IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

GRACEWAY PHARMACEUTICALS, LLC
340 Martin Luther King Jr. Blvd., Suite 500
Bristol, TN 37620,

Plaintiff,

v.

Civil Action No. _____

KATHLEEN SEBELIUS,
in her official capacity as
SECRETARY, DEPARTMENT OF
HEALTH AND HUMAN SERVICES
200 Independence Ave., S.W.
Washington, D.C. 20201,

and

MARGARET HAMBURG, M.D.,
in her official capacity as
COMMISSIONER OF FOOD AND DRUGS,
FOOD AND DRUG ADMINISTRATION,
10903 New Hampshire Avenue,
Silver Spring, MD 20993,

Defendants.

COMPLAINT FOR DECLARATORY, INJUNCTIVE, AND OTHER RELIEF

Plaintiff Graceway Pharmaceuticals, LLC ("Graceway"), by its undersigned counsel, hereby brings this Complaint against Defendants Kathleen Sebelius, solely in her official capacity as Secretary of the Department of Health and Human Services ("HHS"), and Margaret Hamburg, M.D., solely in her official capacity as Commissioner of Food and Drugs, head of the Food and Drug Administration ("FDA" or the "agency"), and alleges as follows:

1. This is an action to hold unlawful and set aside FDA's refusal to reject abbreviated new drug applications ("ANDAs") for generic versions of Graceway's Aldara® (imiquimod) Cream, 5% that fail to include comparative clinical data showing that the proposed generic drugs are "bioequivalent" for use in treating genital warts. Aldara is an FDA-approved topical cream used to treat three very different conditions, only one of which is uniquely located in the genital and perianal area: (1) genital warts, (2) a type of precancerous growth on the face or scalp, and (3) a type of skin cancer. Before FDA can approve a generic drug, its manufacturer must demonstrate (among other things) that the proposed generic drug is "bioequivalent" to the brand name drug. FDA essentially has dispensed with that requirement in the present case by approving a generic formulation without requiring its manufacturer to submit any data showing bioequivalence in treating genital warts, the condition for which Aldara is most often prescribed. FDA's refusal to require such data is based on unsupported leaps of logic, assertions that are inconsistent with long-standing FDA scientific analysis, and incorrect assumptions regarding the burden of proof. As a result, FDA's decision is arbitrary, capricious, an abuse of discretion, and otherwise violates the Administrative Procedure Act (the "APA").

2. FDA already has approved the entry into the marketplace of one generic version of Aldara based upon inadequate data regarding that product's effectiveness and safety. Unless enjoined by this Court, FDA is likely to approve additional generic products based upon inadequate data as early as February 2011, causing severe and irreparable harm to Graceway and potentially to the public at large.

INTRODUCTION

3. The Food, Drug, and Cosmetic Act ("FDCA") requires all new prescription drugs to obtain FDA approval before they can enter the marketplace. 21 U.S.C. § 355(a). Manufacturers of brand name or "pioneer" drugs must demonstrate the safety and effectiveness of their products. Typically, that is done by conducting pre-clinical and clinical studies and submitting the resulting data to FDA in a new drug application ("NDA"). 21 U.S.C. § 355(b)(1).

4. Following a period of statutory marketing exclusivity and, if applicable, patent protection afforded to a pioneer drug, generic manufacturers may seek FDA approval to sell generic drugs containing the same active ingredient as the pioneer drug (which is known as the "reference drug "). Generic drugs are approved by means of an ANDA. Generally, an ANDA must show that the proposed generic contains the same active ingredient as the reference drug, in the same strength, dosage form, and route of administration; is labeled for the same uses as the reference drug; and is "bioequivalent" to the reference drug. See 21 U.S.C. § 355(j)(2)(A). If those requirements are met, FDA is authorized to approve the proposed generic drug. In essence, the agency's previous determination that the reference drug is safe and effective is fully extrapolated to the generic product, based on the demonstration that the generic is "the same as" the reference drug. See id. § 355(j)(4).

5. The reference drug and the proposed generic product are considered to be "bioequivalent" if there are no significant differences between them in the rate or extent of absorption of the active ingredient or active moiety at the site of action. 21 C.F.R. § 320.21(e). Differences in formulation and/or in the manufacturing processes between a proposed generic drug and the approved reference drug can lead to critical differences in the release of the active

ingredient from the product and, in turn, the absorption of the active ingredient onto or into the body. To address this problem, the FDCA requires generic applicants to submit bioequivalence studies to help prove that the proposed generic will, in fact be as safe and effective for the patient as the approved drug.

6. For products like Aldara that are applied to the skin and act locally (that is, at the site of application and not throughout the body), FDA generally relies on comparative clinical trials to establish bioequivalence. In a comparative clinical trial, patients are treated with both the reference drug and the proposed generic, and a determination is made about whether there is a significant difference when it comes to the effect of the two drugs in treating the relevant indication.

7. The bioequivalence analysis becomes even more complicated when a single locally-acting drug is approved for two or more indications. A proposed generic version of that drug may be bioequivalent to the reference drug for the tested indication, but not for a different indication. When a locally acting drug has been approved to treat multiple conditions, FDA has allowed a comparative study in one indication to suffice as proof of bioequivalence in another. However, the agency has only allowed such extrapolation, from one condition to another, in certain limited circumstances, when the indications are "related" and involve the "same site of action." See Westwood Squibb Citizen Petition Response, Docket 95P-0379, dated May 22, 2002 at 4.

8. Graceway's pioneer drug, Aldara®, is a topical, locally-acting cream approved for the treatment of three distinct and wholly unrelated conditions: (i) external genital warts, a sexually-transmitted disease caused by a virus; (ii) a certain type of actinic keratoses, a

pre-cancerous growth on the face and scalp caused by overexposure to the sun; and (iii) primary superficial basal cell carcinoma, a common type of skin cancer.

9. In July 2009, Graceway petitioned the FDA requesting that the agency refuse to approve any ANDA for a generic version of Aldara unless the application contains data from, among other things, a comparative clinical bioequivalence study in patients with genital warts.[1] Ex. 1 (Aldara Citizen Petition). In essence, Graceway was seeking to require FDA to comply with the FDCA, which allows FDA to rely on certain alternative methods of demonstrating bioequivalence only where such methods are "scientifically valid" and may be "expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect." 21 U.S.C. § 355(j)(8)(B)(i).

10. On January 26, 2010, FDA denied Graceway's Citizen Petition. Ex. 2. FDA's decision not to require bioequivalence studies in patients with external genital warts was based on its unsupportable conclusion that genital warts are "related" to and share the same "site of action" as the other two conditions treated by Aldara, both of which result from sun exposure. Id. This determination was unsupported by – and in fact, contrary to – basic science, common sense, and the agency's previous actions in similar situations. While Graceway is not contesting for the purposes of this lawsuit that AK and superficial basal cell carcinoma may be "related" in the sense that both result from sun exposure, neither has anything in common with genital warts, which appear in the pubic area and are caused by an infectious disease – a sexually-transmitted virus.

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[1] In its Citizen Petition, Graceway also requested that FDA require bioequivalence studies in patients with superficial basal cell carcinoma. However, for purposes of the present lawsuit, Graceway is not contesting FDA's decision that comparative clinical studies in actinic keratoses suffice to demonstrate bioequivalence in superficial basal cell carcinoma.

11. On February 25, 2010, FDA approved an ANDA submitted by Nycomed US Inc. ("Nycomed") seeking to market and sell a generic version of Aldara. Following FDA approval, Nycomed started to market and sell its generic imiquimod product. In the few months that the Nycomed product has been in the marketplace, Graceway already has suffered grave harm in the form of lost revenue and significant loss of market share, and Graceway has been forced to introduce its own generic product in an effort to compete with the Nycomed product.

12. Upon information and belief, several other generic manufacturers are poised to obtain FDA approval for generic versions of Aldara in February 2011, when one of Graceway's patents covering Aldara is set to expire. Around the same time that it approved Nycomed's ANDA in February 2010, FDA also issued a draft guidance document on imiquimod. The draft guidance document did not recommend that bioequivalence studies be performed in patients with genital warts. It is clear, then, that FDA's approval of the Nycomed ANDA was not an oversight and not a one-time event. Unless FDA is required to rescind Nycomed's approval and enjoined from approving any other ANDAs for generic versions of Aldara that are missing the types of data described herein, Graceway will suffer even greater harm due to even more drastic reductions in its market share, patient loyalty, and revenue for Aldara.

13. Accordingly, Graceway seeks (i) a declaratory judgment against FDA declaring the agency's actions denying Graceway's Citizen Petition and approving Nycomed's ANDA to be arbitrary, capricious, an abuse of discretion and not in accordance with law; and (ii) injunctive relief ordering FDA to withdraw Nycomed's ANDA approval and refuse to approve

any other ANDAs for general versions of Aldara unless the applications contain comparative clinical bioequivalence studies in patients with genital warts.

PARTIES

14. Plaintiff Graceway Pharmaceuticals, LLC is a Delaware limited liability company with its principal place of business at 340 Martin Luther King Jr. Blvd., Suite 500, Bristol, Tennessee 37620. Graceway develops, acquires, markets, and sells pharmaceutical products for a wide range of conditions, including dermatologic conditions. Graceway holds an approved NDA, No. 20-723, for Aldara® (imiquimod) Cream, 5%.

15. Defendant Kathleen Sebelius is the Secretary of HHS and is responsible for administering and enforcing the Food, Drug, and Cosmetic Act, 21 U.S.C. § 321, et seq. Defendant Sebelius is being sued in her official capacity only. Defendant Sebelius maintains an office at 200 Independence Avenue, S.W., Washington, D.C. 20204.

16. Defendant Margaret Hamburg , M.D., is the Commissioner of Food and Drugs and is responsible for supervising the activities of FDA, an administrative agency within HHS. Defendant Hamburg is being sued in her official capacity only. Defendant Hamburg maintains offices at 10903 New Hampshire Avenue, Silver Spring, MD 20993.

JURISDICTION AND VENUE

17. Jurisdiction in this Court is grounded upon and proper under 28 U.S.C. § 1331 (federal question), in that this is a civil action arising under the laws of the United States; 28 U.S.C. § 1346, in that this case involves claims against the federal government; 5 U.S.C. § 702, in that Graceway is seeking judicial review of an agency action from which it has suffered a legal wrong, has been adversely affected, and has been aggrieved; 28 U.S.C. § 1361, in that

this is an action to compel an officer of the United States to perform his duty; 28 U.S.C. §§ 2201-2202 (declaratory judgment), in that there exists between Graceway and the Defendants an actual, justiciable controversy as to which Graceway requires a declaration of its rights by this Court as well as preliminary and permanent injunctive relief to prohibit the Defendants from violating laws and regulations; and 21 U.S.C. § 355(q) and other sources of law, in that the conduct complained of constitutes final agency action.

18. Venue is proper in this Court under 28 U.S.C. § 1391(b) and (e) because this is a civil action in which the Defendants are officers of the United States acting in their official capacities and one of the Defendants maintains her office and conducts business in this judicial district. Moreover, a substantial part of the events giving rise to the claims herein occurred within this judicial district.

19. Graceway has standing to bring the present lawsuit because it is suffering and faces additional actual injury as a result of FDA's decisions and because it is within the zone of interest of the relevant statutory provisions.

NATURE OF THE CASE

I. Statutory And Regulatory Background

20. As noted above, generic drug manufacturers are required to submit evidence demonstrating, among other things, that their proposed products are "bioequivalent" to an approved pioneer drug. See 21 U.S.C. § 355(j)(2)(A). The FDCA defines bioequivalence to mean that the "rate and extent of absorption of the [proposed generic] drug do not show a significant difference from the rate and extent of absorption of the [approved pioneer] drug when

administered . . . under similar experimental conditions." 21 U.S.C. § 355(j)(8)(B)(i); see also 21 C.F.R. § 320.1(e).

21. For drugs that work systemically by circulating in the bloodstream (*e.g.*, oral tablets and capsules), bioequivalence typically is demonstrated by comparing the rate and extent of absorption of the active ingredients in the blood. This usually is done by administering a dose of the proposed generic drug to healthy subjects and measuring the amount of active ingredient absorbed into the bloodstream, and then repeating the process with the approved pioneer drug. Measuring the amount of the drug in blood is relatively simple, and comparing the amounts of the drug absorbed from the two products is based on well-established statistical methods in general use both by industry and FDA.

22. In contrast, for products like Aldara that are administered topically (*i.e.*, applied to the skin) and act locally (*i.e.*, at the site of application and not throughout the body), bioequivalence must be measured in a different way, using a more subjective approach For such products, FDA often must rely on comparative clinical studies to demonstrate bioequivalence. See 21 C.F.R. § 210.24(b)(4) (describing comparative clinical bioequivalence studies and noting their appropriateness for "dosage forms intended to deliver the active moiety locally, *e.g.*, topical preparations for the skin"); Citizen Petition Response, Docket No. 2004P-0557, dated April 11, 2008 ("Efudex Petition Response") at 5-6; Ex. 2 (Aldara Petition Response) at 4.

23. In standard clinical trials of new drugs, patients are given either a test drug or placebo. The trial determines if the test drug has a clinical effect over and above that seen with the placebo in treating a specific disease or condition. In a comparative clinical trial, patients are given either the test drug, a reference drug, or a placebo, and the goal is to determine

if there is a clinically significant difference in the performance of the two drug products in treating a specific disease or condition. The applicable standard might be cure, or it might be the patient reporting an improvement in symptoms.

24. FDA regulations list methodologies for determining bioavailability and bioequivalence "in descending order of accuracy, sensitivity and reproducibility." 21 C.F.R. § 324(b). "Comparative clinical trials" is fourth (and next to last of the specified methodologies). See 21 C.F.R. § 324(b)(4). A comparative clinical trial does not directly measure "the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of action." See 21 C.F.R. § 320.1(e) (defining bioequivalence). Rather, a comparative clinical trial is a step removed: it measures the effect of the pioneer drug and the proposed generic in treating a specific disease or condition, and compares the results. As a result, there is a finding of bioequivalence even though there is no direct measurement of the rate and extent of drug absorption.

25. The bioequivalence analysis becomes more complicated when a single locally-acting drug is approved for two or more diseases or conditions (sometimes referred to as "indications"). A proposed generic version of that drug may be bioequivalent to the reference drug for the tested indication, but not for any additional indications. Put simply, it is possible that the reference drug and the proposed generic perform the same when used to treat one disease, but may differ when used to treat another disease or condition. If the approved reference drug and the proposed generic release different amounts of active ingredient, or are absorbed at different rates, that fact may be clinically insignificant – and undetectable – in patients with sun damaged skin. However, for patients with genital warts, such differences between the reference

drug and the generic may be very significant indeed. Without data from comparative clinical trials in patients with genital warts, FDA would have no way of knowing whether there was a difference in release or absorption rates between the two drugs that might be significant in treating patients with genital warts.

26. In an effort to address this problem, FDA has allowed a comparative study of a locally acting drug in one approved indication to suffice as proof of bioequivalence in another approved indication only in certain circumstances, including when the indications are "related" and involve the "same site of action." Westwood Squibb Petition Response at 4 ("If the generic drug product is shown to be bioequivalent for one indication, it is expected to be bioequivalent for all related indications with the same site of action."). The rationale behind this practice is that if two indications are related and occur at the same site of action, FDA can properly extrapolate bioequivalence from one condition to the other.

II. Factual Background

A. Aldara® (imiquimod) Cream, 5%

27. Aldara® is a topical, locally-acting cream that was first approved by FDA on February 27, 1997. The product is supplied in single use packets, each of which contains 250 mg of cream, including 12.5 mg (or 5%) of the product's active ingredient, imiquimod. Aldara is applied to the skin and does not depend on systemic absorption for its effect.

28. Aldara currently is approved for the treatment of three distinct conditions: (i) external genital and perianal warts/condyloma acuminate ("EGW"), a form of sexually-transmitted disease typically located on the entrance of the vagina, anus, penis, scrotum, groin, or thigh; (ii) clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses ("AK"), a type

of pre-cancerous growth typically located on the face and scalp; and (iii) primary superficial basal cell carcinoma ("sBCC"), the most common type of skin cancer, found on the trunk (excluding anogenital skin), neck or extremities (excluding the hands and feet). Among the three approved uses for Aldara, EGW is by far the most prevalent.

29. FDA initially approved Aldara in 1997 for the treatment of EGW in patients 12 years or older. EGW is a sexually-transmitted disease caused by infection with certain strains of the human papillomavirus ("HPV"). EGW appears as growths or bumps that appear around the entrance of the vagina, anus, penis, scrotum, groin, or thigh. The growths or bumps may be raised or flat and occur singly or in groups. They may be cauliflower-shaped and are most often flesh-colored and painless.

30. In 2004, FDA approved Aldara for the topical treatment of clinically typical nonhyperkeratotic,[2] nonhypertrophic[3] AK on the face or scalp in immunocompetent adults. AK is a flat, scaly growth on the skin that usually forms on parts of the body that are exposed to direct sunlight like the head, face, arms, neck, and trunk. AKs can be any shape and are skin-colored, reddish-brown, or yellowish-black in color. They range in size from as small as a pinhead to more than an inch across. The surface of the AK is dry and rough to the touch. Occasionally, an AK may itch or feel prickly, especially after sun exposure. AK is most commonly found in fair-skinned people who have spent a lot of time in the sun.

31. Also in 2004, FDA approved Aldara for the topical treatment of biopsy-confirmed, primary sBCC. sBCC is among the most common forms of cancers in humans. A sBCC lesion may appear as a new growth on the skin, as an open sore that fails to heal, or as a

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[2] Hyperkeratosis is thickening of the stratum corneum (the outermost layer of skin).

[3] Hypertrophy is an increase in the size of a cell.

change in appearance of an old growth on the skin. These lesions are usually not painful and may have different shapes and colors, including a small, smooth, shiny pale lump, a firm, red lump, a sore or lump that bleeds or scabs, or a red or brown patch that is rough or scaly and may itch or become tender.

B. EGW is Unrelated to AK and sBCC and Has a Different Site of Action

32. As noted above, in the past, FDA has allowed a comparative study in one indication to suffice as proof of bioequivalence in another only in certain circumstances, including when the two conditions are "related" and have the same "site of action." Westwood Squibb Petition Response at 4 ("If the generic drug product is shown to be bioequivalent for one indication, it is expected to be bioequivalent for all related indications with the same site of action.").

33. EGW is wholly unrelated to either AK or SBCC. Both AK and sBCC involve abnormal proliferations of cells that arise within the epidermis as a result of sun exposure. EGW is a contagious disease caused by a virus that has a fundamentally different pathophysiology than AK and sBCC. There is no basis for assuming that a generic drug that is bioequivalent to Aldara for purposes of treating AK also would be bioequivalent for purposes of treating genital warts. Indeed, as discussed below, an examination of FDA's own pronouncements provides sufficient reason to assume the opposite is true.

34. The site of action for EGW also is the not the same as the site of action for AK and sBCC. EGW occurs at a different anatomical location and on different types of skin than AK and sBCC. While AK and sBCC usually occur on the face, head, and extremities, EGW by definition occurs in the pubic area, an area that is comprised of very different types of

skin (*e.g.,* vaginal tissues, the penis, the anus, and the scrotum). Indeed, FDA recently noted that skin that is penetrated by coarse, thick, "terminal" hairs – *e.g.,* the pubic region, where genital warts are often located – may have different absorption properties than skin that is penetrated by the thinner, finer, "vellus" hairs – for example, the face, neck, trunk and extremities where AK and sBCC often occur. Citizen Petition Response, Docket No. FDA-2004-P-0215, Mar. 25, 2009 at 20. Because FDA itself has recognized the difference in absorption properties between the types of skin located at the different sites of action for EGW and AK, comparative clinical testing is required in patients with EGW as well as AK before bioequivalence can be shown for the product as a whole.

35. There is no established body of evidence demonstrating that the availability of imiquimod at the site of action for AK or sBCC is similar to, or predictive of, the active ingredient's availability at the site of action for EGW. As a result, no study in AK or sBCC may be relied upon for reaching a conclusion about bioequivalence in EGW, and an ANDA for generic version of Aldara must contain data from a comparative trial in patients with EGW.

C. FDA's Denial of Graceway's Citizen Petition

36. On July 30, 2009, Graceway filed a Citizen Petition asking FDA to refuse to approve any generic imiquimod cream product relying on Aldara unless the application contained data from, among other things, a comparative clinical bioequivalence study in patients with EGW, the most prevalent of the three approved uses. Ex. 1 (Aldara Citizen Petition).

37. Graceway's petition identified FDA's previous statements and actions allowing a comparative clinical study in one condition to suffice as a demonstration of bioequivalence in another condition only where, among other things, the conditions are "related"

and delivery of the drug occurs to the same "site of action." Id. The petition also explained how EGW is completely unrelated to AK and sBCC (in terms of the cause and nature of the conditions, for example) and occurs in very different skin at very different locations on the body. See id. Consistent with the statute and FDA precedents, the petition argued, a comparative clinical study establishing bioequivalence in EGW is necessary because a comparative study in AK or sBCC cannot be relied on to predict bioequivalence in such a different condition.

38. On January 26, 2010, FDA denied Graceway's Citizen Petition, concluding that a single comparative clinical study in AK is sufficient to demonstrate bioequivalence in all three conditions. Ex. 2. FDA's decision was based on its unsupportable conclusion that the three conditions treated by Aldara are "related" and share the same "site of action." FDA's decision also relied squarely on scientific assertions that it has consistently rejected, both as part of its long-standing practice and (inexplicably) within its Response itself. While FDA, within limits, is required to treat innovator drugs and generic drugs differently – and it is indisputable that the agency should be afforded a high level of deference on questions of science – the science itself cannot be one thing for one person and the opposite for another. FDA's failure to explain its marked departure from its own precedent on basic points of science flagrantly violates the APA.

39. First, FDA acted arbitrarily, capriciously, and contrary to law when it found that EGW is "related" to AK and sBCC. Tellingly, FDA admitted that "EGW, arising from infection by human papillomavirus, differs pathophysiologically from AK and sBCC, both of which arise from overexposure to ultraviolet light . . ." Ex. 2 (Aldara Petition Response) at 8; see also id. at 6 ("AK, EGW, and sBCC differ pathophysiologically (EGW arises from infection

by human papillomavirus and AK and sBCC arise from overexposure to ulatraviolet light)"). However, FDA asserted that this difference is "not material for purposes of determining an appropriate bioequivalence study design." Id. FDA provided no explanation or analysis on this point, other than to note that all three conditions are responsive to the same drug, imiquimod. Id. at 9. FDA's analysis defies basic logic. If FDA were correct that two different conditions are "related" whenever both are responsive to the same drug, then by definition all conditions would be related to all other conditions for which the same drug is used, and there would be no need for the first prong of FDA's test in the first place. There simply is no basis for extrapolating from the results of a comparative clinical trial on patients with skin cancer that a generic drug would be bioequivalent to Aldara when used on patients with genital warts, an infectious disease.

40. FDA also acted arbitrarily, capriciously, and contrary to law when it found that EGW involves the same "site of action" as AK and sBCC. FDA admitted that EGW arises in "different anatomic locations and skin types" from AK and sBCC. Id. at 6. Nonetheless, FDA rejected Graceway's argument that the "site of action" for EGW is different than that for AK and sBCC because, it asserted, the "site of action" for all three is the epidermis, or outer layer of the skin. Id. at 6, 8. FDA's decision runs counter to its decision in another recent Petition Response, where it found that skin penetrated by coarse, thick, "terminal hairs" (like the pubic region, where EGW are often located) may have different absorption properties than skin penetrated by the thinner, finer "vellus" hairs of the face, neck, trunk, and extremities, where AK and sBCC usually occur. Citizen Petition Response, Docket No. FDA-2004-P-0215, Mar. 25, 2009 at 20.

41. Similarly, FDA asserted in the Aldara Petition Response that "the EGW, AK, or sBCC lesion would respond to treatment with the generic product to the same extent as it would to [Aldara], regardless of the underlying pathophysiology, exact anatomic location, or involved skin type." Ex. 2 (Aldara Petition Response) at 7. But as little as two years ago, FDA's position was that AK protocols could not support requirements for EGW, "due to differences in the disease states, dosing regimens and site of application." Memorandum of Meeting Minutes, Jan. 20, 2008 at 2. FDA has provided no explanation – let alone a reasonable one – for its changed views.

42. In its Aldara Petition Response, FDA also repeatedly (and inexplicably) refuted the very scientific assumptions upon which it premised its ruling in a way that makes the document itself internally inconsistent. For example, FDA took completely inconsistent positions on the reliability of cross-study comparisons at various points in the Response. A cross-study comparison involves the analysis of two different studies for purposes of drawing some conclusion across both of them. FDA relied in numerous places on cross-study comparisons to support the conclusion that bioequivalence in an AK study can be extrapolated to assume bioequivalence in EGW, but then dismissed as inherently unreliable any cross-study comparison that would undermine its conclusion. Compare Ex. 2 at 14 ("efficacy in the primary AK endpoint was only 44%-46% whereas efficacy in the primary sBCC endpoint was 70-80%) with id. ("it is problematic to compare cure rates across products, or across multiple indications for the same product, because there is typically no reason to think dose response curves are similar enough for the various indications that such comparisons would be valid for purposes of assessing bioequivalence methodology."). See also id. at 14, 15-16, 17, 13. FDA cannot have it

both ways: either cross-study comparisons are permissible or they are not. FDA's reliance upon them to support its preferred conclusion while simultaneously rejecting them as inherently unreliable is the epitome of arbitrary and capricious conduct.

43. FDA's Petition Response also fundamentally contorted the burden of proof by asserting that the burden is on *Graceway* to disprove the agency's presumption that all three conditions can be treated the same. Ex. 2 (Aldara Petition Response) at 11 ("You must provide a scientifically grounded reason that demonstrates that, because of the differences you allege, a well-designed study in the AK indication could be expected to miss significant formulation performance differences that an EGW study could be expected to detect."). But that is not the way the regulatory approval process works. The burden is not on Graceway to prove lack of bioequivalence; rather, the burden is on the generic manufacturers to prove bioequivalence as a condition of ANDA approval. 21 U.S.C. § 355(j)(2)(A). The burden also is on FDA and the generic manufacturers to comply with the FDCA's mandate that alternative approaches to establishing bioequivalence may not be used unless they are "scientifically valid" and able to "detect a significant difference between the [generic] drug and the [reference] drug in safety and therapeutic effect." 21 U.S.C. § 355(j)(8)(C); see 21 C.F.R. § 320.24(a) (requiring use of "the most accurate, sensitive, and reproducible approach available.").

44. On February 25, 2010, FDA approved the ANDA submitted by Nycomed seeking to market and sell a generic version of Aldara.

45. The foregoing FDA actions and decisions constitute, among other violations, conduct that is arbitrary, capricious, an abuse of discretion, contrary to law, and that reflects a failure to engage in reasoned decision making.

46. FDA's conduct in approving generic versions of Aldara without requiring adequate comparative clinical studies poses a very real risk to the public. Aside from the risk that an untested generic may undertreat a patient's genital warts, and lead to a worsening of the condition, there are also palpable safety risks associated with a generic that has never been tested at the genital site. Aldara contains imiquimod, which is an immune response modifier. The drug stimulates the body's own immune system to recognize skin cells that are infected with HPV and mount a defense against them. This targeted immune response can also cause intense local skin reactions, including burning, ulceration, and even skin erosion. These inflammatory reactions may be accompanied by flu-like symptoms such as malaise, fever, nausea, muscle pain, and rigors, as the body's immune system is stimulated by the drug. These adverse reactions to imiquimod increase as absorption of the drug increases, and so may be expected to occur with greater frequency in a generic version of Aldara that releases more drug into the skin. It is entirely possible that a generic drug can be tolerated when applied to skin lesions on the scalp or face, but be overly irritating or inflammatory when applied to the genital site.

47. Upon information and belief, several other generic manufacturers are poised to obtain FDA approval for generic versions of Aldara in February 2011, when one of Graceway's patents covering Aldara is set to expire. Around the same time that it approved the Nycomed ANDA in February 2010, FDA issued a draft guidance on imiquimod. The draft guidance recommended only that studies be performed in AK patients, and did not recommend bioequivalence studies in patients with genital warts. It is clear, then, that FDA's approval of the Nycomed product was not an oversight and not a one-time event. Absent judicial intervention,

FDA is likely to approve other generic versions of Aldara without requiring adequate clinical data demonstrating bioequivalence.

48. Revenues from Aldara sales comprise the majority of Graceway's total revenues, and they fund virtually all of Graceway's operations and bank debt. The generic Nycomed product's entry into the marketplace already has had a drastic effect upon Graceway's market share and revenues; the entry of additional generic product will have an irreversible effect upon the marketplace. Unless FDA is enjoined from approving ANDAs for generic versions of Aldara that are missing the types of data described herein, Graceway will suffer grave irreparable harm and drastic reductions in its sales, market share, and patient loyalty.

CLAIMS FOR RELIEF

Count I
(Administrative Procedure Act: Violation of the FDCA and Applicable Regulations)

49. Graceway realleges, reasserts, and incorporates by reference herein each of the allegations contained in paragraphs 1 through 48 of the Complaint as though set forth fully herein.

50. FDA's conduct in denying Graceway's Citizen Petition and approving Nycomed's ANDA was unlawful and in violation of the FDCA and the agency's own regulations.

51. The FDCA and the agency's regulations provide that a sponsor seeking approval of a generic drug product must demonstrate, among other things, that the proposed product is bioequivalent to an approved pioneer product. 21 U.S.C. § 355(j)(2)(A)(iv); 21 C.F.R. § 314.127(a)(6)(i).

52. Bioequivalence generally means that the "rate and extent of absorption of the [proposed] drug do not show a significant difference from the rate and extent of absorption of the [approved] drug when administered . . . under similar experimental conditions . . . ." 21 U.S.C. § 355(j)(8)(B)(i); 21 C.F.R. § 320.1(e).

53. The agency is limited to the use of "scientifically valid" methods to assess the bioequivalence of non-systemic drug products like Aldara, in which the active ingredient is not intended to be absorbed into the bloodstream. 21 U.S.C. § 355(j)(8)(C).

54. As noted above, FDA's refusal to require generic manufacturers to demonstrate bioequivalence through comparative clinical studies in patients with EGW violates the FDCA and applicable regulations, including but not limited to 21 U.S.C. § 355(j)(8)(C), 21 U.S.C. § 355(j)(4)(F) and 21 C.F.R. § 314.127(a)(6)(i).

55. FDA's decision to deny Graceway's Citizen Petition and to approve Nycomed's ANDA constitutes final agency action for which Graceway has no other adequate remedy within the meaning of 5 U.S.C. § 704.

56. FDA's decision to deny Graceway's Citizen Petition and to approve Nycomed's ANDA was not in accordance with federal law and therefore violates 5 U.S.C. § 706(2)(A).

57. FDA's decision to deny Graceway's Citizen Petition and to approve Nycomed's ANDA constitutes agency action in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, in violation of 5 U.S.C. § 706(2)(C).

58. Both Graceway and the patient population will be irreparably harmed unless FDA's approval of Nycomed's ANDA is rescinded and FDA is barred from approving

any other generic versions of Aldara without reliance upon comparative clinical bioequivalence studies in patients with EGW. These generic products will compete with – and in many cases, be automatically substituted for – Graceway's Aldara.

59. There is no mechanism by which Graceway can be made whole for the injury that would result from the entry into the marketplace of Nycomed's generic drug and those of other generic manufacturers.

60. The intent of Congress will be served by an Order directing FDA to withdraw its approval of Nycomed's ANDA and refrain from approving any other generic versions of Aldara unless they can demonstrate bioequivalence through comparative clinical studies in patients with EGW. In addition, the public interest will be served by such an Order.

Count II
(Administrative Procedure Act: FDA's Conduct Was Arbitrary, Capricious, an Abuse of Discretion and Contrary to Law)

61. Graceway realleges, reasserts, and incorporates by reference herein each of the allegations contained in paragraphs 1 through 60 of the Complaint, as though set forth fully herein.

62. The APA prohibits FDA from implementing the FDCA in a manner that is arbitrary, capricious, or an abuse of discretion. 5 U.S.C. § 706(2)(A).

63. FDA's denial of Graceway's Citizen Petition and its approval of Nycomed's ANDA was not based on reasoned decision or rational basis, and therefore was arbitrary, capricious, an abuse of discretion and otherwise not in accordance with law in violation of 5 U.S.C. § 706(2)(A).

64. FDA's denial of Graceway's Citizen Petition and its approval of Nycomed's ANDA was premised on agency determinations that represented abrupt departures from long-standing agency practice and the treatment of similarly-situated entities differently. FDA's conduct there was arbitrary, capricious, an abuse of discretion and otherwise not in accordance with law in violation of 5 U.S.C. § 706(2)(A).

65. FDA's denial of Graceway's Citizen Petition and its approval of Nycomed's ANDA constitutes final agency action for which Graceway has no other adequate remedy within the meaning of 5 U.S.C. § 704.

66. Both Graceway and the patient population will be irreparably harmed unless FDA is required to withdraw its approval of Nycomed's ANDA and ordered to refrain from approving any other generic versions of Aldara without reliance on comparative clinical bioequivalence studies in patients with EGW. These generic products will compete with – and in many cases, be automatically substituted for – Graceway's Aldara.

67. There is no mechanism by which Graceway can be made whole for the injury that would result from the entry into the marketplace of Nycomed's and other manufacturers' generic versions of Aldara. Graceway is without an adequate remedy at law because of the unique nature of the harm.

68. The intent of Congress will be served by an Order directing FDA to withdraw its approval of Nycomed's ANDA and ordering FDA to refrain from approving any other generic versions of Aldara unless they can demonstrate bioequivalence through comparative clinical studies in patients with EGW. In addition, the public interest will be served by such an Order.

PRAYER FOR RELIEF

WHEREFORE, plaintiff respectfully prays for the following relief:

A. A declaration pursuant to 28 U.S.C. § 2201 that FDA's denial of Graceway's Citizen Petition is arbitrary, capricious and unlawful under the APA and the FDCA;

B. A declaration pursuant to 28 U.S.C. § 2201 that FDA's approval of Nycomed's generic version of Aldara is arbitrary, capricious, and unlawful under the APA and the FDCA;

C. A declaration pursuant to 28 U.S.C. § 2201 that FDA's refusal to require generic manufacturers to demonstrate bioequivalence through the submission of clinical test results involving patients with EGW is arbitrary, capricious, and unlawful under the APA and the FDCA;

D. A declaration pursuant to 28 U.S.C. § 2201 that FDA's actions, findings, and conclusions in denying Graceway's Citizen Petition and in approving Nycomed's generic version of Aldara were arbitrary, capricious, an abuse of discretion, and without factual basis;

E. Temporary, preliminary and permanent injunctive relief enjoining FDA from approving any ANDA for a generic version of Aldara unless the application contains data showing that the generic drug is bioequivalent based on clinical testing of patients with EGW;

F. Temporary, preliminary and permanent injunctive relief requiring FDA to predicate approval of any ANDA for a generic version of Aldara upon receipt of satisfactory data demonstrating that the generic drug is bioequivalent based on clinical testing of patients with EGW;

G. Temporary, preliminary and permanent injunctive relief requiring FDA to rescind its approval of the ANDA submitted by Nycomed;

H. An order awarding plaintiff's costs, expenses and attorneys fees pursuant to 28 U.S.C. § 2412; and

I. Such other and further relief as the Court deems just and proper.

Respectfully submitted,

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