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UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY

Graceway Pharmaceuticals, LLC and 3M Innovative Properties Company, Plaintiffs, vs. Perrigo Company, Perrigo Israel Pharmaceuticals Ltd., and Nycomed U.S. Inc., Defendants.	Civil Action No.:_____ **COMPLAINT and JURY TRIAL DEMAND**

Plaintiffs, Graceway Pharmaceuticals, LLC and 3M Innovative Properties Company (collectively, "Plaintiffs"), by their undersigned counsel, for their complaint against Defendants, Perrigo Israel Pharmaceuticals Ltd., Perrigo Company and Nycomed U.S. Inc. (collectively, "Defendants"), allege as follows:

Nature of the Case

1. This is an action for patent infringement arising under the patent laws of the United States, 35 U.S.C. § 1 *et seq.*

The Parties

2. Plaintiff Graceway Pharmaceuticals, LLC ("Graceway") is a Delaware limited liability company with a principal place of business at 340 Martin Luther King Junior Boulevard, Suite 500, Bristol, Tennessee 37620. Graceway is engaged in the business of developing and marketing innovative pharmaceutical products in the United States.

3. Plaintiff 3M Innovative Properties Company ("3M IPC") is a Delaware corporation with a principal place of business at 3M Center, St. Paul, Minnesota 55144. 3M IPC, an affiliate of 3M Company, is the owner of U.S. Patent No. 7,655,672.

4. On information and belief, Defendant Perrigo Company ("Perrigo") is a Michigan corporation with a principal place of business at 515 Eastern Avenue, Allegan, Michigan 49010. On information and belief, Perrigo is engaged in the manufacture and sale of generic pharmaceutical products.

5. On information and belief, Perrigo conducts business and engages in the manufacture and sale of a range of generic pharmaceutical products within the United States generally and in the State of New Jersey and this Judicial District specifically, including to pharmaceutical wholesalers, distributors and/or warehousing chains within this Judicial District.

6. On information and belief, Perrigo is registered to do business in and conducts business in New Jersey, including through its wholly-owned subsidiary L. Perrigo Company ("L. Perrigo").

7. On information and belief, Defendant Perrigo Israel Pharmaceuticals Ltd. ("Perrigo Israel") is an Israeli company with a corporate headquarters and principal place of business at 29 Lehi Street, Bnei Brak 51200, Israel.

8. On information and belief, Perrigo Israel is a wholly-owned subsidiary of Perrigo.

9. On information and belief, Perrigo Israel is an agent and/or alter ego of Perrigo.

10. On information and belief, Perrigo Israel is under the direction, control and/or influence of Perrigo, both generally and with respect to the particular acts and conduct alleged in this complaint.

11. On information and belief, Perrigo conducts operations through Perrigo Israel.

12. On information and belief, Defendant Nycomed US Inc. ("Nycomed"), formerly known as Altana, Inc. ("Altana"), is a New York company with a principal place of business at 60 Baylis Road, Melville, New York 11747, and a division located in 210 Park Avenue, Florham Park, New Jersey 07932.

13. On information and belief, Nycomed, which operates three divisions in the United States, is in the business of manufacturing and marketing pharmaceuticals, including generic pharmaceuticals.

14. On information and belief, Nycomed conducts business and engages in the manufacture and sale of a range of pharmaceutical products within the United States generally and in the State of New Jersey and this Judicial District specifically, including to pharmaceutical wholesalers, distributors and/or warehousing chains within this Judicial District.

Jurisdiction and Venue

15. This is an action for patent infringement under the patent laws of the United States, 35 U.S.C. §§ 271 and 281-283. Subject matter jurisdiction is proper under the 28 U.S.C. §§ 1331 and 1338(a).

16. Personal jurisdiction over Perrigo, Perrigo Israel, and Nycomed is proper in this District because of defendants presence in the State of New Jersey and/or their systematic and continuous contacts with the State of New Jersey. Venue is proper under 28 U.S.C. §§ 1391(b)-(c) and 1400(b).

The '672 Patent

17. United States Patent No. 7,655,672 ("the '672 Patent"), entitled "Immune Response Modifier Formulations Containing Oleic Acid and Methods," a true and correct copy of which is appended hereto as Exhibit A, was duly issued on February 2, 2010 to 3M IPC. The

inventors of the '672 Patent are Alexis S. Statham and Robert J. Nelson. The '672 Patent claims, *inter alia*, pharmaceutical creams for topical application to dermal or mucosal surfaces for topical delivery of 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine ("imiquimod"), wherein the pharmaceutical creams comprise imiquimod and a pharmaceutically acceptable vehicle that includes an oleic acid component.

18. 3M IPC is the record assignee of the '672 Patent. Graceway holds an exclusive license under the '672 Patent, including the right to sublicense, to make, have made, use, develop, have developed, offer for sale, sell, and import products covered by the '672 Patent, and the right to assert, defend, maintain and enforce the '672 Patent.

Background

19. Aldara® (imiquimod) 5% Cream is a topical cream containing imiquimod as the active pharmaceutical ingredient. Aldara® was approved by the United States Food and Drug Administration ("FDA") under New Drug Application ("NDA") 20-723 on February 27, 1997. Graceway is the NDA-holder of NDA 20-723. Aldara® is approved by the FDA for the treatment of: (1) external genital and perianal warts ("EGW") in patients 12 years or older; (2) clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses ("AK") on the face or scalp; and (3) biopsy-confirmed, primary superficial basal cell carcinoma ("sBCC") located on the trunk, neck, or extremities (excluding hands and feet).

20. Aldara® 5% Cream, as approved by the FDA, is formulated with imiquimod and a vehicle that includes isostearic acid for topical application to a dermal or mucosal surface for topical delivery of imiquimod. The inventors of the '672 Patent discovered novel imiquimod creams comprising imiquimod and a vehicle that includes an oleic acid component. The oleic acid component, as claimed in the '672 Patent, is directed to an oleic acid component that at least

meets if not exceeds certain United States Pharmacopeia ("USP") monograph compliance stipulations for super refined oleic acid NF.

21. The active pharmaceutical ingredient in Aldara®, imiquimod, is covered by U.S. Patent No. 4,689,338 ("the '338 Patent"). The '338 Patent expired on August 25, 2009. The pediatric exclusivity for the '338 Patent, that was awarded by the FDA under 21 U.S.C. § 355a, expires on February 25, 2010. Thus, the effective expiration of the '338 Patent as to imiquimod is February 25, 2010.

COUNT I
(INFRINGEMENT OF U.S. PATENT 7,655,672 UNDER 35 U.S.C. § 271 BY PERRIGO AND/OR PERRIGO ISRAEL ("Perrigo Defendants")

22. Plaintiffs repeat and incorporate herein by reference the allegations contained in the foregoing paragraphs 1 through 21.

23. On information and belief, Perrigo Israel filed Abbreviated New Drug Application ("ANDA") No. 78-837 with the FDA under 21 U.S.C. § 355(j) seeking approval for an imiquimod topical cream that it alleged was bioequivalent to Aldara®.

24. On information and belief, by this ANDA No. 78-837 filing, Perrigo Israel has evidenced that immediately upon FDA approval, it intends to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of a pharmaceutical cream containing imiquimod and an oleic acid component for topical application to a dermal or mucosal surface for topical delivery of imiquimod to treat, *inter alia*, actinic keratosis (the "Perrigo Proposed ANDA Product").

25. By a letter ("the Perrigo Notice Letter") dated June 28, 2007, Perrigo Israel informed Graceway that it had filed ANDA No. 78-837 with the FDA under 21 U.S.C. § 355(j), containing a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

26. The Perrigo Notice Letter states that "ANDA [No. 78-837] was submitted under 21 U.S.C. §§ 355 (j)(1) and (2)(A), and contains a paragraph IV certification to obtain approval to engage in the commercial manufacture, use or sale of an imiquimod topical cream formulation product before the expiration date [February 24, 2011] of the '944 patent [Graceway's U.S. Patent No. 5,238,944], which is listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book")".

27. The Perrigo Notice Letter states that the Perrigo Proposed ANDA Product does not contain isostearic acid.

28. On May 15, 2006, Perrigo Israel filed United States Patent Application Serial No. 11/433,471 ("the '471 Patent Application") directed to a pharmaceutical composition for topical application containing imiquimod and oleic acid, among other ingredients. The '471 Patent Application includes six Examples which disclose six different imiquimod pharmaceutical creams. Examples 1-3 and 5-6 of the '471 Patent Application disclose five pharmaceutical creams formulated with imiquimod and 7.4% oleic acid by weight. Example 4 of the '471 Patent Application discloses a pharmaceutical cream formulated with imiquimod and 25% linoleic acid by weight.

29. On information and belief, a pharmaceutical cream formulated with 25% linoleic acid by weight according to Example 4 of the '471 Patent Application is unstable.

30. On information and belief, there are currently only two listings in the FDA's Inactive Ingredients Database ("the FDA's IID") for topical formulations with oleic acid. On information and belief, and as reported in the FDA's IID, the highest FDA approved level of oleic acid for topical formulations with oleic acid is 7.4% in an emulsion or solution (i.e., not a cream). Also on information and belief, and as reported in the FDA's IID, there are two

transdermal patch/film formulations (not creams) that incorporate oleic acid in their patch formulations.

31. On information and belief, standard compendial grade oleic acid NF is an unstable grade of oleic acid that is unsuitable for use as a vehicle in semi-solid topical pharmaceutical formulations, such as creams, lotions, gels or ointments, due to its inherent variability in quality and instability issues, which leads to degradation and rancidity upon exposure to air even at ambient temperature conditions.

32. On information and belief, the United States Pharmacopeia–National Formulary (USP–NF) is a book of public pharmacopeial standards containing standards for medicines, dosage forms, drug substances, excipients, medical devices, and dietary supplements.

33. On information and belief, the USP-NF is a combination of two official compendia, the United States Pharmacopeia (USP) and the National Formulary (NF).

34. On information and belief, the FDA designates the USP–NF as the official compendia for drugs marketed in the United States.

35. On information and belief, excipient monographs, such as for oleic acid, are in the NF.

36. On information and belief, any drug product, including pharmaceutical creams, marketed by the Perrigo Defendants in the United States must conform to at least certain of the standards set forth in the USP–NF.

37. On information and belief, the Perrigo Proposed ANDA Product is formulated with imiquimod and a vehicle that includes an oleic acid component.

38. On information and belief, the Perrigo Proposed ANDA Product is formulated with imiquimod and a vehicle that includes an oleic acid component that conforms to at least

certain of the standards set forth in the monograph compliance stipulations for super refined oleic acid NF.

39. On information and belief, the Perrigo Proposed ANDA Product is formulated with 5% imiquimod and a vehicle that includes a 7.4% oleic acid component by weight.

40. On information and belief, the Perrigo Proposed ANDA Product is formulated with 5% imiquimod and a vehicle that includes a 7.4% oleic acid component that conforms to at least certain of the monograph compliance stipulations for super refined oleic acid NF by weight.

41. On information and belief, once the Perrigo Defendants receive FDA approval for the Perrigo Proposed ANDA Product, they will infringe one or more claims of the '672 Patent by manufacturing, using, offering for sale or selling the Perrigo Proposed ANDA Product, within the United States, or importing into the United States the Perrigo Proposed ANDA Product.

42. Upon information and belief, FDA approval of the Perrigo Proposed ANDA Product is imminent.

43. The Perrigo Notice Letter evidenced the Perrigo Defendants' intent to market the Perrigo Proposed ANDA Product (its generic imiquimod product) immediately following the effective expiration [with pediatric exclusivity] of the '338 Patent on February 25, 2010.

44. Upon information and belief, Perrigo Defendants sought approval of the Perrigo Proposed ANDA Product from the FDA to immediately commercialize the Perrigo Proposed ANDA Product on February 25, 2010, the effective expiration date [with pediatric exclusivity] of the '338 Patent.

45. On information and belief, based on standard industry practice, prior to receiving FDA approval, the Perrigo Defendants will have engaged in activities in preparation for manufacturing, distributing, offering to sell, selling and importing the Perrigo Proposed ANDA

Product in the United States.

46. On information and belief, such activities have already infringed, or imminently will infringe, one or more claims of the '672 Patent.

47. Unless the Perrigo Defendants are enjoined from infringing the '672 Patent, Plaintiffs will suffer substantial and irreparable injury for which Plaintiffs have and will have no adequate remedy at law.

COUNT II
(INFRINGEMENT OF U.S. PATENT 7,655,672 UNDER 35 U.S.C. § 271 BY NYCOMED)

48. Plaintiffs repeat and incorporate herein by reference the allegations contained in the foregoing paragraphs 1 through 47 herein.

49. On information and belief, Nycomed filed ANDA No. 78-548 with the FDA under 21 U.S.C. § 355(j) seeking approval for an imiquimod topical cream that Nycomed alleged was bioequivalent to Aldara®.

50. On information and belief, by this ANDA filing, Nycomed has evidenced that immediately after approval, it intends to engage in the commercial manufacture, use, importation, offer for sale, and/or sale of a pharmaceutical cream containing imiquimod and an oleic acid component for topical application to a dermal or mucosal surface for topical delivery of imiquimod to treat, *inter alia*, actinic keratosis (the "Nycomed Proposed ANDA Product").

51. By a letter ("the Nycomed Notice Letter") dated January 10, 2007, Nycomed informed Graceway that it had filed ANDA No. 78-548 with the FDA under 21 U.S.C. § 355(j), containing a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV). The Nycomed Notice Letter states that the Nycomed Proposed ANDA Product contains imiquimod and oleic acid.

52. On information and belief, there are currently only two listings in the FDA's

Inactive Ingredients Database ("the FDA's IID") for topical formulations with oleic acid. On information and belief, and as reported in the FDA's IID, the highest FDA approved level of oleic acid for topical formulations with oleic acid is 7.4% in an emulsion or solution (i.e., not a cream). Also on information and belief, and as reported in the FDA's IID, there are two transdermal patch/film formulations (not creams) that incorporate oleic acid in their patch formulations.

53. On information and belief, standard compendial grade oleic acid NF is an unstable grade of oleic acid that is unsuitable for use as a vehicle in semi-solid topical pharmaceutical formulations, such as creams, lotions, gels or ointments, due to its inherent variability in quality and instability issues, which leads to degradation and rancidity upon exposure to air even at ambient temperature conditions.

54. On information and belief, the United States Pharmacopeia–National Formulary (USP–NF) is a book of public pharmacopeial standards containing standards for medicines, dosage forms, drug substances, excipients, medical devices, and dietary supplements.

55. On information and belief, the USP-NF is a combination of two official compendia, the United States Pharmacopeia (USP) and the National Formulary (NF).

56. On information and belief, the FDA designates the USP–NF as the official compendia for drugs marketed in the United States.

57. On information and belief, excipient monographs, such as for oleic acid, are in the NF.

58. On information and belief, any drug product, including pharmaceutical creams, marketed by the Nycomed Defendants in the U.S. must conform to at least certain of the standards set forth in the USP–NF.

59. On information and belief, the Nycomed Proposed ANDA Product is formulated with imiquimod and a vehicle that includes an oleic acid component.

60. On information and belief, the Nycomed Proposed ANDA Product is formulated with imiquimod and a vehicle that includes an oleic acid component that conforms to at least certain of the monograph compliance stipulations for super refined oleic acid NF.

61. The Nycomed Notice Letter states that the Nycomed Proposed ANDA Product is formulated with 5% imiquimod and a vehicle that includes a 25% oleic acid component.

62. On information and belief, the Nycomed Proposed ANDA Product is formulated with 5% imiquimod and a vehicle that includes a 25% oleic acid component that conforms to at least certain of the monograph compliance stipulations for super refined oleic acid NF by weight.

63. On information and belief, once Nycomed receives FDA approval for the Nycomed Proposed ANDA Product, Nycomed will infringe one or more claims of the '672 Patent by manufacturing, using, offering for sale, selling and/or importing the Nycomed Proposed ANDA Product in the United States.

64. Upon information and belief, FDA approval of the Nycomed Proposed ANDA Product is imminent.

65. On information and belief, the Nycomed Notice Letter evidences Nycomed's intent to market the Nycomed Proposed ANDA Product (its generic imiquimod product) immediately following the effective expiration date [with pediatric exclusivity] of the '338 Patent on February 25, 2010.

66. Upon information and belief, Nycomed sought approval of the Nycomed Proposed ANDA Product from the FDA to immediately commercialize the Nycomed Proposed ANDA Product upon the effective expiration date [with pediatric exclusivity] of the '338 Patent,

67. On information and belief, based on standard industry practice, prior to receiving FDA approval, Nycomed will have engaged in activities in preparation for manufacturing, distributing, offering to sell, selling and importing the Nycomed Proposed ANDA Product in the United States.

68. On information and belief, such activities have already infringed, or imminently will infringe, one or more claims of the '672 Patent.

69. Unless Nycomed is enjoined from infringing of the '672 Patent, Plaintiffs will suffer substantial and irreparable injury, for which Plaintiffs have and will have no adequate remedy at law.

WHEREFORE, Plaintiffs request the following relief:

(a) A judgment that making, using, selling, or offering to sell the Perrigo Proposed ANDA Product for which the Perrigo Defendants seek FDA approval under ANDA No. 78-837, within the United States, or importing into the United States the Perrigo Proposed ANDA Product for which the Perrigo Defendants seek FDA approval under ANDA No. 78-837 infringes one or more claims of the '672 Patent;

(b) A declaratory judgment pursuant to 28 U.S.C. § 2201 *et seq.* that making, using, selling or offering to sell the Perrigo Proposed ANDA Product for which the Perrigo Defendants seek FDA approval under ANDA No. 78-837, within the United States, or importing into the United States the Perrigo Proposed ANDA Product for which the Perrigo Defendants seek FDA approval under ANDA No. 78-837 will infringe one or more claims of the '672 Patent;

(c) A preliminary and permanent injunction restraining and enjoining against any infringement by Defendants Perrigo, their officers, agents, attorneys, or employees, or those acting in privity or concert with them, of the '672 Patent through the manufacture, use, sale, or

offer for sale, within the United States, the Perrigo Proposed ANDA Product for which the Perrigo defendants seek FDA approval under ANDA No. 78-837, or the importation into the United States of the Perrigo Proposed ANDA Product for which the Perrigo Defendants seek FDA approval under ANDA No. 78-837;

(d) A judgment that making, using, selling, or offering to sell the Nycomed Proposed ANDA Product for which Nycomed seeks FDA approval under ANDA No. 78-548, within the United States, or importing into the United States the Nycomed Proposed ANDA Product for which Nycomed seeks FDA approval under ANDA No. 78-548 infringes one or more claims of the '672 Patent;

(e) A declaratory judgment pursuant to 28 U.S.C. § 2201 *et seq.* that making, using, selling or offering to sell the Nycomed Proposed ANDA Product for which Nycomed seeks FDA approval under ANDA No. 78-548, within the United States, or importing into the United States the Nycomed Proposed ANDA Product for which Nycomed seeks FDA approval under ANDA No. 78-548 will infringe one or more claims of the '672 Patent;

(f) A preliminary and permanent injunction restraining and enjoining against any infringement by Nycomed, its officers, agents, attorneys, or employees, or those acting in privity or concert with Nycomed, of the '672 Patent through the manufacture, use, sale, or offer for sale, within the United States, the Nycomed Proposed ANDA Product for which Nycomed seeks FDA approval under ANDA No. 78-548, or the importation into the of United States the Nycomed Proposed ANDA Product for which Nycomed seeks FDA approval under ANDA No. 78-548;

(g) Attorneys' fees in this action under 35 U.S.C. § 285;

(h) Damages and costs of suit;

(i) Such further and other relief as this Court may deem just and proper.

JURY DEMAND

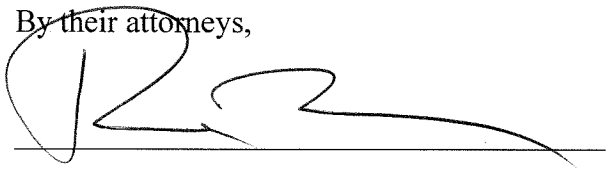
Plaintiffs hereby demand a trial by jury on all issues and claims so triable.

Dated: Madison, New Jersey
February 23, 2010

Respectfully submitted,

Graceway Pharmaceuticals, LLC,
and 3M Innovative Properties Company,

By their attorneys,



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UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY

Graceway Pharmaceuticals, LLC and 3M Innovative Properties Company, Plaintiffs, vs. Perrigo Company, Perrigo Israel Pharmaceuticals Ltd., and Nycomed U.S. Inc., Defendants.	Civil Action No.:

RULE 11.2 STATEMENT

I herby certify that, to the best of my knowledge, the patent at issue in this case is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: Madison, New Jersey
February 23, 2010

By,

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EXHIBIT A


US007655672B2

(12) **United States Patent**
Statham et al.

(10) **Patent No.: US 7,655,672 B2**
(45) **Date of Patent: *Feb. 2, 2010**

(54) **IMMUNE RESPONSE MODIFIER FORMULATIONS CONTAINING OLEIC ACID AND METHODS**

(75) Inventors: **Alexis S. Statham**, Woodbury, MN (US); **Robert J. Nelson**, Cottage Grove, MN (US)

(73) Assignee: **3M Innovative Properties Company**, St. Paul, MN (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/334,255**

(22) Filed: **Dec. 12, 2008**

(65) **Prior Publication Data**

US 2009/0093514 A1 Apr. 9, 2009

Related U.S. Application Data

(63) Continuation of application No. 11/276,324, filed on Feb. 24, 2006, which is a continuation of application No. 11/303,659, filed on Dec. 16, 2005, now abandoned.

(60) Provisional application No. 60/636,916, filed on Dec. 17, 2004.

(51) **Int. Cl.**
A01N 43/42 (2006.01)
A01N 43/52 (2006.01)

(52) **U.S. Cl.** **514/290**; 514/393

(58) **Field of Classification Search** 514/290, 514/393

See application file for complete search history.

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(Continued)

Primary Examiner—Sreeni Padmanabhan
Assistant Examiner—Renee Claytor
(74) *Attorney, Agent, or Firm*—Edwards Angell Palmer & Dodge LLP

(57) **ABSTRACT**

Pharmaceutical formulations and methods including an immune response modifier (IRM) compound and an oleic acid component are provided where stability is improved by using oleic acid have low polar impurities such as peroxides.

20 Claims, No Drawings

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IMMUNE RESPONSE MODIFIER FORMULATIONS CONTAINING OLEIC ACID AND METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of U.S. provisional application 60/636,916, filed Dec. 17, 2004, and Ser. No. 11/303,659 filed Dec. 16, 2005, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to pharmaceutical formulations for the topical or transdermal delivery of immunomodifying drugs.

BACKGROUND

There has been a major effort in recent years, with significant success, to discover new drug compounds that act by stimulating certain key aspects of the immune system, as well as by suppressing certain other aspects. These compounds, referred to herein as immune response modifiers (IRMs), appear to act through immune system mechanisms known as toll-like receptors to induce selected cytokine biosynthesis. They may be useful for treating a wide variety of diseases and conditions. For example, certain IRMs may be useful for treating viral diseases (e.g., human papilloma virus, hepatitis, herpes), neoplasias (e.g., basal cell carcinoma, squamous cell carcinoma, actinic keratosis, melanoma), and TH2-mediated diseases (e.g., asthma, allergic rhinitis, atopic dermatitis), and are also useful as vaccine adjuvants.

Many of the IRM compounds are small organic molecule imidazoquinoline amine derivatives (see, e.g., U.S. Pat. No. 4,689,338), but a number of other compound classes are known as well (see, e.g., U.S. Pat. Nos. 5,446,153, 6,194,425, and 6,110,929) and more are still being discovered.

One of these IRM compounds, known as imiquimod, has been commercialized in a topical formulation, ALDARA, for the treatment of actinic keratosis, basal cell carcinoma, or anogenital warts associated with human papillomavirus.

Pharmaceutical formulations containing IRM compounds are disclosed in U.S. Pat. Nos. 5,238,944; 5,939,090; and 6,425,776; European Patent 0 394 026; and U.S. Patent Publication 2003/0199538.

Although some of the beneficial effects of IRMs are known, the ability to provide therapeutic benefit via topical application of an IRM compound for treatment of a particular condition at a particular location may be hindered by a variety of factors. These factors include: irritation of the skin to which the formulation is applied; formulation wash away; insolubility of the IRM compound in the formulation; chemical degradation of the IRM compound and/or other ingredients, physical instability of the formulation (e.g., separation of components, thickening, precipitation/agglomerization of active ingredient, and the like); poor permeation; and undesired systemic delivery of topical IRM formulations if not intended to be transdermal.

Accordingly, there is a continuing need for new and/or improved IRM formulations.

SUMMARY

It has now been found that, while oleic acid can be used to solublize IRMs, even difficult to formulate, highly insoluble IRMs, formulations comprising an IRM compound in combination with oleic acid can suffer from impaired stability. Somewhat surprisingly, addition of greater amounts of antioxidants to the formulation does not solve the problem. However, it has been found that utilizing an oleic acid component having reduced amounts of polar impurities, such as peroxides, aldehydes, alcohols, and ketones in a formulation containing an IRM can reduce the formation of impurities and thereby provide improved formulation stability. Instability is an important issue for pharmaceutical formulations and can reduce the shelf life of a product or jeopardize regulatory approvability.

It has been discovered that the stability of a formulation containing an IRM compound and oleic acid can be improved by utilizing an oleic acid component that is free of or contains low amounts of polar impurities, such as peroxides, aldehydes, alcohols, and ketones. Although not intending to be bound to any particular theory or mechanism, it is hypothesized that the higher amounts of polar impurities present in the oleic acid component can react with the IRM compound, thereby destabilizing the formulation and increasing the rate of formation of impurities derived from the IRM compound.

In one aspect, the present invention provides a pharmaceutical formulation comprising a therapeutically effective amount of an immune response modifier (IRM) compound and a pharmaceutically acceptable vehicle including an oleic acid component, wherein the formulation is substantially free of polar impurities introduced by the oleic acid component.

In another aspect, the present invention provides a pharmaceutical formulation comprising: a therapeutically effective amount of an IRM compound and a pharmaceutically acceptable vehicle including an oleic acid component, wherein the oleic acid component has a peroxide value no greater than 5.

In another aspect, the present invention provides a pharmaceutical formulation comprising: a therapeutically effective amount of an IRM compound and a pharmaceutically acceptable vehicle including an oleic acid component, wherein the oleic acid component is at least 80% oleic acid.

The present invention also provides methods.

In one aspect, the present invention provides a method of stabilizing a pharmaceutical formulation comprising a therapeutically effective amount of an immune response modifier (IRM) compound and oleic acid by using an oleic acid component that is substantially free of polar impurities.

In one aspect, the present invention provides a method of stabilizing a pharmaceutical formulation comprising a therapeutically effective amount of an IRM compound and oleic acid by using an oleic acid component with a peroxide value no greater than 5.

In one aspect, the present invention provides a method of stabilizing a pharmaceutical formulation comprising a therapeutically effective amount of an IRM compound and oleic acid by using an oleic acid component that is at least 80% oleic acid.

In another aspect, the present invention provides methods for treating disease, including but not limited to the group comprising actinic keratosis, basal cell carcinoma, genital warts, peri-anal warts, malignant melanoma, and molloscum contagiosum. In another aspect, the present invention provides methods to induce cytokine biosynthesis. In another aspect, the present invention provides methods to induce interferon biosynthesis.

A number of additional embodiments can be described as follows:

1. A pharmaceutical formulation comprising:

a therapeutically effective amount of an immune response modifier (IRM) compound selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, 1H-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and combinations thereof; and

a pharmaceutically acceptable vehicle including an oleic acid component, wherein the formulation is substantially free of polar impurities introduced by the oleic acid component.

2. A pharmaceutical formulation comprising:

a therapeutically effective amount of an IRM compound selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, 1H-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and combinations thereof; and

a pharmaceutically acceptable vehicle including an oleic acid component, wherein the oleic acid component has a peroxide value no greater than 5.

3. A pharmaceutical formulation comprising:

a therapeutically effective amount of an IRM compound selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, 1H-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and combinations thereof; and

a pharmaceutically acceptable vehicle including an oleic acid component, wherein the oleic acid component is at least 80% oleic acid.

4. A formulation as in any one of the preceding embodiments wherein the IRM compound is selected from the group consisting of amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea substituted imidazoquinoline amines, aryl ether substituted imidazoquinoline amines, heterocyclic ether substituted imidazoquinoline amines, amido ether substituted imidazoquinoline amines, sulfonamido ether substituted imidazoquinoline amines, urea substituted imidazoquinoline ethers, thioether substituted imidazoquinoline amines, 6-, 7-, 8-, or 9-aryl, heteroaryl, aryloxy or arylalkyleneoxy substituted imidazoquinoline amines, imidazoquinoline diamines, amide substituted tetrahydroimidazoquinoline amines, sulfonamide substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline amines, aryl ether substituted tetrahydroimidazoquinoline amines, heterocyclic ether substituted tetrahydroimidazoquinoline amines, amido ether substituted tetrahydroimidazoquinoline amines, sulfonamido ether substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline ethers, thioether substituted tetrahydroimidazoquinoline amines, tetrahydroimidazoquinoline diamines, amide substituted imidazopyridine amines, sulfonamide substituted imidazopyridine amines, urea substituted imidazopyridine amines, aryl ether substituted imidazopyridine amines, heterocyclic ether substituted imidazopyridine amines, amido ether substituted imidazopyridine amines, sulfonamido ether substituted imidazopyridine amines, urea substituted imidazopyridine ethers, thioether substituted imidazopyridine amines, and combinations thereof.

5. A formulation as in any one of embodiments 1 through 3 wherein the IRM compound is an imidazonaphthyridine amine.

6. A formulation as in any one of embodiments 1 through 3 and 5 wherein the IRM compound is 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine.

7. A formulation as in any one of embodiments 1 through 3 wherein the IRM compound is 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine.

8. A formulation as in any one of the preceding embodiments wherein the IRM compound is present in an amount of at least 3% by weight, based on the total weight of the formulation.

9. A formulation as in any one of the preceding embodiments wherein the IRM compound is present in an amount of at least 5% by weight, based on the total weight of the formulation.

10. A formulation as in any one of the preceding embodiments wherein the oleic acid component is present in an amount of at least 15% by weight based on the total weight of the formulation.

11. A formulation as in any one of the preceding embodiments wherein the oleic acid component is present in an amount of at least 20% by weight based on the total weight of the formulation.

12. A formulation as in any one of the preceding embodiments wherein the oleic acid component is present in an amount of at least 25% by weight based on the total weight of the formulation.

13. A formulation as in any one of the preceding embodiments wherein the oleic acid component has been purified by chromatography prior to use in the formulation.

14. A formulation as in any one of the preceding embodiments wherein the oleic acid component is plant-derived.

15. A formulation as in any one of the preceding embodiments wherein the formulation includes at least one fatty acid other than oleic acid or isostearic acid.

16. A formulation as in any one of the preceding embodiments wherein the formulation includes less than 3% isostearic acid by weight based on the total weight of the formulation.

17. A formulation as in any one of the preceding embodiments wherein the formulation further comprises an antioxidant.

18. A formulation as in any one of the preceding embodiments further comprising an antioxidant, wherein the antioxidant is butylated hydroxyl toluene or butylated hydroxyanisole.

19. A formulation of any one of the preceding embodiments further comprising water.

20. A formulation of any one of the preceding embodiments further comprising a preservative system.

21. A formulation of any one of the preceding embodiments further comprising an emulsifier.

22. A method of stabilizing a pharmaceutical formulation comprising a therapeutically effective amount of an immune response modifier (IRM) compound selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, 1H-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and combinations thereof; and oleic acid by using an oleic acid component that is substantially free of polar impurities.

23. A method of stabilizing a pharmaceutical formulation comprising a therapeutically effective amount of an IRM compound selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, 1H-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and combinations thereof; and oleic acid by using an oleic acid component with a peroxide value no greater than 5.

24. A method of stabilizing a pharmaceutical formulation comprising a therapeutically effective amount of an IRM compound selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, 1H-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and combinations thereof; and oleic acid by using an oleic acid component that is at least 80% oleic acid.

25. The method as in any one of embodiments 22 through 24 wherein the IRM compound is selected from the group consisting of: amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea substituted imidazoquinoline amines, aryl ether substituted imidazoquinoline amines, heterocyclic ether substituted imidazoquinoline amines, amido ether substituted imidazoquinoline amines, sulfonamido ether substituted imidazoquinoline amines, urea substituted imidazoquinoline ethers, thioether substituted imidazoquinoline amines, 6-, 7-, 8-, or 9-aryl, heteroaryl, aryloxy, or arylalkyleneoxy substituted imidazoquinoline amines, imidazoquinoline diamines, amide substituted tetrahydroimidazoquinoline amines, sulfonamide substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline amines, aryl ether substituted tetrahydroimidazoquinoline amines, heterocyclic ether substituted tetrahydroimidazoquinoline amines, amido ether substituted tetrahydroimidazoquinoline amines, sulfonamido ether substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline ethers, thioether substituted tetrahydroimidazoquinoline amines, tetrahydroimidazoquinoline diamines, amide substituted imidazopyridine amines, sulfonamide substituted imidazopyridine amines, urea substituted imidazopyridine amines, aryl ether substituted imidazopyridine amines, heterocyclic ether substituted imidazopyridine amines, amido ether substituted imidazopyridine amines, sulfonamido ether substituted imidazopyridine amines, urea substituted imidazopyridine ethers, thioether substituted imidazopyridine amines, and combinations thereof.

26. The method as in any one of embodiments 22 through 24 wherein the IRM compound is an imidazonaphthyridine amine.

27. The method as in any one of embodiments 22 through 24 and 26 wherein the IRM compound is 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine.

28. The method as in any one of embodiments 22 through 24 wherein the IRM compound is 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine.

29. A method of treating actinic keratosis, the method comprising applying a formulation of any one of embodiments 1 through 21 to the skin of a subject.

30. A method of treating basal cell carcinoma, the method comprising applying a formulation of any one of embodiments 1 through 21 to the skin of a subject.

31. A method of treating genital warts, the method comprising applying a formulation of any one of embodiments 1 through 21 to the skin or mucosal surface of a subject.

32. A method of treating peri-anal warts, the method comprising applying a formulation of any one of embodiments 1 through 21 to the skin or mucosal surface of a subject.

33. A method of treating molloscum contagiosum, the method comprising applying a formulation of any one of embodiments 1 through 21 to the skin of a subject.

34. A method of inducing cytokine biosynthesis, the method comprising applying a formulation of any one of embodiments 1 through 21 to the skin or mucosal surface of a subject.

35. A method of inducing interferon biosynthesis, the method comprising applying a formulation of any one of embodiments 1 through 21 to the skin or mucosal surface of a subject.

36. A method of treating malignant melanoma, the method comprising applying a formulation of any one of the preceding embodiments 1 through 21 to the skin of a subject.

The term "substantially free" is used to indicate that the amount present in the composition or formulation is below the level that causes degradation of the active pharmaceutical agent, such that the formulation is unsuitable for pharmaceutical usage, after storage for 4 months at 40° C. at 75% relative humidity. The term can also be used to describe a composition

containing less than 10%, less than 5%, less than 1%, or less than 0.1% by weight of a given substance.

The term "polar impurities" includes, but is not limited to peroxides, aldehydes, ketones, alcohols, metal ions, and/or substances that cause degradation of the active pharmaceutical agent.

The term "oleic acid component" is used to describe a preformulation source or composition of matter containing oleic acid, and may include other fatty acids in addition to oleic acid, including but not limited to: myristic acid, palmitic acid, palmitoleic acid, margaric acid, isostearic acid, stearic acid, linoleic acid, linolenic acid, and other fatty acids, or combinations thereof.

The peroxide value is the number that expresses in milliequivalents of active oxygen the quantity of peroxide contained in 1000 g of the substance as determined by the methods described in the 5th edition of the European Pharmacopoeia, Section 2.5.5.

Unless otherwise indicated, all numbers expressing quantities, ratios, and numerical properties of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about".

All parts, percentages, ratios, etc. herein are by weight unless indicated otherwise.

As used herein, "a" or "an" or "the" are used interchangeably with "at least one" to mean "one or more" of the listed element.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the application, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

DETAILED DESCRIPTION

The present invention provides pharmaceutical formulations that include a therapeutically effective amount of an immune response modifier (IRM) compound selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, and 1H-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and oleic acid, wherein the oleic acid component contains a low amount of polar impurities, especially peroxides. Surprisingly, the stability of such formulations is substantially greater than that of similar formulations containing an IRM compound and oleic acid containing conventional oleic acid with higher amounts of polar impurities such as peroxides, even when the oleic acid component is of compendial grade. Furthermore, the instability problem of these formulations is not eliminated by additional antioxidants.

Through utilization of an oleic acid component containing a very low amount of polar impurities, the subsequent formation of impurities in IRM formulations is significantly reduced as compared to other IRM formulations comprising compendial grades of oleic acid after both the initial measurement (i.e., its measurement when initially formulated) and under accelerated conditions (when stored for at least 4 months at 40° C. and 75% relative humidity), resulting in an increased formulation shelf life.

For certain embodiments, the formulation comprises an IRM compound and a pharmaceutically acceptable vehicle including an oleic acid component wherein the formulation is substantially free of polar impurities introduced by the oleic acid component. For certain embodiments, the formulation comprises an IRM compound and a pharmaceutically acceptable vehicle including an oleic acid component, wherein the oleic acid component has a peroxide value no greater than 5. For certain embodiments, the formulation comprises an IRM compound and a pharmaceutically acceptable vehicle including an oleic acid component, wherein the oleic acid component is at least 80% oleic acid.

In certain embodiments, formulations described herein can be in the form of an oil-in-water emulsion such as a cream or a lotion. The oil component of the formulation includes an IRM compound and one or more fatty acids, including oleic acid in an amount sufficient to solubilize the IRM compound. Optionally, a cream or lotion of the invention can contain emollients, antioxidants, emulsifiers, viscosity enhancing agents, and/or preservatives. Such components, as well as all others of the formulations described herein, are preferably pharmaceutically acceptable.

Immune Response Modifying Compounds

Formulations of the invention include an IRM compound. Such compounds include, for example, imidazoquinoline amines including, but not limited to, substituted imidazoquinoline amines such as, for example, amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea substituted imidazoquinoline amines, aryl ether substituted imidazoquinoline amines, heterocyclic ether substituted imidazoquinoline amines, amido ether substituted imidazoquinoline amines, sulfonamido ether substituted imidazoquinoline amines, urea substituted imidazoquinoline ethers, thioether substituted imidazoquinoline amines, 6-, 7-, 8-, or 9-aryl, heteroaryl, aryloxy or arylalkyleneoxy substituted imidazoquinoline amines, and imidazoquinoline diamines; tetrahydroimidazoquinoline amines including, but not limited to, amide substituted tetrahydroimidazoquinoline amines, sulfonamide substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline amines, aryl ether substituted tetrahydroimidazoquinoline amines, heterocyclic ether substituted tetrahydroimidazoquinoline amines, amido ether substituted tetrahydroimidazoquinoline amines, sulfonamido ether substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline ethers, thioether substituted tetrahydroimidazoquinoline amines, and tetrahydroquinoline diamines; imidazopyridine amines including, but not limited to, amide substituted imidazopyridine amines, sulfonamide substituted imidazopyridine amines, urea substituted imidazopyridine amines, aryl ether substituted imidazopyridine amines, heterocyclic ether substituted imidazopyridine amines, amido ether substituted imidazopyridine amines, sulfonamido ether substituted imidazopyridine amines, urea substituted imidazopyridine ethers, and thioether substituted imidazopyridine amines; 1,2-bridged imidazoquinoline amines; 6,7-fused cycloalkylimidazopyridine amines; imidazonaphthyridine amines; tetrahydroimidazonaphthyridine amines; oxazoloquinoline amines; thiazoloquinoline amines; oxazolopyridine amines; thiazolopyridine amines; oxazolonaphthyridine amines; thiazolonaphthyridine amines; and 1H-imidazo dimers fused to pyridine

amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines.

These immune response modifier compounds are disclosed in, e.g., U.S. Pat. Nos. 4,689,338, 4,929,624; 5,266,575; 5,268,376; 5,346,905; 5,352,784; 5,389,640; 5,446,153; 5,482,936; 5,756,747; 6,110,929; 6,194,425; 6,331,539; 6,376,669; 6,451,810; 6,525,064; 6,541,485; 6,545,016; 6,545,017; 6,573,273; 6,656,938; 6,660,735; 6,660,747; 6,664,260; 6,664,264; 6,664,265; 6,667,312; 6,670,372; 6,677,347; 6,677,348; 6,677,349; 6,683,088; 6,756,382; U.S. Patent Publication Nos. 2004/0091491; 2004/0132766; 2004/0147543; and 2004/0176367; and International Patent Application No. PCT/US04/28021 filed on Aug. 27, 2004.

For certain of these embodiments, the IRM compound is an imidazonaphthyridine amine. For certain of these embodiments, the IRM compound is 2-methyl-1-(2-methylpropyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine. For certain of these embodiments, the IRM compound is an imidazoquinoline amine. For certain of these embodiments, the IRM compound is 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imiquimod). For some embodiments, the IRM may have low solubility in water, for example less than about 1 ug/mL (e.g., 0.79 ug/mL in the case of imiquimod), making them difficult to solubilize in aqueous formulations, and potentially using relatively large amounts of oleic acid in the formulation.

The amount of IRM compound that will be therapeutically effective in a specific situation will depend on such things as the activity of the particular compound, the dosing regimen, the application site, the particular formulation and the condition being treated. As such, it is generally not practical to identify specific administration amounts herein; however, those skilled in the art will be able to determine appropriate therapeutically effective amounts based on the guidance provided herein, information available in the art pertaining to IRM compounds, and routine testing. The term "a therapeutically effective amount" means an amount of the IRM compound sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, inhibition of TH2 immune response, antiviral or antitumor activity, reduction or elimination of postsurgical scarring, reduction or resolution of actinic keratosis or pre-actinic keratosis lesions, reduction in the recurrence of actinic keratosis, treatment of basal cell carcinoma, genital warts, peri-anal warts, molloscum contagiosum, or protection against uv-induced epidermal neoplasia.

In general, the amount of IRM compound present in a topical formulation of the invention will be an amount effective to treat a targeted condition, to prevent recurrence of the condition, or to promote immunity against the condition. In certain embodiments, the amount or concentration of IRM compound is at least 3% by weight, such as, for example, at least 5%, and at least 10%, by weight based on the total weight of the formulation. In other embodiments, the amount of IRM compound is at most 10% by weight, such as, for example, at most 5%, at most 3%, by weight based on the total weight of the formulation. In certain embodiments, the amount or concentration of IRM compound is at least 0.02% by weight, such as, for example, at least 0.03%, at least 0.10%, and at least 0.30% by weight based on the total weight of the formulation.

Fatty Acids

The topical formulations of the invention include fatty acids. In particular, the topical formulations of the invention contain an oleic acid component. As used herein, the term "fatty acid" means a carboxylic acid, either saturated or unsaturated having 6 to 28 carbon atoms, such as, for example, from 10 to 22 carbon atoms.

The fatty acids, including the oleic acid component, may be present in the formulation in an amount sufficient to solubilize the IRM compound. In certain embodiments, the amount of oleic acid component is at least 0.05% by weight at least 1.0% by weight, at least 3.0% by weight, at least 5.0%, at least 10%, at least 15%, or at least 25%, based on the total weight of the formulation. In certain embodiments, the amount of oleic acid component is at most 40% by weight, at most 30% by weight, at most 15% by weight, or at most 10%, based on the total weight of the formulation.

Compendial grade oleic acid typically contains from 65 to 88 percent (Z)-octadec-9-enoic acid (oleic acid) together with varying amounts of saturated and other unsaturated fatty acids. The composition of fat acids is determined by gas chromatography using the method described in European Pharmacopeia monograph 01/2005:0799.

For certain embodiments, the oleic acid component contains at least 50%, at least 60%, at least 70% or at least 80% oleic acid. For certain embodiments, the oleic acid component contains at least 80% oleic acid.

For certain embodiments, the oleic acid component is substantially free of polar impurities, such as peroxides. For certain embodiments, the oleic acid component contains less than 10%, less than 5%, less than 1%, or less than 0.1% by weight of polar impurities. For certain embodiments, the oleic acid component has a peroxide value less than 10. For certain embodiments, the oleic acid component has a peroxide value less than 5.

For certain embodiments, the oleic acid component comprises SUPER REFINED Oleic Acid NF, available from Croda Inc., Edison, N.J., USA.

For certain embodiments, the topical formulations of the invention can include fatty acids in addition to those included in the oleic acid component. For example, certain embodiments can include isostearic acid. In some embodiments, the total amount of fatty acids, including those in the oleic acid component, is at least 0.05% by weight, at least 1.0% by weight, at least 3.0% by weight, at least 5.0%, at least 10%, at least 15%, or at least 25%, based on the total weight of the formulation. In certain embodiments, the total amount of fatty acids, including those in the oleic acid component, is at most 40% by weight, at most 30% by weight, at most 15% by weight, or at most 10%, based on the total weight of the formulation.

Antioxidants

For certain embodiments, the topical formulations of the invention can include an antioxidant.

Suitable antioxidants are those that are pharmaceutically acceptable and described in the International Cosmetic Ingredient Dictionary and Handbook, Ninth Edition, Volume 4, 2002, and in the USP NF 2004: The United States Pharmacopeia, 27th Revision and The National Formulary, 22nd Edition.

Examples of suitable antioxidants include ascorbic acid (D and/or L enantiomers), ascorbyl palmitate (D and/or L enantiomers), butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), cysteine (D and/or L enantiomers), propyl gallate, sodium formaldehyde sulfoxylate, sodium thiosulfate, and tocopherol.

For certain embodiments, the antioxidant is selected from the group comprising aromatic hydroxy groups capable of hydrogen atom donation. Examples of such antioxidants include BHA, BHT, propyl gallate, and tocopherol.

For certain embodiments, the antioxidant is selected from the group consisting of BHA, BHT, and combinations thereof. For certain embodiments, the antioxidant is BHA.

Preservative System

The formulation often will include a preservative system. The preservative system includes one or more compounds that inhibit microbial growth (e.g., fungal and bacterial growth) within the formulation (for example, during manufacturing and use). The preservative system will generally include at least one preservative compound, such as, for example, methylparaben, ethylparaben, propylparaben, butylparaben, benzyl alcohol, phenoxyethanol, and sorbic acid or derivatives of sorbic acid such as esters and salts. Various combinations of these compounds can be included in the preservative system. In some embodiments of the invention, the preservative system includes methylparaben, propylparaben and benzyl alcohol.

In some embodiments of the invention, the preservative compound is present in an amount of at least 0.01% by weight, such as for example, at least 0.02%, at least 0.03%, at least 0.04%, and at least 0.05%, by weight based on the total weight of the formulation. In other embodiments of the invention the preservative compound is present in an amount of at most 3%, such as for example, at most 2.5%, at most 2.0%, at most 1.0%, at most 0.5%, at most 0.4%, at most 0.3%, and at most 0.2%, by weight based on the total weight of the formulation.

Emollients

The topical formulations of the invention may also include at least one emollient. Examples of useful emollients include but are not limited to long chain alcohols, for example, cetyl alcohol, stearyl alcohol, cetearyl alcohol; fatty acid esters, for example, isopropyl mysristate, isopropyl palmitate, diisopropyl dimer dilinoleate; medium-chain (e.g., 8 to 14 carbon atoms) triglycerides, for example, caprylic/capric triglyceride, cetyl esters; hydrocarbons of 8 or more carbon atoms, for example, light mineral oil, white petrolatum; and waxes, for example, beeswax. Various combinations of such emollients can be used if desired.

In certain embodiments, the amount of the emollient is at least 1.0% by weight, at least 3.0% by weight, at least 5.0% by weight, or at least 10% by weight, based on the total weight of the formulation. In certain embodiments, the amount of emollient is at most 30% by weight, at most 15% by weight, or at most 10% by weight, based on the total weight of the formulation.

Formulations intended for dermal or topical use typically have amounts of an oil phase and an emollient sufficient to provide desirable qualities such as spreadability and feel.

Viscosity Enhancing Agent

The formulations of the present invention can also comprise a viscosity-enhancing agent. Examples of suitable viscosity enhancing agents include long chain alcohols, for example, cetyl alcohol, stearyl alcohol, cetearyl alcohol; cellulose ethers such as hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and carboxymethylcellulose; polysaccharide gums such as xanthan gum; and homopolymers and copolymers of acrylic acid crosslinked with allyl sucrose or allyl pentaerythriol such as those polymers designated as carbomers in the United States Pharmacopoeia. Suitable carbomers include, for example, those available as CARBOPOL 934P, CARBOPOL 971P, CARBOPOL 940, CARBOPOL 974P, CARBOPOL 980, and PEMULEN TR-1 (USP/NF Monograph; Carbomer 1342), all available from Noveon, Cleveland, Ohio.

In certain embodiments, the amount of the viscosity enhancing agent, when used, is at least 0.1% by weight, at least 0.2% by weight, at least 0.5% by weight, at least 0.6% by weight, at least 0.7% by weight, at least 0.9% by weight, or at least 1.0% by weight, based on the total weight of the formulation. In certain embodiments, the amount of the viscosity-enhancing agent, when used, is at most 10% by weight, at most 5.0% by weight, at most 3.0% by weight, at most 2.0% by weight, or at most 1.5% by weight, based on the total weight of the formulation.

Emulsifier

The formulations of the invention can additionally comprise an emulsifier. Suitable emulsifiers include non-ionic surfactants such as, for example, polysorbate 60, sorbitan monostearate, polyglyceryl-4 oleate, polyoxyethylene(4) lauryl ether, etc. In certain embodiments, the emulsifier is chosen from poloxamers (e.g., PLURONIC F68, also known as POLOXAMER 188, a poly(ethylene glycol)-block-poly (propylene glycol)-block-poly(ethylene glycol), available from BASF, Ludwigshafen, Germany) and sorbitan trioleate (e.g., SPAN 85 available from Uniqema, New Castle, Del.).

If included, the emulsifier is generally present in an amount of 0.1% to 10% by weight of total formulation weight, for example, from 0.5% to 5.0% by weight, and from 0.75% to 4.0% by weight. In certain embodiments, the amount of the emulsifier, if used, is present in an amount of at least 0.1% by weight, at least 0.5% by weight, at least 0.75% by weight, at least 1.0% by weight, at least 2.5% by weight, at least 3.5% by weight, at least 4.0% by weight, or at least 5.0% by weight, based on the total weight of the formulation. In certain embodiments, the amount of the emulsifier, if used, is present in an amount of at most 10% by weight, at most 5.0% by weight, or at most 3.5% by weight, based on the total weight of the formulation.

Some formulations of the invention are oil-in-water emulsions. The water used in these formulations is typically purified water

Optionally, a formulation of the invention can contain additional pharmaceutically acceptable excipients such as humectants, such as for example, glycerin; chelating agents, such as for example, ethylenediaminetetraacetic acid; and pH adjusting agents, such as for example, potassium hydroxide or sodium hydroxide.

In some instances, a single ingredient can perform more than one function in a formulation. For example, cetyl alcohol can serve as both an emollient and a viscosity enhancer.

Illustrative Formulation

In one embodiment of the present invention, a pharmaceutical formulation includes:

5% by weight of 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine;
28% by weight SUPER REFINED oleic acid;
2.2% by weight cetyl alcohol;
3.1% by weight stearyl alcohol;
3% by weight petrolatum;
3.4% by weight polysorbate 60;
0.6% by weight sorbitan monostearate;
2% by weight glycerin;
0.2% by weight methyl hydroxybenzoate;
0.02% by weight propyl hydroxybenzoate;
0.5% by weight xanthan gum;
2% by weight of benzyl alcohol; and
49.98% by weight water;

Methods of Application

Formulations according to the present invention can be applied to any suitable location, for example topically to dermal and/or mucosal surfaces. In the case of dermal application, for example, depending on the IRM compound concentration, formulation composition, and dermal surface, the therapeutic effect of the IRM compound may extend only to the superficial layers of the dermal surface or to tissues below the dermal surface. Thus, another aspect of the present invention is directed to a method for the treatment of a dermal and/or mucosal associated condition comprising applying to skin one of the foregoing formulations. As used herein, a "dermal and/or mucosal associated condition" means an inflammatory, infectious, neoplastic or other condition that involves a dermal and/or mucosal surface or that is in sufficient proximity to a dermal and/or mucosal surface to be affected by a therapeutic agent topically applied to the surface. Examples of a dermal and/or mucosal associated condition include warts, atopic dermatitis, postsurgical scars, lesions caused by a herpes virus, and epidermal neoplasias, such as for example actinic keratosis, pre-actinic keratosis lesions, malignant melanomas, basal cell carcinoma, and squamous cell carcinoma.

In one embodiment, the formulations can be applied to the surface of skin for treatment of actinic keratosis (AK). Actinic keratosis are premalignant lesions considered biologically to be either carcinoma in-situ or squamous intraepidermal neoplasia. AK is the most frequent epidermal tumor and is induced by ultraviolet (UV) radiation, typically from sunlight. Because of its precancerous nature, AK may be considered the most important manifestation of sun-induced skin damage.

In some embodiments, the above-described formulations are particularly advantageous for dermal and/or mucosal application for a period of time sufficient to obtain a desired therapeutic effect without undesired systemic absorption of the IRM compound.

Examples

The following Examples are provided to further describe various formulations and methods according to the invention. The examples, however, are not intended to limit the formulations and methods within the spirit and scope of the invention.

Test Method

A reversed phase high performance liquid chromatography (HPLC) method was used to determine the amount of impurities in cream formulations containing oleic acid.

HPLC parameters: Analytical column: ZORBAX RX C8, 5 micron particle, 15.0×0.46 cm, (available from Agilent Technologies, Wilmington, Del., USA); Detector: UV at 308 nm; Mobile phase: gradient mixture of aqueous ammonium phosphate buffer (prepared by combining 5.1 mL of orthophosphoric acid with 985 mL of water and then adjusting to pH 2.5 with concentrated ammonium hydroxide) and acetonitrile; Gradient: start run at 10% acetonitrile, zero initial hold time, then linear gradient to 70% acetonitrile over 15 minutes, zero final hold time; Flow rate: 2.0 mL/minute; Injection volume: 200 μL; Run time: 15 minutes.

Sample solution: A portion (about 300 mg) of the cream formulation was accurately weighed into a volumetric flask (100 mL). Diluent (50 to 60 mL, prepared by combining 250 parts of acetonitrile, 740 parts of water and 10 parts of hydrochloric acid, all parts by volume) was added to the flask. The flask was vortexed until the cream was completely dispersed and then sonicated for a minimum of 5 minutes. The solution was allowed to cool to ambient temperature and then diluted to volume with diluent and mixed. A portion of the solution was filtered using a syringe equipped with a 0.45 micron polypropylene or polytetralfluoroethylene filter to provide the sample solution.

Preparation of Cream Formulations

The cream formulations in Table 1 below were prepared using the following method.

Water phase preparation: A paraben premix was prepared by combining methyl hydroxybenzoate (methylparaben), propyl hydroxybenzoate (propylparaben), and water; heating the mixture with stirring until the parabens were dissolved; and then allowing the resulting solution to cool to ambient temperature. Glycerin was added to the premix and the mixture was heated to 55±5° C. Xanthan gum was slowly added with mixing. Mixing with heating was continued until the xanthan gum was dispersed.

Oil phase preparation: An imiquimod/oleic acid premix was prepared by combining imiquimod and the oleic acid and then stirring at ambient temperature overnight. Petrolatum, cetyl alcohol, stearyl alcohol, polysorbate 60, sorbitan monostearate, and butylated hydroxyanisole (BHA), if included, were added to the premix. The oil phase was then heated with stirring to 55±5° C. Benzyl alcohol was added to the oil phase just prior to phase combination.

Phase combination: Both phases were removed from their heat source. The aqueous phase was added to the oil phase and the emulsion was homogenized at high speed for at least 5 minutes. The cream was placed in an ice/water bath while homogenizing and homogenization was continued until the temperature of the cream was 35° C., The homogenizer speed was reduced and homogenization was continued until the temperature of the cream was 25° C.

Table 1 summarizes creams A-D in percentage weight-by-weight basis. The formulations were packaged in glass containers.

TABLE 1

Ingredient	A	B	C	D
[1]Imiquimod	5	5	5	5
[2]Oleic acid, NF	28	28	—	—
[3]SUPER REFINED oleic acid, NF	—	—	28	28
Cetyl alcohol	2.2	2.2	2.2	2.2
Stearyl alcohol	3.1	3.1	3.1	3.1
Petrolatum	3	3	3	3
Polysorbate 60	3.4	3.4	3.4	3.4
Sorbitan monostearate	0.6	0.6	0.6	0.6
Benzyl alcohol	2	2	2	2
BHA	—	1	—	1
Glycerin	2	2	2	2
Methylparaben	0.2	0.2	0.2	0.2
Propylparaben	0.02	0.02	0.02	0.02
Xanthan gum	0.5	0.5	0.5	0.5
Water	qs 100	qs 100	qs 100	qs 100

[1]1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine
[2]J. T. Baker, a division of Mallinckrodt Baker, Inc, Phillipsburg, NJ, USA
[3]Croda, Inc, Edison, NJ, USA

One set of containers was stored at ambient conditions; the samples used to determine initial values came from these containers. The remaining containers were stored in a constant temperature and humidity chamber at 40° C. at 75% relative humidity. At selected time points, containers were removed from the chamber and then stored at ambient con-

ditions until analyzed. Samples were analyzed using the test method described above for impurities. At the 2, 4, and 6 month time points samples were taken from both the top and the bottom of the containers. The results are shown in Table 2 below where each value is the result of a single determination. Values are not normalized for weight loss that may have occurred during storage.

TABLE 2

	Impurities (% wt/wt)			
Timepoint	A	B	C	D
[1]Initial - top	0.09	0.08	0.02	0.03
[2]2 months - top	0.25	0.32	0.07	0.09
[2]2 months - bottom	0.33	0.30	0.04	0.15
[3]4 months - top	0.42	0.76	0.18	0.15
[3]4 months - bottom	0.46	0.56	0.04	0.29
[4]6 months - top	0.81	0.30	0.07	0.14
[4]6 months - bottom	0.49	0.29	0.04	0.07

[1]Creams A, B, C, and D were analyzed 16 days, 15 days, 14 days, and 15 days respectively after they were prepared.
[2]All samples were analyzed 10 days after the containers were removed from the constant temperature and humidity chamber.
[3]All samples were analyzed 12 days after the containers were removed from the constant temperature and humidity chamber.
[4]All samples were analyzed 7 days after the containers were removed from the constant temperature and humidity chamber.

The complete disclosures of the patents, patent documents and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. In case of conflict, the present specification, including definitions, shall control. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. Illustrative embodiments and examples are provided as examples only and are not intended to limit the scope of the present invention. The scope of the invention is limited only by the claims set forth as follows.

What is claimed is:

1. A pharmaceutical cream for topical application to a dermal or mucosal surface for topical delivery of 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imiquimod), said pharmaceutical cream comprising:

a therapeutically effective amount of imiquimod; and

a pharmaceutically acceptable vehicle including an oleic acid component,

wherein the oleic acid component at or prior to formulation of said pharmaceutical cream contains at least about 80% oleic acid by weight as a fatty acid, and

wherein the oleic acid component at or prior to formulation of said pharmaceutical cream has a peroxide value of less than about 5 milliequivalents of oxygen per kilogram and contains less than about 1% by weight polar impurities, and

wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of no more than about 0.03% wt./wt. after storage of said pharmaceutical cream at ambient conditions for about 15 days, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.

2. The pharmaceutical cream of claim **1**, wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of no more than about 0.02% wt./wt. after storage of said pharmaceutical cream at ambient conditions for about 15 days, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.

3. The pharmaceutical cream of claim **1**, wherein said pharmaceutical cream further comprises an antioxidant selected from a group of antioxidants consisting of butylated hydroxyl toluene and butylated hydroxyanisole.

4. The pharmaceutical formulation of claim **1**, wherein the imiquimod is present in an amount of no more than about 10% by weight based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of no more than about 40% by weight based on the total weight of said pharmaceutical cream.

5. The pharmaceutical cream of claim **1**, wherein the imiquimod is present in an amount of about 5% by weight based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of no more than about 30% by weight based on the total weight of said pharmaceutical cream.

6. The pharmaceutical cream of claim **1**, wherein the imiquimod is present in an amount of about 5% by weight based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of about 28% by weight based on the total weight of said cream formulation.

7. A pharmaceutical cream for topical application to a dermal or mucosal surface for topical delivery of 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imiquimod), said pharmaceutical cream comprising:

a therapeutically effective amount of imiquimod; and

a pharmaceutically acceptable vehicle including an oleic acid component,

wherein the oleic acid component at or prior to formulation of said pharmaceutical cream contains at least about 80% oleic acid by weight as a fatty acid, and

wherein the oleic acid component at or prior to formulation of said pharmaceutical cream has a peroxide value of less than about 5 milliequivalents of oxygen per kilogram and contains less than about 1% by weight polar impurities, and

wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of no more than about 0.15% wt./wt. after storage of said pharmaceutical cream for at least about 2 months at about 40° C. and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.

8. The pharmaceutical cream of claim **7**, wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of no more than about 0.07% wt./wt. after storage of said pharmaceutical cream for at least about 2 months at about 40° C. and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.

9. The pharmaceutical cream of claim **7**, wherein said pharmaceutical cream further comprises an antioxidant selected from a group of antioxidants consisting of butylated hydroxyl toluene and butylated hydroxyanisole.

10. The pharmaceutical cream of claim **7**, wherein the imiquimod is present in an amount of no more than about 10% by weight based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of no more than about 40% by weight based on the total weight of said pharmaceutical cream.

11. The pharmaceutical cream of claim **7**, wherein the imiquimod is present in an amount of about 5% by weight based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of no more than about 30% by weight based on the total weight of said pharmaceutical cream.

12. The pharmaceutical cream of claim **7**, wherein the imiquimod is present in an amount of about 5% by weight

based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of about 28% by weight based on the total weight of said pharmaceutical cream.

13. A pharmaceutical cream for topical or application to a dermal or mucosal surface to deliver 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imiquimod) to treat a dermal and/or mucosal associated condition, said pharmaceutical cream having enhanced imiquimod stability and comprising:

a therapeutically effective amount of imiquimod; and

a pharmaceutically acceptable vehicle including an oleic acid component,

wherein the oleic acid component at or prior to formulation of said pharmaceutical cream contains at least about 80% oleic acid by weight as a fatty acid, and

wherein the oleic acid component at or prior to formulation of said pharmaceutical cream has a peroxide value of less than about 5 milliequivalents of oxygen per kilogram and contains less than about 1% by weight polar impurities, and

wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of no more than about 0.29% wt./wt. after storage for at least about 4 months at about 40° C. and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.

14. The pharmaceutical cream of claim **13**, wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of no more than about 0.15% wt./wt. after storage of said pharmaceutical cream for at least about 4 months at about 40° C. and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.

15. The pharmaceutical cream of claim **13**, wherein said pharmaceutical cream further comprises an antioxidant selected from a group of antioxidants consisting of butylated hydroxyl toluene and butylated hydroxyanisole.

16. The pharmaceutical cream of claim **13**, wherein the imiquimod is present in an amount of no more than about 10% by weight based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of no more than about 40% by weight based on the total weight of said pharmaceutical cream.

17. The pharmaceutical formulation of claim **13**, wherein the imiquimod is present in an amount of about 5% by weight based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of no more than about 30% by weight based on the total weight of said pharmaceutical cream.

18. The pharmaceutical cream of claim **13**, wherein the imiquimod is present in an amount of about 5% by weight based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of about 28% by weight based on the total weight of said pharmaceutical cream.

19. The pharmaceutical cream of claim **7**, wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of (a) no more than about 0.04% wt./wt. after storage of said pharmaceutical cream for at least about 2 months at about 40° C. and about 75% humidity and (b) no more than about 0.04% wt./wt. after storage of said pharmaceutical cream for at least about 4 months at about 40° C. and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.

20. The pharmaceutical cream of claim **7**, wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of (a) no more than about 0.15% wt./wt. after storage of said pharmaceutical cream for at least about 2 months at about 40° C. and about 75% humidity and (b) no more than about 0.15% wt./wt. after storage of said pharmaceutical cream for at least about 4 months at about 40° C. and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.

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