the skin, but does not provide any data to substantiate this claim, nor have the petitioners defined the "upper limit." The Duragesic drug labeling states that it should be applied to non-irritated and non-irradiated skin and instructs Duragesic users to rotate application sites, presumably to avoid applying a new system to stripped skin. In addition, the *Warnings* section of the drug labeling specifically advises against exposing a patient to sources of heat, which could potentially increase the rate of fentanyl delivery from the patch. All of this suggests that even with the Duragesic patch, the rate-controlling membrane does not act as a comprehensive safety mechanism for preventing delivery of fentanyl at unsafe rates. Because we did not require a demonstration of safety on stripped skin for Duragesic and the labeling directs patients to apply the patch to intact skin, we deny your request to require a safety demonstration of new fentanyl transdermal systems on stripped skin.

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[12] 21 CFR 314.94(a)(8)(iv).

We do not find that a product-specific guidance for fentanyl is required. FDA's current guidance documents adequately cover the bioequivalence determination for a fentanyl transdermal system. The bioequivalence testing required is consistent with the *Dosage and Administration* instructions for the product and evaluation using skin in which the stratum corneum has been intentionally removed would be contrary to the labeled use of the RLD.

III. CONCLUSION

We deny all four petitions. FDA does not believe that the matrix system should be classified as a dosage form different from a reservoir system, nor do we believe that ANDAs for fentanyl transdermal systems using a matrix system present a greater safety risk than fentanyl products that use a reservoir system. At this time, we do not think it is necessary to require either more restrictive bioequivalence testing or testing on stripped skin for fentanyl ANDAs that do not have a rate-controlling membrane. Finally, we will continue to monitor incidents of abuse, misuse, and diversion and we may consider whether to request a voluntary RMP for all generic and innovator matrix and reservoir fentanyl transdermal systems.

Sincerely yours,

Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research