Summary Report

Niacinamide ascorbate

Prepared for:

United States Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 5U01FD005946-06

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December 2021

This report was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U01FD005946) totaling $2,342,364, with 100 percent funded by the FDA/HHS. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the FDA/HHS or the U.S. Government.

Table of Contents

Table of Tables

Frequently Used Abbreviations

ADC	Automated dispensing cabinets
API	Active Pharmaceutical Ingredient
ED	Emergency department
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
OR	Operating room
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
ssUV	Solar simulated ultraviolet
TEWL	Transepidermal water loss
UK	United Kingdom
US	United States
UV	Ultraviolet

INTRODUCTION

This report was created to assist the United States (US) Food and Drug Administration (FDA) in its evaluation of the use of niacinamide ascorbate (niacinamide; UNII code: JTL8B7TVW7) which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how niacinamide is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how niacinamide has been used historically and currently.[1-3] Assessments of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of niacinamide and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

Niacinamide was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association. Niacinamide was nominated for use in combination with additional active pharmaceutical ingredients (API) (refer to Table 8).

While the exact medical condition for which niacinamide will be used to treat is generally unknown, niacinamide is generally used as an antifungal. Niacinamide will be compounded as a topical cream, emulsion, foam, gel, lotion, ointment, solution, or spray in strengths based on the prescriber's request, with therapeutic doses typically ranging from 2% to 5%.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of niacinamide.[6-9]

Reasons provided for nomination to the 503B Bulks List included:

- The compounded drug product may be the only formulation to effectively treat the indication for which it is intended to treat.
- There are no FDA-approved drugs that contain this API.
- Compounding from bulk means using only the ingredients necessary to achieve the desired clinical outcomes. This means starting with the API in its purest form without any fillers, excipients, binders, dyes, preservatives, or other materials that may be irritating, hazardous, or allergens.
- Need for accuracy; individual finished products have considerable variance in the actual API and use of a finished product has the potential to introduce unacceptable inaccuracies into the compounded medication.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of niacinamide products in the US and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and

desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for niacinamide; name variations of niacinamide were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; and approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing niacinamide. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: niacinamide; topical administration or form; and therapeutic use (refer to Appendix 1 for full search strategies). Results were limited to human studies in English language. Searches were conducted February 17, 2021. In addition, the ECRI Guidelines Trust® repository was searched February 17, 2021 for clinical practice guidelines that recommended the use of niacinamide and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.3.3 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which niacinamide was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if niacinamide was used as a dosage form or ROA that was not nominated; in an unspecified dosage form or ROA; niacinamide not used clinically; or niacinamide mentioned briefly as a rescue treatment or as a previously failed treatment. Studies in which niacinamide was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of niacinamide; setting; total number of patients; number of patients who received niacinamide; patient population; indication for use of niacinamide; dosage form and strength; dose; ROA; frequency and duration of therapy; use of niacinamide in a combination product; use and formulation of niacinamide in a compounded product; use of niacinamide compared to FDA-approved drugs or other treatments; outcome measures; and authors' conclusions. One reviewer extracted data from the included studies, and a second reviewer checked the data extraction.

Interviews

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances niacinamide was used in a clinical setting. The systematic literature review and indications from the nomination were reviewed to identify medical specialties that would potentially use niacinamide. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. Select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided verbal informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

In addition to interviews with individual SMEs, a roundtable discussion with pharmacists was held. Participants were identified through outreach to professional associations that would potentially purchase compounded products from outsourcing facilities. A prequestionnaire was distributed to those who agreed to participate to collect information about the types of facilities at which participants worked and the products they purchased from outsourcing facilities (refer to Appendix 3 for complete survey and *Results of survey* section for results of prequestionnaire). The roundtable lasted 60 minutes and was conducted via Zoom, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

Survey

A survey was distributed to the members of professional medical associations to determine the use of niacinamide in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 3 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Years 1 and 2 were not contacted to distribute the project Year 3 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 4 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Niacinamide is not available as an FDA-approved product in the nominated dosage form and ROA. Niacinamide is available in FDA-approved intravenous (IV) solutions in combination with other vitamins.
- Niacinamide is available in topical OTC products in the US.
- There is a current United States Pharmacopeia (USP) monograph for niacinamide.
- Niacinamide is available in the nominated dosage form and ROA in Ireland and the UK. Niacinamide is also available in topical OTC products in Latvia and the UK.

Table 1. Currently approved products – US

No approved topical products in the US

Table 2. Currently approved products – select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Niacinamide	4%	Gel	Topical	Ireland	Pharmacy-only[c]	10/13/1992
				United Kingdom	Pharmacy[c]	9/10/2002

Abbreviation: –, not provided.

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

[c]Pharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Results of literature review

Study selection

Database searches yielded 1266 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 1014 titles and abstracts were screened. After screening, the full text of 372 articles was reviewed. Thirty studies were included; after multiple reports of the same study were merged, there were 27 included studies. Three hundred forty-two studies were excluded for the following reasons: wrong study design (259 studies); non-nominated formulation (49); unspecified formulation (8); unable to obtain (7); wrong substance (7); niacinamide only mentioned briefly (6); duplicate study (2); FDA-approved formulation (2); and language other than English (2).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 27 included studies were published between 1995 and 2020. There were 27 experimental studies, 0 observational studies, 0 descriptive studies, and 0 clinical practice guidelines. The 27 studies were conducted in the following countries: Australia, Brazil, France, Germany, Iran, Italy, Japan, Mexico, Serbia, South Africa, Taiwan, and the US.

A total of 2198 patients participated in the 27 included studies. The number of patients in each study ranged from 8 to 232.

Outcome measures differed among the included studies and included: expert assessment of ultraviolet (UV) barrier, clinical signs of facial photoaging, skin yellowing, elasticity, hyperpigmentation, compliance, facial spot count, minimal erythema dose, single solar (ss) UV-induced immunosuppression, transepidermal water loss (TEWL), sebum-excretion-rate measurements, clinical measures, evaluate of antiwrinkle effects, acne grade, percent of patients who achieve clear-to-almost-clear psoriatic symptoms, triplicate stratum corneum hydration, actinic keratoses count, adverse events, irritation, change from baseline in corneometer values, reduction of acne severity index score, patient satisfaction, psoriasis severity, difference in Mantoux-induced erythema, clinical scoring of seborrhea, and Dermatology Life Quantity Index (DLQI) score.

Refer to Table 5 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of niacinamide

Two hundred seventy-six patients received niacinamide as a treatment for acne, administered as a topical 4-5% cream or gel twice daily for 8 weeks. Two hundred twenty-four patients received niacinamide for anti-aging, administered as a topical 5% moisturizer in a dose of 0.8 g/day for 12 weeks. A couple of studies mentioned topical niacinamide cream or 4% lotion twice daily for 4-8 weeks. Ninety-one patients received niacinamide for hyperpigmentation, administered as a topical 5% moisturizer in a dose of 0.6 mL/day for 8 weeks. Some studies administered niacinamide as a topical 4-5% cream or moisturizer in a dose of 0.9 g/day for 8-9 weeks. One study specified topical niacinamide 4% cream in a dose of 0.8 mL/day for 12 weeks, while another study specified the use of a topical niacinamide 3% cream in a dose of 2 mg/cm^2 twice daily for 4 weeks. One hundred sixty-five patients received niacinamide for prevention of photodynamic therapy or UV-induced immunosuppression, administered as a topical 5% cream or 0.2-5% lotion for 1-3 days. The dose

stated varied from a daily topical application, 2 mcg/cm² of skin per application, to 2 μL/cm² of skin daily.

Fifty-two patients received niacinamide for erythema and/or irritated skin, administered as a topical gel or 5% emulsion for 2-4 weeks. Sixty-five patients received niacinamide as a treatment for psoriasis, administered as a topical 0.05-4% ointment twice daily for 12 weeks. Thirteen patients received niacinamide as a treatment for actinic keratosis, administered as a topical 1% gel in a dose of 1.6 mL/day to each area (face, forearms, and/or scalp if bald) for 6 months. Fifty-one patients received niacinamide as a treatment for androgenetic alopecia, administered as a topical 0.1% lotion in a dose of 6 mL/day for 6 months. Eighty patients received niacinamide for facial sebum control, administered as a topical 2% gel twice daily for 4-6 weeks. Ninety patients received niacinamide for male skin health, administered as a topical 4% moisturizer for 3 weeks. Twenty-seven patients received niacinamide as a treatment for melasma, administered as a topical 4% cream for 8 weeks. Ninety-four patients received niacinamide for prevention of chemotherapy-induced cutaneous symptoms, administered as a topical 4% cream twice daily for 6 weeks. Twenty-four patients received niacinamide as a treatment for seborrheic dermatitis, administered as a topical 4% cream daily for 12 weeks.

Refer to Tables 6 and 7 for summaries of dosage by indication.

Niacinamide was used as a compounded product, and it was also used in a combination product (refer to Tables 8-10).

In 11 studies, the authors' concluding statement recommended the use of niacinamide for the treatment of acne,[10] anti-aging effects,[11] erythema and/or irritated skin,[12,13] hyperpigmentation,[8,14] male skin health,[15] melasma,[16] prevention of UV-induced immunosuppression,[17,18] and seborrheic dermatitis.[19] In 2 studies, the authors concluded that the use of niacinamide was similar to the comparator for the treatment of acne.[20,21] In 10 studies, the authors concluded that further studies were necessary for the use of niacinamide for treatment of acne,[22,23] actinic keratosis,[24] anti-aging effects,[25-27] prevention of chemotherapy-induced cutaneous symptoms,[28] prevention of photodynamic therapy induced immunosuppression,[29] and psoriasis.[30,31] In 4 studies, the authors' conclusions did not provide a definitive conclusion for the use of niacinamide.[32-35]

Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

Additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of niacinamide.

Niacinamide is the biologically active amide of vitamin B3. Vitamin B3 is not stored in the body and is an essential water-soluble vitamin.[36] Niacinamide is the precursor of nicotinamide adenine dinucleotide (NAD), a key coenzyme in the production of adenosine triphosphate (ATP). ATP transports chemical energy within cells.[36] In vitro, niacinamide increases levels of nicotinamide adenine dinucleotide (NADP) in aging human skin as well as increases synthesis of collagen, involucrin, filaggrin, and keratin.[37] Additionally, niacinamide improves the epidermal barrier and decreases TEWL by increasing the synthesis of ceramides and other stratum corneum lipids.[37] Niacinamide also reduces oxidative damage by suppressing reactive oxygen species in cells and "may decrease skin pigmentation by preventing melanosome transfer."[38-40] Studies have shown that niacinamide has "significant penetration through the stratum corneum."[41]

Studies disagree regarding the use of niacinamide or nicotinic acid with some stating that in vivo niacinamide and nicotinic acid are readily converted into each other while other studies hypothesize that they have different pharmaceutical activities with nicotinic acid providing more benefits because it is able to interact with nicotinic acid receptors on the skin.[42] However, nicotinic acid is associated with facial flushing whereas niacinamide is not.[42] Bisset discussed formulation challenges with using niacinamide due to the potential for hydrolysis to nicotinic acid and recommends formulations fall in the pH range of 4 to 7 to avoid hydrolysis and to avoid including acids, such as salicylic acid; or bases, such as zinc oxide.[43]

Niacinamide has been evaluated for use in several dermatologic conditions including acne, rosacea, aging, atopic dermatitis, blistering disorders, and prevention of skin cancer.[36,40] Niacinamide is included in several skin care products. Multiple studies have been conducted evaluating the cosmetic effects of niacinamide, which include improving skin barrier by reducing TEWL; improving texture; and reducing skin pore size, facial red blotchiness, fine lines, wrinkles, hyperpigmentation, skin yellowing, and acne.[43,44] Levin et al stated that "the topical use of niacinamide has proven to be effective not only when there are signs of niacin deficiency" and that "niacinamide is one of the best studied cosmeceutical ingredients for antiaging."[45]

Melasma is a "chronic, acquired pigmentary" skin disease that is characterized by hypermelanosis, "symmetric patches of hyperpigmentation on sun-exposed areas such as the cheeks, forehead, chin, nose, and upper lips."[39,40] Topical first-line treatment includes hydroquinone; and a triple combination therapy that includes hydroquinone, a retinoid, and a steroid. However, hydroquinone is "associated with ochronosis, a bluish-gray discoloration of the skin" and there have been concerns about the long-term safety and efficacy.[39] As a result, there has been interest in identifying alternative topical treatment options. Austin et al performed a systematic review of randomized controlled trials that used topical agents to treat melasma. One randomized controlled trial was included that evaluated the use of niacinamide, and while the benefits outweigh the risks and burdens, it only received a weak recommendation but the study did show "promising efficacy."[39]

Anwar et al conducted a multicenter trial in which 66 patients with epidermal and/or mixed-type melasma applied a serum followed by a cream containing tranexamic acid 3%/*Galactomyces* ferment filtrate 2%/niacinamide 4%/alpha-arbutin 2% twice daily using a layering technique. After 4 weeks of treatment, the melasma severity score showed a significant reduction compared to baseline as well as a significant decrease of spot UV value from baseline. As a result, the authors concluded that the combination was effective in treating melasma.[46]

Crocco et al performed a study in which a cream containing nicotinamide 4%/arbutin 3%/bisabolol 1%/retinaldehyde 0.05% was used to treat 33 women with epidermal melasma. Participants applied the cream daily for 60 days, after which efficacy was assessed by the change in Melasma Area and Severity Index (MASI) score and change in melasma surface area. After the 60 days of treatment, there was a significant reduction in both MASI score and melasma surface area. Additionally, patients responded favorably to the product regarding "improvement in facial skin texture, skin oiliness, brightness, overall appearance, and hydration." The authors concluded that the cream "offers a safe and effective treatment option for treatment of epidermal melasma."[47]

Desai et al conducted a study evaluating the use of a facial serum containing tranexamic acid (TXA) 3%/kojic acid 1%/niacinamide 5% to treat mild-to-moderate melasma, postinflammatory hyperpigmentation (PIH), and hyperpigmentation in 55 women. Participants applied the serum in the morning and as needed throughout the day for 12 weeks, and then were evaluated using a modified MASI score. After the 12 weeks, participants had "significant improvement in the appearance of PIH,

hyperpigmentation, melasma, skin texture, and skin tone homogeneity," as well as a decrease in the melanin index.[48]

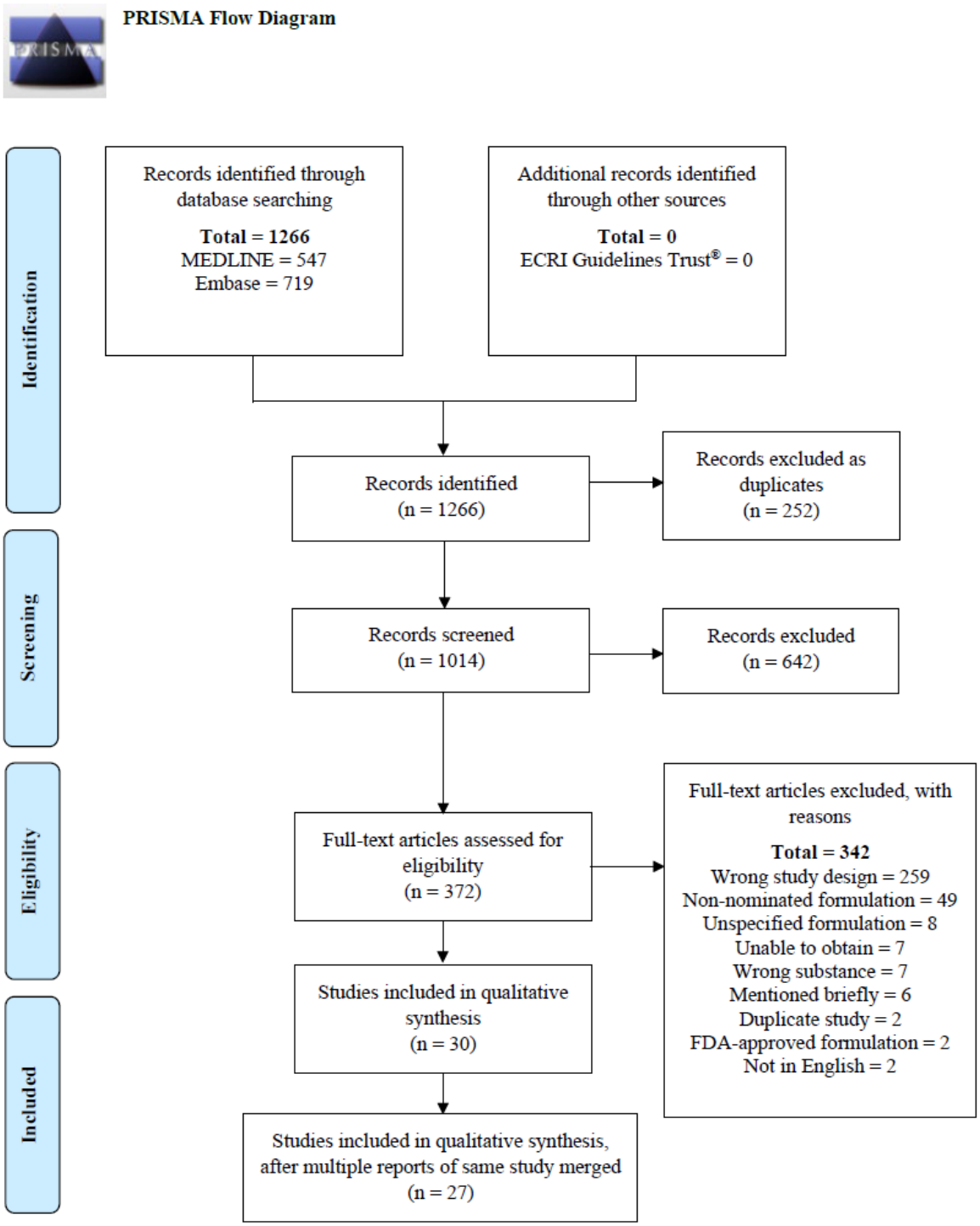
Atopic dermatitis is "a chronic, recurrent, and pruritic skin disorder usually beginning in childhood, with the typical feature of skin dryness."[49] Studies have shown that patients with atopic dermatitis have a decreased water content of the stratum corneum as well as a "defective barrier function" that may be due to "abnormalities in lipid components of the stratum corneum."[49] Soma et al evaluated the effect of a 2% topical nicotinamide cream in 28 patients with atopic dry skin lesions compared to white petrolatum. Patients applied the nicotinamide cream to their left forearm and white petrolatum to their right forearm twice daily for 8 weeks. The authors found that niacinamide significantly decreased TEWL and increased stratum corneum hydration and concluded that nicotinamide "is a more effective moisturizer than white petrolatum on atopic dry skin, and may be used as a treatment adjunct in atopic dermatitis."[49]

Acne vulgaris is a common inflammatory condition that is caused by hypercornification and excess sebum production that leads to the clogging of pores.[50] *Propionobacterium acnes (P. acnes)* is able to grow in this environment, leading to an "increase in inflammatory cytokines and free fatty acids, which then leads to further irriation."[50] Additionally, genetic, neuroendocrine, and dietary factors may also contribute to the pathogenesis.[50] The most commonly used topical treatment includes retinoids, antibiotics, and comedolytic agents; however, there are adverse effects associated with the use of retinoids and an increase in resistance to antibacterial agents leading to the identification of alternative treatments. Nicotinamide has anti-inflammatory properties as well as has shown to decrease the sebum excretion rate, provide a barrier to prevent infection, and may have a bacteriostatic effect against *P. acnes*.

Walocko et al conducted a review of studies that used topical niacinamide and concluded that due to the limited available literature, niacinamide has an unclear effect on acne vulgaris and that additional studies are needed.[50] Dos et al formulated a gel containing clindamycin phosphate 1% with nicotinamide 4% and conducted a study comparing this formulation to clindamycin phosphate 1% alone in 80 patients with moderate acne vulgaris. However, after 6 weeks of treatment there was no significant difference in response between the groups, and the authors concluded that there was no advantage to using the clindamycin and niacinamide product over clindamycin alone.[51]

Kozan et al evaluated the efficacy of 3 different gel products for the treatment of acne vulgaris. Ninety patients were randomly assigned to receive benzoyl peroxide 5% alone, benzoyl peroxide 5% and erythromycin 3%, or niacinamide 4%/gallic acid 1%/lauric acid 1% all administered twice daily for 8 weeks. At the end of treatment, all 3 groups had a statistically significant reduction in lesion counts from baseline, and there was no difference between groups. As a result, the authors concluded that the combination of niacinamide 4%/gallic acid 1%/lauric acid 1% can be used as an alternative treatment for acne vulgaris.[52] However, Liu et al conducted a systematic literature review to assess the effects of several topical treatments for acne, including niacinamide. Four studies were included; however, the authors stated that the "quality of evidence was low or very low."[53] There is a published formulation for a spironolactone-niacinamide-cimetidine gel for the treatment of acne.[54]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	**Number of Studies**
Descriptive	0
Observational	0
Experimental[8,10-35]	27

Table 4. Number of studies by country

Country	**Number of Studies**
Australia[17,18,24,29]	4
Brazil[22]	1
France[21]	1
Germany[26,28]	2
Iran[10,23,31]	3
Italy[19]	1
Japan[25,32]	2
Mexico[16]	1
Serbia[13]	1
South Africa[27]	1
Taiwan[34]	1
United States[8,11,12,14,15,20,30]	7
Multiple Countries • Japan, United States[33,35]	2
	Total US[a]: 9 Total Non-US Countries[a]: 20

[a]Studies 33 and 35 counted in both US and non-US total.

Table 5. Summary of included studies

Refer to Appendix 2

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Hyperpigmentation[8,14,33]	0.9 g/day	4-5%	Cream, moisturizer	Topical	8-9 weeks
Acne[20]	Twice daily	4%	Gel	Topical	8 weeks
Anti-aging[11]	0.8 g/day	5%	Moisturizer	Topical	12 weeks
Erythema[12]	–	5%	Emulsion	Topical	2 weeks
Facial sebum control[35]	Twice daily	2%	Gel	Topical	6 weeks
Male skin health[15]	–	5%	Moisturizer	Topical	3 weeks
Psoriasis[30]	Twice daily	0.05-1.4%	Ointment	Topical	12 weeks

Abbreviation: –, not provided.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Anti-aging[25-27,34]	Twice daily 2 mg/cm² of skin, twice daily 0.8 mL/day	3-4%	Cream, lotion	Topical	4-12 weeks
Acne[10,21-23]	Twice daily	4-5%	Cream, gel	Topical	8 weeks
Prevention of photodynamic therapy or UV radiation-induced immunosuppression[17,18,29]	Once daily	5%	Cream	Topical	3 days
	2 μL/cm² or 2 mcg/cm² of skin, once daily	0.2-5%	Lotion	Topical	1-3 days
Actinic keratosis[24]	1.6 mL/day to each area (face; forearms; and scalp, if bald)	1%	Gel	Topical	6 months
Androgenetic alopecia[32]	6 mL/day	0.1%	Lotion	Topical	6 months
Facial sebum control[35]	Twice daily	2%	Gel	Topical	4 weeks
Hyperpigmentation[33]	0.6 mL/day	5%	Moisturizer	Topical	8 weeks
Melasma[16]	–	4%	Cream	Topical	8 weeks
Prevention of chemotherapy-induced cutaneous symptoms[28]	Twice daily	4%	Cream	Topical	6 weeks
Psoriasis[31]	Twice daily	4%	–	Topical	12 weeks
Seborrheic dermatitis[19]	Once daily	4%	Cream	Topical	12 weeks
Irritated skin[13]	Four times daily	–	Gel	Topical	4 weeks

Abbreviation: –, not provided; UV, ultraviolet.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Niacinamide 4% / Adapalene 0.1-0.3%	0
	Niacinamide 4% / Benzoyl peroxide 8%	0
	Niacinamide 4% / Betamethasone dipropionate 0.05%	0
	Niacinamide 0.05-4% / Calcipotriene 0.005% – topical ointment[30,31]	2
	Niacinamide 4% / Clindamycin 1%	0
	Niacinamide 4% / Clobetasol propionate 0.05%	0
	Niacinamide 4% / Dapsone 6-8.5%	0
	Niacinamide 4% / Desoximetasone 0.25%	0
	Niacinamide 4% / Econazole nitrate 1%	0
	Niacinamide 4% / Fluocinolone acetonide 0.01-0.025%	0
	Niacinamide 4% / Fluocinonide 0.05%	0
	Niacinamide 4% / Fluticasone propionate 0.05%	0
	Niacinamide 4% / Gentamicin 0.1%	0
	Niacinamide 4% / Ketoconazole 2%	0
	Niacinamide 4% / Metronidazole 1%	0
	Niacinamide 4% / Minoxidil 7%	0
	Niacinamide 4% / Sodium sulfacetamide 10-15%	0

	Niacinamide 4% / Spironolactone 5%	0
	Niacinamide 4% / Tacrolimus 0.03-0.1%	0
	Niacinamide 4% / Tazarotene 0.05-0.1%	0
	Niacinamide 4% / Tretinoin 0.025-0.1%	0
	Niacinamide 4% / Triamcinolone acetonide 0.1%	0
	Niacinamide 4% / Adapalene 0.1-0.3% / Benzoyl peroxide 2.5%	0
	Niacinamide 4% / Aloe vera 1% / Urea 40%	0
	Niacinamide 2% / Benzoyl peroxide 2.5-5% / Clindamycin 1%	0
	Niacinamide 2% / Benzoyl peroxide 5% / Tretinoin 0.025%	0
	Niacinamide 4% / Clindamycin 1% / Hydrocortisone 2.5%	0
	Niacinamide 2% / Clindamycin 1% / Spironolactone 2%	0
	Niacinamide 2% / Clindamycin 1% / Tazarotene 0.05%	0
	Niacinamide 4% / Clindamycin 1% / Tretinoin 0.025-0.05%	0
	Niacinamide 4% / Clobetasol propionate 0.05% / Hyaluronic acid sodium salt 1%	0
	Niacinamide 4% / Clobetasol propionate 0.05% / Zinc pyrithione 0.2%	0
	Niacinamide 2% / Dapsone 6-8.5% / Spironolactone 5%	0
	Niacinamide 2% / Dapsone 6-8.5% / Tretinoin 0.025%	0
	Niacinamide 4% / Desoximetasone 0.05% / Zinc pyrithione 1%	0
	Niacinamide 4% / Diclofenac sodium 3% / Hyaluronic acid sodium salt 2%	0

	Niacinamide 4% / Fluocinonide 0.05% / Hyaluronic acid sodium salt 0.5%	0
	Niacinamide 4% / Hyaluronic acid sodium salt 2% / Mometasone furoate 0.1%	0
	Niacinamide 4% / Hyaluronic acid sodium salt 0.5% / Mupirocin 2%	0
	Niacinamide 4% / Hyaluronic acid sodium salt 1% / Tacrolimus 0.1%	0
	Niacinamide 4% / Hyaluronic acid sodium salt 0.5% / Tretinoin 0.0125-0.1%	0
	Niacinamide 4% / Hyaluronic acid sodium salt 1% / Triamcinolone acetonide 0.1%	0
	Niacinamide 2% / Imiquimod 5% / Levocetirizine dihydrochloride 1%	0
	Niacinamide 4% / Imiquimod 5% / Tea tree oil 2%	0
	Niacinamide 2% / Spironolactone 5% / Tretinoin 0.025-0.05%	0
	Niacinamide 4% / Tacrolimus 0.03-0.1% / Zinc oxide 5%	0
	Niacinamide 4% / Tranilast 1% / Triamcinolone acetonide 0.1%	0
	Niacinamide 4% / Arbutin 3% / Bisabolol 1% / Tretinoin 0.05%	0
	Niacinamide 4% / Ascorbyl palmitate 2% / Hyaluronic acid 0.5% / Tretinoin 0.1%	0
	Niacinamide 2% / Benzoyl peroxide 5% / Clindamycin 1% / Spironolactone 2%	0
	Niacinamide 2% / Benzoyl peroxide 2.5-5% / Clindamycin 1% / Tretinoin 0.025-0.1%	0
	Niacinamide 2% / Betamethasone dipropionate 0.05% / Minoxidil 5% / Pentoxifylline 0.5%	0
	Niacinamide 2% / Calcipotriene 0.005% / Diclofenac sodium 3% / Hyaluronic acid sodium salt 2%	0
	Niacinamide 2% / Calcipotriene 0.005% / Hyaluronic acid sodium salt 2% / Imiquimod 2.5%	0
	Niacinamide 4% / Clindamycin 1% / Spironolactone 2% / Tretinoin 0.025%	0

	Niacinamide 4% / Ascorbyl palmitate 1% / Kojic acid 4% / Lactic acid 10% / Potassium azeloyl diglycinate 10%	0
	Niacinamide 2-4% / Benzoyl peroxide 2.5-5% / Clindamycin 1% / Spironolactone 2% / Tretinoin 0.025-0.05%	0
	Niacinamide 2% / Clindamycin 1% / Hydrocortisone 0.5% / Spironolactone 2% / Tretinoin 0.025%	0
	Niacinamide 2% / Clindamycin 1% / Salicylic acid 2% / Sodium sulfacetamide 5% / Tretinoin 0.05%	0
	Niacinamide 2% / Hydroquinone 4% / Kojic acid 6% / Soya protein 1% / Tretinoin 0.025%	0
	Niacinamide 2% / Ascorbyl palmitate 2% / Betamethasone dipropionate 0.05% / Hyaluronic acid sodium salt 0.2% / Hydroquinone 8% / Kojic acid 6% / Potassium azeloyl diglycinate 8%	0

Table 9. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Hyperpigmentation[8]	2013	"Niacinamide cream was formulated by combining niacinamide powder with Cetaphil® moisturizing cream."	Cream	4%

Table 10. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Actinic keratosis[24]	"Nicotinamide powder was added to 1 mL compound hydroxybenzoate, 0.6 g Carbomer 940, and 0.6 mL trolamine (PCCA), to 100 mL in water."	Gel	1%
Prevention of photodynamic therapy or UV-induced immunosuppression [18,29]	"Nicotinamide was prepared in 1:2:1 propylene glycol, ethanol, and distilled water vehicle at a concentration of 5%."	Cream	5%
	"Vehicle lotion contained 1 part propylene glycol, 2 parts ethanol, and 1 part distilled water. Nicotinamide lotion was prepared using nicotinamide power dissolved in the base lotion."	Lotion	5%

Results of interviews

One hundred ninety-nine SMEs were contacted for interviews; 63 agreed to be interviewed, and 136 declined or failed to respond to the interview request. One SME discussed niacinamide. The SME was a medical doctor who specialized and/or was board-certified in dermatology, working in an academic medical institution. The SME had been in practice for 1 year. Additional information was collected as part of the Expanded Information Initiative project, referred to as Phase 3, in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

Niacinamide is "essentially a vitamin" that is likely providing some skin conditioning benefits, as well as acting as "a general anti-inflammatory" agent. The SME stated that "it has a very unclear effect" and was unsure of the effectiveness stating, "I don't think that there's going to be a great efficacy" and that "the delta, when you add it, is probably small." The SME mentioned, "I don't know that it actually does a whole lot… in the sense of, we think of drugs as active molecules that are hitting a target and really making a big change in the disease pathogenesis" and that it is probably providing more of a cosmetic effect. However, the SME commented, "I don't think that there's any harm to it necessarily, it's a pretty benign thing to put on topically." Niacinamide will not cause the same flushing reaction that is associated with niacin, and "it's available in a lot of cosmetic over-the-counter products, so it's pretty safe."

The SME referenced a randomized, controlled trial conducted in Australia that found that oral niacinamide reduces nonmelanoma skin cancer. There may be a benefit in administering it to patients who "are prone to developing squamous or basal cell carcinoma" but the SME was not aware of what the mechanism or effectiveness would be when applied topically.

As part of Phase 3, 1 nominator provided additional information regarding the multi-ingredient products contained within the niacinamide nomination.

Niacinamide 4% / adapalene 0.1% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: methylparaben, propylene glycol, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants, and their hazardous concerns include classified as expected to be toxic or harmful; classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen; or human skin toxicant or allergen. Niacinamide is added for its skin-conditioning benefits and adapalene for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / adapalene 0.3% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: methylparaben, propylene glycol, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants and their hazardous concerns include classified as expected to be toxic or harmful,; classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen; or human skin toxicant or allergen. Niacinamide is added for its skin-conditioning benefits and adapalene for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this

combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / urea 40% / aloe vera 1% will be compounded as a topical cream to treat eczema applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. Niacinamide is added for its skin-conditioning benefits and urea for its moisturizing properties. The reason for including aloe vera in this product was not provided. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / tretinoin 0.05% / arubtin 3% / bisabolol 1% will be compounded as a topical cream to treat melasma applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, methylparaben, propylene glycol, and titanium dioxide, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful; classified as skin irritant, endocrine disruptor, human immune and respiratory toxicant or allergen, human respiratory irritant; human skin toxicant or allergen; or possible human carcinogen. Niacinamide is added for its skin-conditioning benefits and tretinoin for its anti-inflammatory properties. The reasons for including arubtin and bisabolol in this product were not provided. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / lactic acid 10% / kojic acid 4% will be compounded as a topical cream to treat melasma applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. Niacinamide is added for its skin-conditioning benefits and lactic acid for its keratolytic properties. The reason for including kojic acid in this product was not provided. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / betamethasone dipropionate 0.05% / minoxidil 5% / pentoxifylline 0.5% will be compounded as a topical solution to treat alopecia applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: chlorocresol, propylparaben, sodium hydroxide, and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, human endocrine disruptor, human irritant, human skin toxicant or allergen, restricted in cosmetics (recommendations or requirements) - use, concentration, or manufacturing restrictions, violation of industry recommendations - Restricted in cosmetics; use, concentration, or manufacturing restrictions - not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits; betamethasone dipropionate for its anti-inflammatory properties; minoxidil for its capability to promote hair growth; and pentoxifylline to promote circulation. This product is needed because it will result in a clinical difference to patients as it

does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / betamethasone dipropionate 0.05% will be compounded as a topical cream to treat dermatitis applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: chlorocresol, propylene glycol, sodium hydroxide, and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human irritant, human skin toxicant or allergen, Restricted in cosmetics (recommendations or requirements) - use, concentration, or manufacturing restrictions, violation of industry recommendations - restricted in cosmetics; use, concentration, or manufacturing restrictions - not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits and betamethasone dipropionate for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / calcipotriene 0.005% will be compounded as a topical cream to treat psoriasis applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, petrolatum, propylene glycol, and sodium hydroxide, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, contamination concerns, human immune and respiratory toxicant or allergen, human endocrine disruptor, human irritant, human respiratory irritant, human, skin toxicant or allergen, possible human carcinogen, restricted in cosmetics (recommendations or requirements) - use, concentration, or manufacturer restrictions, violation of industry recommendations - restricted in cosmetics; use, concentration, or manufacturing restrictions - not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits, and calcipotriene for its anti-inflammatory and skin-softening properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / hydrocortisone 0.5% / spironolactone 2% / tretinoin 0.025% / clindamycin 1% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: benzalkonium chloride, butylated hydroxytoluene, butylparaben, butylene glycol, ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, potassium hydroxide, propylene glycol, titanium dioxide, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, human endocrine disruptor, human immune and respiratory toxicant or allergen, human respiratory irritant, human skin toxicant or allergen possible human carcinogen, violation of industry recommendations - restricted in cosmetics; use, concentration, or manufacturing restrictions - not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits, spironolactone for its antiandrogen properties, tretinoin for its anti-

inflammatory properties, and clindamycin for its antibacterial properties. The reason for including hydrocortisone in this product was not provided. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / salicylic acid 2% / sulfacetamide sodium monohydrate 5% / tretinoin 0.05% / clindamycin 1% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, potassium hydroxide, propylene glycol, and titanium dioxide, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, violation of industry recommendations - restricted in cosmetics; use, concentration, or manufacturing restrictions - not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits, salicylic acid for its keratolytic properties, sodium sulfacetamide for its antibacterial properties, tretinoin for its anti-inflammatory properties, and clindamycin for its anti-bacterial properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / spironolactone 2% / clindamycin 1% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, potassium hydroxide, and propylene glycol, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, violation of industry recommendations - restricted in cosmetics; use, concentration, or manufacturing restrictions - not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits, spironolactone for its antiandrogen properties, and clindamycin for its antibacterial properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / clobetasol propionate 0.05% will be compounded as a topical solution to treat dermatitis applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, cetearyl alcohol, chlorocresol, methylparaben, mineral oil, propylene glycol, sodium hydroxide, sodium laureth sulfate, and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include: allergen, classified as expected to be toxic or harmful, classified as skin irritant, contamination concerns, human immune and respiratory toxicant or allergen, human irritant, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen, restricted in cosmetics (recommendations or requirements) - use, concentration, or manufacturing restrictions, violation of industry recommendations -

restricted in cosmetics; use, concentration, or manufacturing restrictions - not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits and clobetasol propionate for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / dapsone 6% / spironolactone 5% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredient: methylparaben, which is a component of the commercially available products. These inactive ingredients are known to be harmful allergen or irritant; its hazardous concerns include human endocrine disruptor, human immune and respiratory toxicant, or allergen. Niacinamide is added for its skin-conditioning benefits, dapsone for its antibacterial properties and anti-inflammatory properties, and spironolactone for its antiandrogen properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / dapsone 6% / tretinoin 0.025% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylparaben, methylparaben, mineral oil, titanium dioxide, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, human skin toxicant or allergen, possible human carcinogen. Niacinamide is added for its skin-conditioning benefits, dapsone for its antibacterial properties, and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA -approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / dapsone 6% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredient: methylparaben, which is component of the commercially available products. These inactive ingredients are known to be harmful allergen or irritant; its hazardous concerns include human endocrine disruptor, human immune and respiratory toxicant, or allergen. Niacinamide is added for its skin-conditioning benefits; dapsone for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / dapsone 8.5% / spironolactone 5% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredient: methylparaben, which is component of the commercially available products. These inactive ingredients are known to be a harmful allergen or

irritant; its hazardous concerns include human endocrine disruptor, human immune and respiratory toxicant, or allergen. Niacinamide is added for its skin-conditioning, dapsone for its anti-inflammatory properties, and spironolactone for its antiandrogen properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / dapsone 8.5% / tretinoin 0.025% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylparaben, methylparaben, mineral oil, titanium dioxide, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, human skin toxicant or allergen, possible human carcinogen. Niacinamide is added for its skin-conditioning benefits, dapsone for its anti-inflammatory properties, and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / dapsone 8.5% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredient: methylparaben, which is component of the commercially available products. These inactive ingredients are known to be harmful allergen or irritant; its hazardous concerns include human endocrine disruptor, human immune and respiratory toxicant, or allergen. Niacinamide is added for its skin-conditioning benefits and dapsone for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / desoximetasone 0.05% will be compounded as a topical cream to treat dermatitis applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredient: petrolatum, which is component of the commercially available products. These inactive ingredients are known to be a harmful allergen or irritant; its hazardous concerns include classified as expected to be toxic or harmful, and restricted in cosmetics (recommendations or requirements) – use concentration or manufacturing restrictions. Niacinamide is added for its skin-conditioning benefits and desoximetasone for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / desoximetasone 0.25% will be compounded as a topical solution to treat dermatitis applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredient: petrolatum, which is component of the commercially available products. These inactive ingredients are known to be a harmful allergen or

irritant; its hazardous concerns include classified as expected to be toxic or harmful, and restricted in cosmetics (recommendations or requirements) - use concentration or manufacturing restrictions. Niacinamide is added for its skin-conditioning benefits and desoximetasone for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / econazole nitrate 1% will be compounded as a topical cream to treat antifungal applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butane, propylene glycol, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, human immune and respiratory toxicant or allergen, human irritant, human respiratory irritant, human skin toxicant or allergen, human toxicant or allergen, restricted in cosmetics (recommendations or requirements) - use, concentration, or manufacturing restrictions. Niacinamide is added for its skin-conditioning benefits and econazole nitrate for its anti-fungal properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / fluocinolone acetonide 0.01% will be compounded as a topical cream to treat dermatitis applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, benzalkonium chloride, boric acid, methylparaben, propylene glycol, sodium laureth sulfate, talc, trolamine, white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, contamination concerns, human endocrine disruptor, human immune and respiratory toxicant or allergen, human irritant, human respiratory irritant, human skin toxicant or allergen, human toxicant or allergen, restricted in cosmetics (recommendations or requirements) - use, concentration, or manufacturing restrictions, violation of industry recommendations - restricted in cosmetics; use, concentration, or manufacturing restrictions - not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits and fluocinolone acetonide for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / fluocinolone acetonide 0.025% will be compounded as a topical ointment to treat dermatitis applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, benzalkonium chloride, boric acid, methylparaben, propylene glycol, sodium laureth sulfate, talc, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, contamination concerns, human endocrine disruptor, human immune and respiratory toxicant or allergen, human irritant, human respiratory irritant,

human skin toxicant or allergen, human toxicant or allergen, restricted in cosmetics (recommendations or requirements) - use, concentration, or manufacturing restrictions, violation of industry recommendations - restricted in cosmetics; use, concentration, or manufacturing restrictions - not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits and fluocinolone acetonide for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / fluocinonide 0.05% will be compounded as a topical ointment to treat dermatitis applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, benzalkonium chloride, boric acid, methylparaben, propylene glycol, sodium laureth sulfate, talc, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include: allergen, classified as expected to be toxic or harmful, classified as skin irritant, contamination concerns, human endocrine disruptor, human immune and respiratory toxicant or allergen, human irritant, human respiratory irritant, human skin toxicant or allergen, human toxicant or allergen, restricted in cosmetics (recommendations or requirements) - use, concentration, or manufacturing restrictions, violation of industry recommendations - restricted in cosmetics; use, concentration, or manufacturing restrictions - not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits and fluocinolone acetonide for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / fluticasone propionate 0.05% will be compounded as a topical cream to treat dermatitis applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: methylparaben, propylene glycol, and benzalkonium chloride, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include: classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen. Niacinamide is added for its skin-conditioning benefits and fluticasone propionate for its anti-itching properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / gentamicin 0.1% will be compounded as a topical gel to treat antibacterial applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredient: methylparaben, which is component of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen. Niacinamide is added for its skin-conditioning benefits and gentamicin for its antibacterial properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients

found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / hydroquinone 4% / tretinoin 0.025% will be compounded as a topical cream to treat melasma applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, ethanol, propylene glycol, and titanium dioxide, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, human immune and respiratory toxicant or allergen, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen. Niacinamide is added for its skin-conditioning benefits, hydroquinone for its skin-lightening properties, and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug product, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / imiquimod 5% / levocetirizine dihydrochloride 1% will be compounded as a topical gel to treat actinic keratosis applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient -specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: methylparaben and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, human endocrine disruptor, human immune and respiratory toxicant or allergen, restricted in cosmetics (recommendations or requirements) - use, concentration, or manufacturing restrictions. Niacinamide is added for its skin-conditioning benefits, imiquimod for its immune response modifying effects, and levocetirizine dihydrochloride for its anti-itching properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products. and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / imiquimod 5% will be compounded as a topical gel to treat actinic keratosis applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: methylparaben and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, human endocrine disruptor, human immune and respiratory toxicant or allergen, restricted in cosmetics (recommendations or requirements) - use, concentration, or manufacturing restrictions. Niacinamide is added for its skin-conditioning benefits and imiquimod for its immune response modifying effects. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / ketoconazole 2% will be compounded as a topical gel to treat dermatitis applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, ethanol, propylene glycol, sodium hydroxide, and sodium laureth sulfate, which are components of the commercially

available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, contamination concerns, human irritant, human respiratory irritant, violation of industry recommendations - Restricted in cosmetics; use, concentration, or manufacturing restrictions - Not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits and ketoconazole for its anti-fungal properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / metronidazole 1% will be compounded as a topical gel to treat rosacea applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: oleyl alcohol, methylparaben, mineral oil, and polyethylene glycol, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, found to cause seizures and severe neurological symptoms, possible human carcinogen, violation of industry recommendations - restricted in cosmetics; use, concentration, or manufacturing restrictions- not safe for use on injured or damaged skin, human immune and respiratory toxicant or allergen, human endocrine disruptor, classified as skin irritant. Niacinamide is added for its skin-conditioning benefits and metronidazole for its antibacterial properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / minoxidil 7% will be compounded as a topical solution to treat alopecia applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. Niacinamide is added for its skin conditioning benefits and minoxidil for its capability to promote hair growth. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / spironolactone 5% / tretinoin 0.025% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, methylparaben, mineral oil, titanium dioxide, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, human endocrine disruptor, human immune and respiratory toxicant or allergen, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen. Niacinamide is added for its skin-conditioning benefits; spironolactone for its antiandrogen properties; and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / spironolactone 5% / tretinoin 0.05% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a

non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, methylparaben, mineral oil, titanium dioxide, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, human endocrine disruptor, human immune and respiratory toxicant or allergen, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen. Niacinamide is added for its skin-conditioning benefits, spironolactone for its antiandrogen properties, and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / clobetasol propionate 0.05% / zinc pyrithione 0.2% will be compounded as a topical solution to treat dermatitis applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, cetearyl alcohol, chlorocresol, methylparaben, mineral oil, propylene glycol, sodium hydroxide, and sodium laureth sulfate, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, Contamination concerns, human immune and respiratory toxicant or allergen, human irritant, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen. Niacinamide is added for its skin-conditioning benefits and clobetasol propionate for its anti-inflammatory properties. The reason for including zinc pyrithione in this product was not provided. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / sulfacetamide sodium monohydrate 10% will be compounded as a topical lotion to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: methylparaben and propylene glycol, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include human immune and respiratory toxicant or allergen, human endocrine disruptor, classified as expected to be toxic or harmful, classified as skin irritant. Niacinamide is added for its skin-conditioning benefits and sodium sulfacetamide for its antibacterial properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / sulfacetamide sodium monohydrate 15% will be compounded as a topical lotion to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: methylparaben and propylene glycol, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include human immune and respiratory toxicant or allergen, human endocrine disruptor, classified as expected to be toxic or harmful, classified as skin irritant. Niacinamide is added for its skin-conditioning benefits and sodium

sulfacetamide for its antibacterial properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / spironolactone 5% will be compounded as a topical lotion to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. Niacinamide is added for its skin-conditioning benefits and spironolactone for its antiandrogen properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / tacrolimus 0.03% will be compounded as a topical ointment to treat eczema applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredient: mineral oil, which is component of the commercially available products. These inactive ingredients are known to be harmful allergen or irritant; its hazardous concerns include possible human carcinogen. Niacinamide is added for its skin conditioning benefits and tacrolimus for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / tacrolimus 0.1% will be compounded as a topical ointment to treat eczema applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredient: mineral oil, which is component of the commercially available products. These inactive ingredients are known to be a harmful allergen or irritant; its hazardous concerns include possible human carcinogen. Niacinamide is added for its skin-conditioning benefits and tacrolimus for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / tazarotene 0.05% will be compounded as a topical ointment to treat eczema applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, hexylene glycol, and sodium hydroxide, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as irritant, human respiratory irritant, violation of industry recommendations - restricted in cosmetics; use, concentration, or manufacturing restrictions - Not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits and tazarotene for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / tazarotene 0.1% will be compounded as a topical ointment to treat eczema applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, hexylene glycol, and mineral oil, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as irritant, human respiratory irritant, possible human carcinogen. Niacinamide is added for its skin-conditioning benefits and tazarotene for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / tranilast 1% / triamcinolone acetonide 0.1% will be compounded as a topical cream to treat dermatitis applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: ethanol, isopropyl palmitate, silicon dioxide, lactic acid, laureth-7, methylparaben, propylene glycol, trolamine, and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, classified as skin irritant, contamination concerns, human endocrine disruptor, human immune and respiratory toxicant or allergen, human skin toxicant or allergen, persistent or bioaccumulative, restricted in cosmetics (recommendations or requirements) - use, concentration, or manufacturing restrictions. Niacinamide is added for its skin-conditioning benefits, tranilast for its anti-inflammatory properties, and triamcinolone acetonide for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / tretinoin 0.025% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, methylparaben, mineral oil, propylene glycol, and titanium dioxide, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen. Niacinamide is added for its skin-conditioning benefits and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / tretinoin 0.05% will be compounded as a topical cream to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, methylparaben, propylene glycol, and titanium dioxide, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their

hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, endocrine disruptor, human immune and respiratory toxicant or allergen, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen. Niacinamide is added for its skin-conditioning benefits and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / tretinoin 0.1% will be compounded as a topical cream to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, methylparaben, propylene glycol, and titanium dioxide, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, human immune and respiratory toxicant or allergen, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen. Niacinamide is added for its skin-conditioning benefits and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / triamcinolone acetonide 0.1% will be compounded as a topical cream to treat dermatitis applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: ethanol, silicon dioxide, butylene glycol, lactic acid, laureth-7, methylparaben, propylene glycol, trolamine, and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, classified as skin irritant, contamination concerns, human endocrine disruptor, human immune and respiratory toxicant or allergen, human irritant, human skin toxicant or allergen, persistent or bio accumulative, restricted in cosmetics (recommendations or requirements) - use, concentration, or manufacturing restrictions. The reasons for including niacinamide and triamcinolone acetonide in this product were not provided. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 5% / tretinoin 0.025% will be compounded as a topical cream to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, methylparaben, propylene glycol, and titanium dioxide, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, human respiratory irritant, human skin toxicant or allergen, and possible human carcinogen. Niacinamide is added for its skin-conditioning benefits and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients

found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / adapalene 0.3% / benzoyl peroxide 2.5% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: methylparaben, propylene glycol, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, human skin toxicant or allergen. Niacinamide is added for its skin conditioning benefits, adapalene for its anti-inflammatory properties, and benzoyl peroxide for its ability to remove oil from skin. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / benzoyl peroxide 2.5% / clindamycin 1% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, potassium hydroxide, and propylene glycol, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, violation of industry recommendations - Restricted in cosmetics; use, concentration, or manufacturing restrictions - Not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits, benzoyl peroxide for its ability to remove oil from the skin, and clindamycin for its antibacterial properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / benzoyl peroxide 5% / clindamycin 1% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, potassium hydroxide, and propylene glycol, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, violation of industry recommendations - Restricted in cosmetics; use, concentration, or manufacturing restrictions - Not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits, benzoyl peroxide for its ability to remove oil from the skin, and clindamycin for its antibacterial properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / benzoyl peroxide 2.5% / tretinoin 0.05% / clindamycin 1% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices.

This product will be compounded without the following inactive ingredients: butylparaben, ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, mineral oil, potassium hydroxide, propylene glycol, titanium dioxide, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, human skin toxicant or allergen, possible human carcinogen, violation of industry recommendations - Restricted in cosmetics; use, concentration, or manufacturing restrictions - Not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits, benzoyl peroxide for its ability to remove oil from skin, tretinoin for its anti-inflammatory properties, and clindamycin for its antibacterial properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / benzoyl peroxide 2.5% / tretinoin 0.025% / clindamycin 1% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylparaben, ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, mineral oil, potassium hydroxide, propylene glycol, titanium dioxide, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, human skin toxicant or allergen, possible human carcinogen, violation of industry recommendations - Restricted in cosmetics; use, concentration, or manufacturing restrictions - Not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits, benzoyl peroxide for its ability to remove oil from the skin, tretinoin for its anti-inflammatory properties, and clindamycin for its antibacterial properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / benzoyl peroxide 5% / tretinoin 0.025% / clindamycin 1% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylparaben, ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, mineral oil, potassium hydroxide, propylene glycol, titanium dioxide, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, human skin toxicant or allergen, possible human carcinogen, violation of industry recommendations - Restricted in cosmetics; use, concentration, or manufacturing restrictions - Not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits, benzoyl peroxide for its ability to remove oil from the skin, tretinoin for its anti-inflammatory properties, and clindamycin for its antibacterial properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / benzoyl peroxide 5% / tretinoin 0.05% / clindamycin 1% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylparaben, ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, mineral oil, potassium hydroxide, propylene glycol, titanium dioxide, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, human skin toxicant or allergen, possible human carcinogen, violation of industry recommendations - Restricted in cosmetics; use, concentration, or manufacturing restrictions - Not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits, benzoyl peroxide for its ability to remove oil from the skin, tretinoin for its anti-inflammatory properties, and clindamycin for its antibacterial properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / benzoyl peroxide 5% / tretinoin 0.1% / clindamycin 1% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylparaben, ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, mineral oil, potassium hydroxide, propylene glycol, titanium dioxide, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, human skin toxicant or allergen, possible human carcinogen, violation of industry recommendations - Restricted in cosmetics; use, concentration, or manufacturing restrictions - Not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits, benzoyl peroxide for its ability to remove oil from the skin, tretinoin for its anti-inflammatory properties, and clindamycin for its antibacterial properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / benzoyl peroxide 5% / spironolactone 2% / tretinoin 0.025% / clindamycin 1% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylparaben, ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, mineral oil, potassium hydroxide, propylene glycol, titanium dioxide, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, human skin toxicant or allergen, possible human carcinogen, violation of industry recommendations - Restricted in cosmetics; use, concentration, or manufacturing restrictions - Not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits, benzoyl peroxide for its ability to remove oil from the skin, spironolactone for its antiandrogen properties, tretinoin for its anti-inflammatory properties, and clindamycin for its antibacterial properties. This product is needed because

it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 2% / benzoyl peroxide 5% / spironolactone 2% / tretinoin 0.05% / clindamycin 1% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylparaben, ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, mineral oil, potassium hydroxide, propylene glycol, titanium dioxide, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, human skin toxicant or allergen, possible human carcinogen, violation of industry recommendations - Restricted in cosmetics; use, concentration, or manufacturing restrictions - Not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits, benzoyl peroxide for its ability to remove oil from the skin, spironolactone for its antiandrogen properties, tretinoin for its anti-inflammatory properties, and clindamycin for its ant-bacterial properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / clindamycin phosphate 1% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, potassium hydroxide, and propylene glycol, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, violation of industry recommendations - Restricted in cosmetics; use, concentration, or manufacturing restrictions - Not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits and clindamycin phosphate for its antibacterial properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / clindamycin phosphate 1% / tretinoin 0.025% will be compounded as a topical cream solution to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, dioctyl sodium sulfosuccinate, methylparaben, potassium hydroxide, propylene glycol, sodium hydroxide, titanium dioxide, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen, violation of industry recommendations - Restricted in cosmetics; use, concentration, or manufacturing restrictions - Not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits, clindamycin

phosphate for its antibacterial properties, and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / clindamycin phosphate 1% / tretinoin 0.05% will be compounded as a topical cream to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, dioctyl sodium sulfosuccinate, methylparaben, potassium hydroxide, propylene glycol, sodium hydroxide, and titanium dioxide, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen, violation of industry recommendations - Restricted in cosmetics; use, concentration, or manufacturing restrictions - Not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits, clindamycin phosphate for its antibacterial properties, and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Niacinamide 4% / clindamycin phosphate 1% / spironolactone 2% / tretinoin 0.025% will be compounded as a topical gel to treat acne applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, cetearyl alcohol, dioctyl sodium sulfosuccinate, methylparaben, mineral oil, potassium hydroxide, titanium dioxide, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, human endocrine disruptor, human immune and respiratory toxicant or allergen, human respiratory irritant, human skin toxicant or allergen possible human carcinogen, violation of industry recommendations - Restricted in cosmetics; use, concentration, or manufacturing restrictions - Not safe for use on injured or damaged skin. Niacinamide is added for its skin-conditioning benefits, clindamycin phosphate for its antibacterial properties, spironolactone for its antiandrogen properties, and tretinoin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

A roundtable discussion with representatives from a variety of practice settings was held to discuss the use of outsourcing facilities to obtain compounded products. Forty-three participants attended the event (refer to Table 15 for characteristics of the facilities that the participants represented). A prequestionnaire was also distributed to participants (refer to Tables 15-18 for results of the prequestionnaire).

While a majority of the participants purchased some compounded products from an outsourcing facility, the percentage of products obtained varied from less than 1% to the majority of compounded products used at 1 participant's facility. A participant stated, "We have this method that we use where if we can buy it commercially ready to administer, we do that. If we can't buy it in that format, then we buy it in a

vial, for example, that can be snapped into a Mini-Bag Plus, because we're a Baxter house, as a second preference. If we can't buy it in either of those two formats and we can get it from a 503B, then we do that. And our last resort is compounding internally." Two participants commented that they will not outsource a product unless 2 outsourcing facilities that they contract with are able to compound the product. This redundancy will allow for a quick flip to the other outsourcing facility if there is an issue with a product compounded from 1 outsourcing facility, minimizing the impact to the participant's facility.

Participants were asked to discuss the decision-making process used at their facility to determine what products to obtain from an outsourcing facility. One major theme that emerged from this discussion was that many of the products purchased from outsourcing facilities are used in critical care areas, such as emergency departments (EDs) and operating rooms (ORs). Participants commented that outsourcing facilities are able to provide ready-to-use products that have longer beyond-use dates compared to products compounded in-house, allowing these products to be stocked in automated dispensing cabinets (ADCs) in these units. One participant commented that "we're always going to outsource a PCA [patient-controlled analgesia] syringe because we can store it in a Pyxis machine versus us making it and storing it in a fridge." Another participant commented on the benefits of storing medications in an ADC, stating that "operationally, if you have a stat medication or something that needs to be delivered within 10 to 15 minutes, if you're looking at us doing it, you're looking at a 5-minute gown and glove. If we don't have somebody in the IV [intravenous] room, if you're doing <797> right, it's 5 minutes. It's 4 minutes to tube it. It's 3 minutes to make it, and then you have a dosage system or a camera system, a few minutes more. We are not able to meet that need or they're just contaminating the IV room if they are trying to do it."

Having ready-to-use products available also minimizes the need for compounding and product manipulations to occur on the floor. This can be especially beneficial in children's hospitals as they face a unique need in that they are already having to perform a lot of manipulations to products due to a lack of concentrations or sizes available. One participant commented that "at baseline, already, we manipulate about 80% of what we dispense to patients" and another stated that "there's a number of drugs that require additional manipulation to get them to a concentration that's appropriate for kids." One participant stated that "we're trying to minimize compounding, expedite actual therapies to patients in that setting [OR], minimize manipulations as much as possible." Similarly, in the ED, 1 participant stated they prefer ready-to-use products for some floor-stock items, like vasopressor infusions, to prevent compounding from occurring on the floor. Another commented that "we absolutely buy as many pressor drips as we can." One participant remarked that they have received requests from anesthesiologists for products that are commercially available in vials that require manipulation prior to administration to be purchased as syringes from outsourcing facilities, stating that "they would prefer to have a syringe form."

Another theme regarding regarding the decision of what products to purchase from an outsourcing facility was focused on the use and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, such as the ED and OR, typically have a high-product utilization and overall turnover, leading to several participants obtaining products intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency with which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant commented that "we look at the impact that it'll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the patient demand, then those are the items that we're going to look to potentially move out." Another participant stated that, while they do not obtain a lot of products from outsourcing facilities, "when we do purchase from 503Bs, typically it would be if we just don't have the capacity to keep up with what the demand is." One participant also commented that they will obtain labor-intensive and more complicated products, such as

epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The COVID-19 pandemic has also impacted the operations of hospitals, as noted by 1 participant who stated that "it's just really high volume, and the bigger the hospital, the higher the volume, especially when you have one disease state in half of your hospital" and another who expressed that "without 503B, we would've been in significant trouble." One participant commented that "even though the number might be small [percent of products obtained from outsourcing facilities], some of the reasoning is quite critical, and the amount of time that it saves is very significant for beyond what we're able to do and when." Additionally, challenges with recruiting and retaining pharmacy technicians impact decision-making, with 1 participant stating "it is not feasible for us to meet the high volume for some common medications to repackage or compound from commercial presentations to a convenient, ready-to-use dosage form or package. The outsourcing facilities thus become a force multiplier, if you will, to offset some of the shortages in staffing."

In addition to evaluating the workload on pharmacy staff, the type and capabilities of the facility also impacted the decision-making process. One participant commented that they do not have an established cleanroom; therefore, they perform sterile compounding in a segregated compounding area. United States Pharmacopeia (USP) <797> standards limit the beyond-use date that can be assigned to these products and, as the participant stated, "We obviously need to provide product with much [more] extensive beyond-use dating than we can provide." Several participants also commented that they do not perform high-risk compounding in-house, and therefore, all of these products are outsourced. There are challenges with midsize hospitals being able "to operationalize testing compounds we make for extended stability." One participant stated, "We might make our own syringes if we could get extended dating, but I believe my operations colleagues don't always know how to do this and adhere to the letter of the law."

One participant also commented on the impact that The Joint Commission has had on encouraging pharmacies to obtain products from outsourcing facilities. The 2018 medication management standard MM.05.01.07 was intended to move IV admixture preparation out of the nursing unit. This forced pharmacies to consider strategies to make IV admixtures available for use on the floor. Additionally, NPSG.03.04.01 states that all medications and solutions should be labeled adequately, including in the OR and other settings in which procedures are performed. USP <795> and <797> are applicable in operating room settings, stating that products should be labeled and used within 1 hour, which may be problematic if syringes are drawn up at the beginning of the day, and cases are canceled or delayed. The participant also commented on the cost related to purchasing premade products from manufacturers, stating that "predatory pricing on premixes is present in the market."

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products used. However, the products used in a facility are often developed in-house over decades based on physician and nurse requests, and more recently, appropriateness for an automated dispensing cabinet. As a result, 1 participant observed, "These practices had evolved somewhat disparately. Even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines." This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said, "I think we made nine different epidural concentrations, all driven by anesthesia, and they want what they want, and 503Bs may not offer that. If no one else in the country is buying that same concentration, a 503B isn't going to go through the expense of adding that to their product list." The participant also said that "similar with the ADCs [automated dispensing cabinets], we've run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart

reasons, without having to retrain thousands of nurses of where things are placed, they said, 'No, we can't have it, and that's too big, it won't fit. We want it in this format,' and then we're stuck again because there's no 503B offering a format during that shortage that fits where it needs to go. Then we're stuck in sourcing." Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that "3% saline, for instance, is sold in a 500 mL bag, but the clinical guideline is a 150 mL bolus. We're either going to draw that out or we're sending it to the ER [emergency room] with stickers all over it saying only give 150 [mL]." The participant continued that "it would be great if the FDA could look at the size of the container that they're approving and whether that's a realistic dose: Is it a unit dose, or isn't it?"

Participants had differing opinions on the use of outsourcing facilities to obtain drugs during a shortage. Several participants stated that they will typically first restrict use of a drug on shortage, in order to conserve supply, before turning to an outsourcing facility. One participant commented that "most of the time, I will probably pursue restricting, conserving, and looking at all available options prior to going to an outsourcer on my end," and another stated, "I can only think of one time in recent history where we went to an outsourcer." One participant commented that "503Bs can't accept the additional volume if it's a true shortage. If you're not with them pre-shortage, you're not going to get products when you need it during the shortage" continuing that "typically in a shortage, you learn to live without them. You have to." Additionally, in the event of the shortage being the result of lack of an API, outsourcing facilities are likely to be affected equally and unable to provide assistance. However, 1 participant stated that they first began working with outsourcing facilities because of shortages. This participant commented that "what the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on API. If sterile becomes short, they quickly switch to producing through API, which ASHP [American Society of Health-System Pharmacists] and the FDA allow." This "adds a lot of flexibility so they can bounce back and forth and really try to insulate us from shortages."

A few participants commented on the use of API by outsourcing facilities. One commented that as long as they are conducting end-product sterility and stability testing and the product meets quality standards, they are not concerned with the starting ingredients. According to 1 participant, as long as buyers are familiar with regulations and know what to look for, there should not be any issues with purchasing products compounded starting from API. Another participant stated that as more outsourcing facilities began using API, they became more comfortable with them doing so. However, 1 participant observed that most outsourcing facilities are switching to sterile-to-sterile and only using API if there is a shortage, stating, "I think the FDA has really looked closely at API, and they're slowly pushing the 503B outsourcers to a sterile-to-sterile." Only 1 participant commented that they prefer sterile-to-sterile. Another participant stated that the companies they use are all sterile-to-sterile.

A few participants commented on the need for preservative-free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative-containing product. There is a need for this product to be compounded from API as a preservative-free product. One participant stated that "if there's not a preservative-free containing option, it really should be something that should be able to be compounded from bulk . . . especially for the pediatric patient population." However, another participant from a children's hospital said that they have never needed to use an outsourcing facility for preservative-free products. Preservative-free is also an issue for ophthalmic products; however, 1 participant observed this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they would like to obtain from outsourcing facilities but cannot, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products, but when they reviewed the facilities,

they did not pass their internal quality standards; 1 facility had been banned from distributing products in California by the Board of Pharmacy. There is an additional challenge with obtaining cephalosporins and beta-lactams due to the potential cross-reactivity in patients with allergies. One participant stated that there are some cephalosporins they would like to obtain from an outsourcing facility but cannot because "they would have to build a separate cleanroom with a dedicated HVAC [heating, ventilation, and air conditioning], so you're talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn't there." Another participant stated that the concentrations required for ophthalmic antibiotics are not available, but the labor and risk of compounding these products in-house are not worth it.

A few participants commented on purchasing nonsterile products from outsourcing facilities. Lidocaine-epinephrine-tetracaine (LET) gel, for use as a topical anesthetic, was the most commonly obtained product along with buffered lidocaine to put in J-Tips. Another participant stated that they obtain diclofenac suppositories from an outsourcing facility due to the high cost of indomethacin suppositories. One participant commented that most of the products they outsource are nonsterile products, generally for oral or topical administration due to a lack of availability of commercial products. The participant stated that they purchase low-dose naltrexone for oral use in patients with refractory fibromyalgia and ketamine troches for patients with chronic pain. The participant continued that while the evidence does not support many of the ingredients used in topical pain products, "there are select patients. It's very rare that taking that cream away from them actually causes more harm than good." A few participants commented that there is a gap in the market for nonsterile products, with 1 stating, "I think that there is a large opportunity for more nonsterile products to be produced by 503Bs." Another stated that as their facility grows and acquires more outpatient clinics, they receive a lot of questions regarding obtaining products for office use. The participant noted that they often have to refer these clinics to outsourcing facilities but stated, "There's not many 503Bs [that] are doing the nonsterile for clinic use." As a result, the inpatient pharmacy is often asked to take on this role but "you don't have the space or the staff to do that."

Based on the responses to the prequestionnaire (refer to *Results of survey*), participants were asked questions regarding specific products obtained from outsourcing facilities. Several participants reported using alum (aluminum potassium) as a bladder irrigation for hemorrhagic cystitis refractory to other treatment options. Participants commented that this is high-risk compounding; they purchase alum from an outsourcing facility because they do not perform high-risk compounding in their facility. One participant commented that their policy states that high-risk compounding is not allowed except for alum. This participant wanted to move away from compounding alum in-house and stated that the addition of aluminum potassium to the bulks list might allow this to happen. Another participant had compounded alum in-house from nonsterile ingredients; however, there had been challenges with crystallization after storage. A few participants commented that there is a sterile alum powder available, which they purchase to compound in-house. One participant had concerns regarding this powder, stating that "I've talked to that company, but I've had some concerns for them because they don't sell it as a drug. The owner was selling you a chemical, we're selling you a bulk API. It's just sterile. They were fuzzy and I never followed up, but when I asked about their process for verifying the sterility, as you would with a sterile product—we do USP <71> Sterility Testing. They couldn't really give me an answer. They just say they tested for sterility." The participants commented that alum is only needed a few times a year. However, as 1 participant observed, "When you need it, it's an emergency," and another noted that it "is a challenge for anybody who has cyclophosphamide-induced hemorrhagic cystitis." As a result, 1 participant maintains a small inventory of alum product that is purchased from an outsourcing facility but "more times than not, they go unused and expire." Another stated that they do not keep it in stock because there is a minimum purchase and there are only a few cases a year for which they need to use alum. The

participant had it STAT shipped when needed. Another participant stated that "we had a meeting with the head of urology who was baffled, why they're even ordering it. He was like, 'this is . . . old, really old. I don't even know why we're using it' and basically approved for us to not even make it anymore for now."

Two participants commented on the use of glycerin at their facility. One stated that they purchase it from a 503A because they were not able to find an outsourcing facility that provides this product. The participant commented that glycerin is used in 3 different concentrations at their facility, 1 for ophthalmic use, 1 for neurologic use in trigeminal neuralgia, and 1 for instilling into "a very specific kind of pump that's used to deliver a very specific kind of chemotherapy." When there are breaks in the chemotherapy regimen, the pump has to be filled with something and by using glycerin "it can go 3 months or something like that, so it's a huge patient satisfier to have that concentration available." The participant also commented that since they have been unable to find an outsourcing facility that compounds the concentration needed for trigeminal neuralgia, they have patients who have been waiting years for treatment. The other participant stated that they compound it in-house but said that it is infrequent. The participant commented that it is very difficult to sterilize due to the thickness of the product.

Four participants stated that they obtain sodium citrate as ready-to-use syringes for use as a locking solution in patients undergoing dialysis, with 1 commenting that "our nephrologists like it in place of heparin for some patients to keep the ports patent or so they don't have to go to alteplase or some of the other drugs." There is a commercially available product; however, it is only available as a 500 mL bag and the dose needed is typically less than 30 mL. If the syringes are prepared in-house, then the beyond-use date is limited to 12 to 24 hours depending on storage, which results in waste.

One participant stated that they obtain papaverine from outsourcing facilities for use in urology as Bimix (papaverine/phentolamine) and Trimix (papaverine/phentolamine/alprostadil).

While none of the participants obtained sodium phosphate or aspartic acid from outsourcing facilities for use in cardioplegic solutions, a few commented that they do obtain cardioplegic solutions from outsourcing facilities. The del Nido formulation was the product most commonly obtained. One participant commented that they compound this formulation in-house because the outsourcing facilities did not offer the volume needed at their institution. Another participant commented that while they do obtain the del Nido formulation from an outsourcing facility, they also compound a proprietary formulation in-house. This participant observed that "it is complicated to do in-house. We do it on a Baxa 1200 or 2400, either one, compounder. Then we send it up to [*sic*] for pH and potassium testing. Obviously, then we're confined to <797> beyond-use dates versus longer beyond-use dates that we get from the 503B." Another participant commented that cardioplegic solutions are managed by the perfusion department, not the pharmacy, and they use the del Nido formulation as well as 3 other formulations.

The participants also discussed challenges with using outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because "it just hasn't been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to. . . . It just isn't worth the dating that they gave us or can give us." Another commented that they obtain very little product from outsourcing facilities due to "the amount of work for vetting and continually validating quality of these 503B outsourcing facilities." The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented, "Traditionally, we've found 503Bs to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed, but we've had some other smaller 503Bs where we've had agreements for certain products to take it off our plate, and then lo and behold they're shut down, or

closed, or whatever it may be." Minimum purchase amounts were also reported as a concern with 1 participant stating that "what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients." Another challenge was related to outsourcing facilities using API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration places on the quantity that can be produced. The participant stated that "they [outsourcing facilities] want to buy the product that we're trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don't end up with a shortage year after year after year, and then chasing our tail. Also, we may actually want to tell 503Bs they can't buy those products or that they're limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products because it actually induces the shortage in many ways."

Results of survey

The survey was not approved for distribution by any professional medical associations.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 3.2 for survey instrument).

Forty-three people responded to the prequestionnaire (refer to Table 15 for respondent characteristics). Among respondents, 35 (81% of 43 total respondents) used outsourcing facilities to obtain drug products, 4 (9%) did not use outsourcing facilities, and 4 (9%) did not respond to this question.

Twenty-seven respondents (19% of 143 responses, where respondents were allowed to select multiple responses) obtained drug products from outsourcing facilities due to a need for ready-to-use products and 20 respondents (14%) obtained drug products from outsourcing facilities due to backorders (refer to Table 16).

Fourteen respondents (31% of 45 total responses, where respondents were allowed to select multiple types) obtained nonsterile products from outsourcing facilities and 31 (69%) obtained sterile products from outsourcing facilities (refer to Table 17 for the categories of products obtained from outsourcing facilities).

Niacinamide was not included on the prequestionnaire (refer to Table 18).

Table 11. Characteristics of survey respondents

Survey not distributed by any professional medical associations

Table 12. Conditions for which niacinamide was prescribed or administered

Survey not distributed by any professional medical associations

Table 13. Reasons for using compounded niacinamide

Survey not distributed by any professional medical associations

Table 14. Use of non-patient-specific compounded niacinamide

Survey not distributed by any professional medical associations

Table 15. Demographics of prequestionnaire respondents' facilities

Type of Facility	**Responses, n (N = 102)[a]**
Academic medical center	15
Acute care hospital	16
Children's hospital	8
Community hospital	11
Critical access hospital	2
Dialysis center	2
Federal government hospital	4
Health system	15
Inpatient rehabilitation center	4
Long-term acute care hospital	3
Outpatient surgery center	6
Rural hospital	2
Skilled nursing facility	0
Specialty hospital[b]	4
Trauma center	5
Urban hospital	5
Number of Beds	**Responses, n (N = 39)**
< 50	4
50-99	3
100-199	1
200-299	4

300-399	5
400-599	3
> 600	19

[a]Respondents were allowed to select multiple facilities.
[b]Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, and oncology.

Table 16. Reasons for obtaining products from outsourcing facilities

Categories	**Responses, n (N = 143)[a]**
Backorders	20
Convenience	19
Cost	10
Need for concentrations not commercially available	19
Need for multi-ingredient products not commercially available	10
Need for preservative-free products	3
Need for ready-to-use products	27
No FDA-approved product available	7
No onsite compounding facility	1
Onsite compounding facility not equipped to compound all necessary products	19
Other[b]	8

[a]Respondents were allowed to select multiple categories.
[b]Respondents reported staffing shortages, need for extended dating, volume of product used, and standardization projects as additional reasons for using outsourcing facilities.

Table 17. Categories of products obtained from outsourcing facilities

Categories	**Responses, n (N = 142)[a]**
Cardioplegic solutions	14
Dermatologic preparations	6
Dialysate solutions	0

Fluids	8
Ophthalmic preparations	10
Patient-controlled analgesia	20
Ready-to-use anesthesia syringes	25
Ready-to-use antibiotic syringes and/or bags	14
Ready-to-use electrolyte solutions	5
Ready-to-use vasopressor solutions	18
Total parenteral nutrition solutions	16
Other[b]	6

[a]Respondents were allowed to select multiple categories.
[b]Respondents reported obtaining alum for bladder irrigation, oxytocin, anticoagulant sodium citrate solution, narcotic drips, high-cost anti-seizure medications, antiviral medications, topical pain, and oral tablets/capsules.

Table 18. Products obtained from an outsourcing facility

Product	**Responses, n (N = 108)[a]**
Acetylcysteine	1
Adenosine	2
Aluminum potassium sulfate	2
Aspartic acid	0
Atenolol	0
Atropine	9
Baclofen	4
Betamethasone	0
Biotin	0
Bupivacaine	8
Calcium chloride	1
Caffeine sodium benzoate	0
Cholecalciferol	1

Chromium chloride	0
Clonidine	0
Dexamethasone sodium phosphate	0
Diclofenac	0
Gentamicin	0
Glycerin	1
Hydroxyzine	0
Ketamine	14
Levocarnitine	0
Lidocaine	8
Lorazepam	2
Magnesium sulfate	4
Manganese chloride	0
Methylprednisolone	0
Midazolam	15
Mupirocin	1
Norepinephrine	15
Ondansetron	0
Phytonadione	0
Potassium chloride	0
Potassium phosphate	0
Prilocaine	0
Proline	0
Propranolol	1
Ropivacaine	6
Sodium chloride	0

Sodium citrate	3
Sodium phosphate	0
Tetracaine	2
Triamcinolone acetonide	0
Tropicamide	0
None of the above	8

[a]Respondents were allowed to select multiple products.

CONCLUSION

Niacinamide was nominated for inclusion on the 503B Bulks List to treat unknown medical conditions, but is generally used as an antifungal, as a topical cream, emulsion, foam, gel, lotion, ointment, solution, or spray in strengths based on the prescriber's request, with therapeutic doses typically ranging from 2 to 5%. Niacinamide is available in the nominated dosage form and ROA in Ireland and the UK. Niacinamide is available in topical OTC products in Latvia, the UK, and the US.

Twenty-seven studies were included from the literature review. In the included studies, niacinamide was used as various topical products in strengths ranging from 0.05% to 5% to treat hyperpigmentation, acne, antiaging, erythema, facial sebum control, male skin health, psoriasis, prevention of photodynamic therapy or UV radiation induced immunosuppression, actinic keratosis, androgenetic alopecia, melasma, prevention of chemotherapy-induced cutaneous symptoms, seborrheic dermatitis, and irritated skin. Niacinamide was used as 1 of the nominated combinations and as a compounded product. In 11 studies the authors recommended the use of niacinamide, 2 studies concluded that the use of niacinamide was similar to the comparator, 10 studies concluded that further studies were needed, and 4 studies did not provide a definitive conclusion regarding the use of niacinamide.

From the interviews, 1 SME discussed niacinamide. Niacinamide is a vitamin that is likely added to various formulations to provide a skin-conditioning benefit and a generally anti-inflammatory action. The SME was not sure what the effectiveness of niacinamide would be when applied topically but mentioned that is relatively safe and found in several OTC cosmetic products.

The survey was not approved for distribution by any professional medical associations. Niacinamide was not included on the prequestionnaire.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to February 15, 2021
- Date last searched: February 17, 2021
- Limits: Humans (search hedge); English language
- Number of results: 547

1	niacinamide/	12,605
2	amid$ pp.tw.	4
3	nicotinamid$.tw.	21,934
4	niacetamid$.tw.	0
5	niacinamid$.tw.	521
6	niacin amid$.tw.	3
7	nicamid$.tw.	0
8	nicosedin$.tw.	0
9	nicotamid$.tw.	14
10	(nicotinic adj2 amid$).tw.	115
11	nicotinoylamid$.tw.	1
12	ni#otinsaureamid$.tw.	0
13	nikotamin$.tw.	0
14	vitamin$ b3.tw.	447
15	vitamin$ b 3.tw.	54
16	vitamin$ pp.tw.	164
17	or/1-16	31,012
18	administration, topical/	38,889
19	administration, cutaneous/	22,495
20	skin absorption/	11,855

21	topical$.tw.	108,892
22	transcutaneous$.tw.	14,884
23	epicutaneous$.tw.	2047
24	transdermal$.tw.	15,053
25	((cutanous$ or dermal$ or skin) adj3 (absorb$ or absorpt$ or appl$)).tw.	11,638
26	exp gels/	53,703
27	emulsions/	18,535
28	suspensions/	7853
29	liniments/	124
30	ointments/	12,869
31	skin cream/	1105
32	pharmaceutical solutions/	3318
33	gel?.tw.	312,791
34	emulsion?.tw.	34,471
35	suspension?.tw.	111,680
36	liniment?.tw.	148
37	ointment?.tw.	12,175
38	salve?.tw.	345
39	paste?.tw.	12,971
40	unguent$.tw.	114
41	lotion?.tw.	2387
42	cream?.tw.	19,567
43	shampoo?.tw.	1451
44	solution?.tw.	724,460
45	foam?.tw.	26,959
46	spray?.tw.	29,279

47	or/18-46	1,393,811
48	drug combinations/	74,281
49	drug therapy/	30,745
50	ad.fs.	1,440,913
51	dt.fs.	2,279,437
52	de.fs.	3,038,277
53	tu.fs.	2,266,830
54	pc.fs.	1,320,022
55	therap$.tw.	2,912,001
56	treat$.tw.	5,728,068
57	prevent$.tw.	1,481,240
58	prophyl$.tw.	170,862
59	or/48-58	11,330,971
60	and/17,47,59	987
61	exp animals/ not humans/	4,788,182
62	60 not 61	600
63	limit 62 to english language	547

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: February 17, 2021
- Limits: Humans (search hedge); English language
- Number of results: 719

1	‘nicotinamide’/de	16,352
2	‘amid* pp’:ti,ab,tn	7
3	‘nicotinamid*’:ti,ab,tn	26,488
4	‘niacetamid*’:ti,ab,tn	0
5	‘niacinamid*’:ti,ab,tn	817
6	‘nicamid*’:ti,ab,tn	1
7	‘nicosedin*’:ti,ab,tn	0
8	‘nicotamid*’:ti,ab,tn	26
9	(nicotinic NEAR/2 acid*):ti,ab,tn	9655
10	‘nicotinoylamid*’:ti,ab,tn	2
11	‘nicotinsaureamid*’:ti,ab,tn	6
12	‘nikotinsaureamid*’:ti,ab,tn	2
13	‘nikotamin*’:ti,ab,tn	0
14	‘vitamin* b3’:ti,ab,tn	528
15	‘vitamin* b 3’:ti,ab,tn	20
16	‘vitamin* pp’:ti,ab,tn	297
17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	43,433
18	‘topical drug administration’/de	84,340
19	‘cutaneous drug administration’/de	756
20	‘transdermal drug administration’/de	9303
21	‘skin absorption’/de	8173
22	‘topical treatment’/de	13,841

23	‘topical*’:ti,ab	154,166
24	‘epicutaneous*’:ti,ab	3472
25	‘transdermal*’:ti,ab	21,973
26	((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorp* OR appl*)):ti,ab	18,393
27	‘cream’/de	9831
28	‘gel’/exp	81,210
29	‘liniment’/de	257
30	‘lotion’/de	2968
31	‘ointment’/de	18,280
32	‘paste’/de	2552
33	‘salve’/de	170
34	‘suspension’/de	28,635
35	‘emulsion’/exp	47,909
36	‘shampoo’/de	2344
37	‘foam’/de	8507
38	‘aerosol’/de	65,844
39	‘cream$’:ti,ab	30,590
40	‘emulsion$’:ti,ab	46,594
41	‘liniment$’:ti,ab	242
42	‘lotion$’:ti,ab	4119
43	‘ointment$’:ti,ab	22,009
44	‘paste$’:ti,ab	15,484
45	‘salve$’:ti,ab	485
46	‘unguent*’:ti,ab	242
47	‘gel$’:ti,ab	367,818
48	‘suspension$’:ti,ab	148,453

49	‘shampoo$’:ti,ab	2271
50	‘foam$’:ti,ab	35,415
51	‘spray$’:ti,ab	38,973
52	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51	1,015,468
53	‘drug combination’/de	172,266
54	‘drug therapy’/de	793,878
55	‘drug dose’:lnk	629,758
56	‘drug administration’:lnk	1,797,602
57	‘drug therapy’:lnk	4,019,840
58	‘prevention’:lnk	1,199,296
59	‘therap*’:ti,ab	4,363,252
60	‘treat*’:ti,ab	8,276,184
61	‘prevent*’:ti,ab	2,007,332
62	‘prophyl*’:ti,ab	272,296
63	#53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62	13,822,305
64	#17 AND #52 AND #63	1035
65	[animals]/lim NOT [humans]/lim	617,0289
66	#64 NOT #65	822
67	#64 NOT #65 AND [english]/lim	719

Appendix 2. Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Acne					
Khodaeiani et al, 2013, Iran[10]	Randomized, double-blinded, clinical trial	80 Patients with moderate inflammatory acne vulgaris • Clindamycin (32.5%, mean: 23.25 y ± 3.77) • Nicotinamide (37.5%, mean: 23.88 y ± 3.67)	• Nicotinamide 4% (40) • Clindamycin 1% (40)	Acne grade	"The efficacies of 4% nicotinamide and 1% clindamycin gels are comparable in treating moderate inflammatory facial acne vulgaris. However, nicotinamide is preferred in oily and clindamycin in non-oily skin because of better function and outcome."
Santos-Caetano et al, 2020, Brazil[22]	Randomized, parallel-group, evaluator-blind, controlled, proof-of-concept clinical study	132 Patients with oily, blemish-prone skin • Test group: (0%, mean 25.4 y ± 5.8) • Control group (0%, mean 25.8 y ± 6.1) • Positive control group (24.8 y ± 5.7)	• Test group: test product containing niacinamide plus standard cleanser (44) • Control group: standard cleanser (44) • Positive control group: cream with niacinamide (44)	Change from baseline in corneometer values at 8 hours, for the test regimen vs. the control regimen	"Overall, these results indicate that the next-generation biomimetic lamellar skincare formulation containing niacinamide, in combination with a standard cleanser, can help moisturize the skin and provide an overall improvement in the appearance of the complexion of people with blemish-prone skin. These clinical data warrant further research into the role of topical biomimetic technologies in blemish-prone skin."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Shahmoradi et al, 2013, Iran[23]	Double-blinded, randomized, clinical trial	60 Patients with mild or moderate acne vulgaris • Nicotinamide (0%, mean 20.8 y ± 3.34) • Clindamycin (0%, mean 21.2 y ± 3.5)	• Nicotinamide gel (30) • Clindamycin gel (30)	Reduction of mean Acne Severity Index score, level of patient satisfaction, presence of side effects	"Our results clearly showed that 5% nicotinamide gel is at least as effective as 2% clindamycin gel for treatment of mild to moderate acne vulgaris. Moreover, we observed no side effect[s] during the treatment and the patients tolerated the treatment very well. Considering these results along with the anti-inflammatory effects of the nicotinamide that may help to reduce post acne erythema and its anti-pigmentary effect that may help to reduce the severity of post-inflammatory hyperpigmention after acne may suggest 5% nicotinamide gel as an appropriate treatment for acne vulgaris. To better evaluate the efficacy of 5% nicotinamide gel in the treatment of the acne vulgaris, more randomized clinical trial (RCT) with higher number of the patients and longer follow-up is recommended."
Shalita et al, 1995, US[20]	Multicenter, double-blind, randomized, parallel, active-control study	76 Patients with moderate inflammatory acne (30%, mean 21.3 y)	• Nicotinamide gel (38) • Clindamycin phosphate gel (38)	Improvement of acne (Physician's Global Evaluation of inflammatory Acne score), percent change from baseline in acne lesion counts and ratings of acne severity	"After 8 weeks of therapy, 4% nicotinamide and 1% clindamycin gels were equivalent in efficacy for the treatment of inflammatory acne vulgaris as shown by Physician's Global Evaluation, Acne Lesion Count, and Acne Severity Rating. Unlike topical clindamycin, topical nicotinamide use is not associated with the emergence of resistant strains of microorganisms nor with psuedomembranous colitis. Caution regarding the use of topical and systemic antimicrobial agents, such as clindamycin, erythromycin, and tetracycline, is now commonly advised due to concern about antimicrobial resistance."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Weltert et al, 2004, France[21]	Double-blind comparative study	160 Patients who have facial acne with inflammatory predominance (gender and age not specified)	• Nicotinamide (Exfoliac® NC Gel) (80) • Erythromycin gel (80)	Retention and inflammatory lesion count, clinical scoring of seborrhea	"Under the conditions of this study, Exfoliac® NC Gel and the erythomycin-based gel led to an equivalent regression of inflammatory lesions (papules + pustules), visible from the first month. Seborrhoea scores presented a more important decrease within the group treated with Exfoliac® NC Gel. The effect on cysts was better with Exfoliac® NC Gel." "The cutaneous safety of both products was similar and average, consistent with the safety generally observed with this category of product. Exfoliac® NC Gel can thus be an interesting alternative to topical antibiotics in the treatment of acne with inflammatory predominance."
Indication 2: Anti-aging					
Bissett et al, 2005, US[11] Bissett et al, 2004, US[55]	Double-blind, placebo controlled	50 Healthy subjects with clinical signs of facial photoaging (0%, range 35-60 y)	• Niacinamide moisturizer (50) • Placebo (50) • Each side of the face was assigned a test formulation	Clinical signs of facial photoaging (hyperpigmented spots, red blotchiness, fine lines/wrinkles), skin yellowing, elasticity	"In addition to previously reported skin benefits for topical niacinamide (improvement in the appearance of facial skin texture, red blotchiness, and hyperpigmentation and enhancement of skin barrier function),[6–9] the work here reveals effects against fine lines and wrinkles, skin yellowing, and elasticity. In addition, the treatment is extremely well tolerated by the skin (no irritation, redness, burn, sting, itch issues)."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Chiu et al, 2007, Taiwan[34]	Randomized, double-blind, placebo controlled, split-face, left-right randomized clinical trial	52 Patients with Fitzpatrick skin types II, III, or IV (10%, range 30-60 y)	• Kinetin and niacinamide on one side of the face and vehicle on the other side (27) • Niacinamide on one side of the face and vehicle on the other side (25)	Facial spot count	"In conclusion, we have demonstrated for the first time that the combination of kinetin and niacinamide can effectively improve many facial aging signs in Asians. The study is not conducted restrictedly due to the restrain of measuring instrument, personnel variation, and in-adequate sample size. No significant differences between niacinamide alone group and kinetin plus niacinamide group are revealed in the final results, but the clinical effects of kinetin plus niacinamide seem to be better. Our data suggest that both compounds have the capacity to exert multiactive, multifunctional and pluripotent effects on the skin. And they are promising candidates for potential use in future cutaneous anti-aging formulation."
Kawada et al, 2008, Japan[25] Kawada et al, 2009, Japan[56]	Double-blind, placebo controlled, split face study with left-right randomization	30 Japanese subjects (0%, range 31-49 y)	Split face study: • Side 1: niacinamide (30) • Side 2: control cream (30)	Evaluation of anti-wrinkle effects via physicians' observation and photographs, and average roughness of skin surface	"In conclusion, our study indicates that the topical niacinamide-containing cosmetic reduced wrinkles in the eye area of Japanese women. Further study is needed to reveal the precise mechanism of anti-wrinkle effects of niacinamide."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Nisbet et al, 2019, Germany[26]	Two randomized, controlled, evaluator-blind, clinical studies	Study 1 66 Patients with self-reported dry, sensitive skin on the face and body (0%, mean 48.0 y ± 12.7) Study 2 72 Patients with self-reported sensitive skin and with visible signs of aging (0%, mean 50.3 y ± 7.7)	In both studies, each subject was assigned two of three possible treatments: one treatment for the test areas on the left side of the body (both the face and volar forearm in Study 1, or only the face in Study 2) and a different treatment for the right side: • Group 1: test cream and no treatment • Group 2: Olay ProX Wrinkle Smoothing Cream and no treatment • Group 3: test cream and Olay ProX Wrinkle Smoothing Cream Test cream is a novel cosmetic biomimetic lamellar formulation, that also contains niacinamide Each intervention group contained 22 participants in Study 1 and 24 participants in Study 2	Study 1: Change from baseline in skin barrier function (TEWL measurements) Study 2: Change from baseline in the wrinkle dimensions on the periocular/crow's feet area (DermaTOP roughness parameter) at 28 days	"Twice daily application of the test cream over 4 weeks had beneficial effects on skin barrier function, moisturization, wrinkle dimensions and elasticity compared to no treatment. These studies provide proof-of-concept evidence and highlight the cosmetic benefit of the biomimetic lamellar cream formulation." "Based on these promising efficacy and safety results, pivotal studies of the niacinamide-containing lamellar formulation are warranted."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Voegeli et al, 2020, South Africa[27]	Placebo-controlled, randomized topical study	48 Caucasian study participants equally comprised of young and old participants • Young (gender not specified, mean 20.8 y ± 1.7) • Old (gender not specified, mean 57.5 y ± 2.9)	• Vehicle cream • Test cream (vehicle cream plus niacinamide) Number of participants not specified	Effect of niacinamide on corneocyte envelope maturation parameters (size, hydrophobicity, rigidity, and relative corneocyte envelope maturity) on four facial test sites: central forehead, cheek, top nasolabial sulcus, midpoint nasolabial sulcus	"Clearly, niacinamide treatment improved CE [corneocyte envelope] maturation as measured by our methodology but CE hydrophobicity is not improved as much in the NM [midpoint nasolabial sulcus] area . . . we specifically demonstrated the differences in increased CE hydrophobicity and increased mechanical resilience following treatment with niacinamide . . . these study results support further investigations into the effect of niacinamide on ceramide EOS-linoleate levels together with enzymes involved in its processing and attachment to the CE. It is possible that the regional differences in skin permeability may reflect differences in barrier function as facial barrier function is complex."
Indication 3: Hyperpigmentation					
Bissett et al, 2007, US[14]	Randomized, double-blind, placebo-controlled 2 Clinical studies but only information from the Caucasian facial study provided since the other clinical study did not use niacinamide	35 Subjects (0%, range 35-65 y)	• Niacinamide + N-acetyl Glucosamine (NAG) (35) • Niacinamide (35) Each treatment was applied to a randomly pre-assigned side of the face. There were also additional subjects that were paired. "The experimental treatments were also paired against the same control (4% niacinamide; additional n = 70) and against placebo formulation (no niacinamide; n = 35)"	Hyperpigmentation	"Both of these agents are well tolerated by the skin. This high tolerance coupled with relative ease of formulation and stability in solution make NAG, especially in combination with niacinamide, a suitable cosmetic ingredient for use in skin care products dealing with issues of skin hyperpigmentation."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Bissett et al, 2009, Japan, US[33]	2 Double-blind, left-right randomized, split-face clinical studies	Japan study: 80 Healthy subjects (0%, range: 25 -55 y) US Study: 152 healthy subjects (0%, range: 40 -65 y)	Japan study: • Niacinamide on 1 side and vehicle control on the other side (40) • Niacinamide on 1 side and niacinamide plus N-undecylenoyl-phenylalanine formulation on the other side (40) US Study: Each subject applied one of three emulsions to a randomly assigned side of the face • Vehicle control (not specified) • Niacinamide 5% (not specified) • Niacinamide plus N-undecylenoyl-phenylalanine formulation (not specified)	Hyperpigmented spot quantification (mean % spot area fraction), compliance	"In conclusion, both niacinamide and N undecylenoyl-phenylalanine penetrate the skin. Both clinical studies showed that the combination of 5% niacinamide plus 1% N-undecylenoyl-phenylalanine was significantly more effective than 5% niacinamide alone in reducing the appearance of facial hyperpigmented spots."
Castanedo-Cazares et al, 2013, US[8]	Randomized, double-blind, placebo controlled	24 Patients with axillary hyperpigmentation (0%, mean 21.7 y ± 1.6)	• Niacinamide (16) • Desonide (16) • Placebo cream (16) Each patient received 2 of 3 treatments randomized to either left or right axillae	Reduction in axillary hyperpigmentation	"Niacinamide and desonide showed depigmenting properties in women with axillary hyperpigmentation. These findings may be explained by their antimelanogenic and anti-inflammatory properties, respectively."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 4: Prevention of photodynamic therapy or ultraviolet-induced immunosuppression					
Damian et al, 2008, Australia[18]	Randomized, double-blinded	75 Volunteers • Nicotinamide application before ssUV (solar simulated) exposure (gender not specified, range 22-63 y) • Nicotinamide application after ssUV exposure (50%, range 23-62 y) • UVA only plus Nicotinamide application (47%, range 20-50 y) • UVB only plus Nicotinamide application (53%, range 21-50 y) • Microarray plus nicotinamide (80%, range 21-50 y)	• Nicotinamide application before ssUV exposure (20) • Nicotinamide application after ssUV exposure (20) • UVA only plus nicotinamide application (15) • UVB only plus nicotinamide application (15) • Microarray (5)	Minimal erythema dose, ssUV-induced immunosuppression	"Topical nicotinamide prevented immunosuppression, with gene chip microarrays suggesting that the mechanisms of protection may include alterations in complement, energy metabolism and apoptosis pathways. Nicotinamide is a safe and inexpensive compound that could be added to sunscreens or after-sun lotions to improve protection from immunosuppression."

Sivapirabu et al, 2009, Australia[17]	4 Randomized, double-blinded studies	70 Healthy volunteers, Mantoux-positive from previous Bacille Calmain-Guerin vaccination participated in four studies: Study 1 (12%, mean 37 y, range 24-66 y) Study 2 (28%, mean 39 y, range 22-70 y) Study 3 (40%, mean 37 y, range 23-54 y) Study 4 (20%, mean 34 y, range 23-51 y)	Study 1 (17) • ssUV (solar-simulated ultraviolet, UVB + UVA) irradiation once and nicotinamide 5% Study 2 (18) • ssUV irradiation daily for 3 days and nicotinamide 5% Study 3 (20) • ssUV irradiation daily for 3 days and nicotinamide 0.2% Discrete areas of skin were irradiated on each side of the lower back. A separate site on each side of the back served as the unirradiated control. Nicotinamide and vehicle were applied to opposite sides of the back immediately after each irradiation. Study 4 (15) • UVA or UVB irradiation once and nicotinamide 5% Each side of the back was treated with single doses of UVA or UVB with a fourth site on each side acting as an unirradiated control. One side was treated with nicotinamide and the other with vehicle immediately after irradiation.	Difference in Mantoux-induced erythema between the control site and each of the treatment sites	"In conclusion, we found that longwave UVA [ultraviolet A] and UVB [ultraviolet B] are immunosuppressive in humans, and that nicotinamide protects against the immune effects of both. A cosmetically unacceptable opaque sunscreen would be required to attenuate the longer wavelengths, which abut the visible spectrum. With its broad-spectrum immune protection, lack of toxicity and extremely low cost, nicotinamide is promising as an agent which could be used with sunscreens to optimise photoprotection."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Thanos et al, 2012, Australia[29]	– 2 Studies were performed, 1 on topical nicotinamide and the other for oral nicotinamide. Only information related to topical nicotinamide was provided.	20 Healthy Mantoux-positive volunteers (25%, mean 44 y, range 27-73)	• Nicotinamide lotion (20) • Vehicle lotion (20)	Difference in Mantoux-induced erythema between the control site and each of the treatment sites	"In conclusion, we have shown . . . topical nicotinamide significantly reduce[s] PDT [photodynamic therapy]-induced suppression of Mantoux responses in humans. The clinical relevance of this reduced delayed-type hypersensitivity in the days following PDT is as yet unclear, but nicotinamide may provide an inexpensive, nontoxic means of potentiating the anticancer effectiveness of PDT by protecting PDT-mediated antitumour responses. Further research is now required to determine the optimal PDT protocol and to examine the potential clinical benefits of adjuvant nicotinamide therapy."
Indication 5: Erythema, irritated skin					
Bierman et al, 2013, US[12]	–	44 Fitzpatrick II and III panelist (0%, age not mentioned)	• Vehicle control (44) • Niacinamide (44) • No treatment site (44) Patients applied 1 intervention each according to a pre-assigned site on their backs	Expert assessment of UV barrier	"These findings show that niacinamide is able to reduce the immediate microdamage elicited by acute UV exposure in human skin. We hypothesize that its mechanism of action is to enhance NAD+ levels and stabilize cellular bioenergetics. This in turn allows a controlled cellular response to mitigate the inflammatory cascade induced by UV."
Lukic et al, 2019, Serbia[13]	Randomized, investigator-blind study	8 Volunteers (gender and age not mentioned)	• DENI gel containing nicotinamide (8) • Non-treated controls (8)	Triplicate stratum corneum hydration and transepidermal water loss (TEWL) measurements	"The study has demonstrated that when applied to dry and irritated skin, a novel anti-inflammatory emollient gel containing nicotinamide (DENI gel), achieved significant improvement in skin barrier function within 7 days (as opposed to within 14 days if no treatment was used). DENI gel also provided effective skin hydration."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 6: Psoriasis					
Levine et al, 2010, US[30]	Randomized, double-blinded, multicenter, 7-arm, bilateral comparison-controlled trial	168 Patients with moderate psoriasis (gender and age not specified)	Patients were randomized to 2 of 7 treatments: • Placebo (48) • Calcipotriene 0.005% (46) • Nicotinamide 1.4% (47) • Calcipotriene plus nicotinamide 0.05% (47) • Calcipotriene plus nicotinamide 0.1% (47) • Calcipotriene plus nicotinamide 0.7% (46) • Calcipotriene plus nicotinamide 1.4% (47)	Percent of patients who achieved clear to almost clear psoriatic symptoms	"In summary, this is a promising dose-ranging study that, in our opinion, justifies further investigation using the 1.4% combination product (DPS-101 1.4%) compared with nicotinamide alone, calcipotriene alone, placebo arm, and ultimately comparing it with calcipotriene corticosteroid combination therapy to determine whether nicotinamide-based therapy has potential as a steroid-sparing agent."
Siadat et al, 2013, Iran[31]	Randomized, double-blinded, controlled trial	65 Patients with mild to moderate psoriasis (54%, mean 36.5 y ± 8.5)	• Calcipotriol and nicotinamide (65) • Calcipotriol alone (65) 2 Lesions at 2 opposite sides (right and left) were selected in each patient and randomized to treatment	Psoriasis severity (Modified Psoriasis Area and Severity Index score), patient satisfaction	"Nicotinamide can enhance the efficacy of calcipotriol when used in combination for topical psoriasis treatment and may be a good adjuvant to be added to the treatment regimens of psoriasis. Further trials with long-term follow-up are required to confirm these results and also to evaluate possible adverse effects with long-term use of nicotinamide."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 7: Actinic keratosis					
Moloney et al, 2010, Australia[24] Moloney et al, 2009, Australia[57]	Randomized, double-blinded, placebo-controlled trial	30 Patients with at least 4 nonhyperkeratotic actinic keratoses in 1 or more treatment areas • Nicotinamide (92%, mean 75 y, range 48-89 y) • Vehicle (82%, mean 75 y, range 55-85 y)	• Nicotinamide gel (13) • Vehicle gel (17)	AKs count at 3 and 6 months compared with baseline, adverse events	"Our study was designed as a pilot to rapidly assess the potential for a safe, inexpensive intervention to reduce AKs [actinic keratoses]. We found a more rapid rate of AK resolution with nicotinamide compared with vehicle in a group of heavily sun-damaged individuals. Future, larger studies using nicotinamide at higher concentrations, or with concurrent sunscreen are now warranted."
Indication 8: Androgenetic alopecia					
Watanabe et al, 2015, Japan[32]	Randomized, double-blind, clinical study	101 Patients with androgenetic alopecia • Adenosine (100%, mean 41.5 y ± 6.4) • Niacinamide (100%, mean 41.5 y ± 6.0)	• Adenosine (51) • Niacinamide (50) *1 Patient withdrawn from each arm due to administration of hypotensive drugs before using the test lotions	Global improvement score (6-point evaluation scale based on hair quality, percentages of vellus-like and thick hairs among vertex hairs, and hair density).	"In conclusion, this study demonstrated the enhanced efficacy of adenosine compared with niacinamide for the treatment of AGA [androgenetic alopecia], especially regarding the thickness of vellus-like hairs." "Improvements in the thick hair ratio, but not in the vellus-like hair ratio were significantly augmented for the adenosine-treated group vs. the niacinamide-treated group."
Indication 9: Facial sebum control					
Draelos et al, 2006, Japan, US[35]	2 Randomized, double-blind, clinical trials	Japan Study 100 Healthy Japanese subjects, (0%, mean 36.4 y ± 6.2, range 20-49 y) US Study 30 Healthy Caucasian subjects (0%, range 20 – 49 y)	Japan study • Niacinamide 2% gel (50) • Placebo gel (50) US Study • Niacinamide 2% gel (30)	Sebum excretion rate measurements	"This research demonstrated the potential use of 2% niacinamide and 1% d-panthenol for facial shine reduction. It is possible that a moisturizer using these ingredients might aid in an improved cosmetic appearance for both Oriental and Caucasian individuals."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 10: Male skin health					
Draelos, 2012, US[15]	Randomized, double-blinded round robin split-face design	90 Subjects with moderate to heavy beard growth were studied post-shave (100%, range: 18-45 y)	• Daily shave with a three-blade razor and commercial shave gel without post-shave moisturizer treatment (90) • Daily shave followed by application of a post-shave placebo moisturizer containing emollients and high levels of glycerine (90) • Daily shave followed by application of a post-shave 5% niacinamide moisturizer (5% niacinamide added to placebo moisturizer) (90) Patients were randomly pre-assigned to receive each treatment to a side of their faces	TEWL	"Further, moisturizers containing glycerine and emollients can create an environment for barrier repair that may be enhanced by incorporating specific cosmetic ingredients, such as 5% niacinamide. This new understanding of the importance of skin care in obtaining optimal shave results will aid the dermatologist in treating patients with shaving-related issues."
Indication 11: Melasma					
Navarrete-Solis et al, 2011, Mexico[16]	Double-blind, left-right, randomized clinical trial	27 Patients with melasma (0%, mean 37 y, range 25-53 y)	Patients randomized to receive each treatment, 1 on the left side and the other on the right side of the face: • Niacinamide (27) • Hydroquinone (27)	Skin pigment, Melasma Area and Severity Index score, Physician Global Assessment, irritation, side effects	"Niacinamide induces a decrease in pigmentation, inflammatory infiltrate, and solar elastosis. Niacinamide is a safe and effective therapeutic agent for this condition."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 12: Prevention of chemotherapy-induced cutaneous symptoms					
Wohlrab et al, 2014, Germany[28]	Multicenter, prospective, randomized, reference-controlled crossover study	95 Patients diagnosed with breast cancer (0%, range 25-77 y)	• Test preparation for 6 weeks then standard care for 6 weeks (46) • Standard care for 6 weeks then the test preparation for 6 weeks (48) Standard care is the patient's usual body care routine. The test preparation contains niacinamide *1 Patient in the study was excluded for protocol deviation	Dermatology Life Quality Index score, pruritus, dryness, and irritability	"The results of this study favor the niacinamide-containing TP [test preparation] for proactive treatment accompanying cytostatic therapies with classic antiproliferative substances. Certainly, further investigations are necessary in order to strengthen the evidence for the supportive use of topical niacinamide in oncology."
Indication 13: Seborrheic dermatitis					
Fabbrocini et al, 2014, Italy[19]	Open randomized study	48 Patients with mild to moderate seborrheic dermatitis (75%, range 20 -50 y)	• Group 1: Nicotinamide 4% (24) • Group 2: Placebo (24)	Clinical measures	"Topical NCT [nicotinamide] 4% can have a potential for the treatment of SD [seborrheic dermatitis]."

Abbreviations: AGA, androgenetic alopecia; AK, actinic keratoses; CE, corneocyte envelope; NAD+, nicotinamide adenine dinucleotide; NCT, nicotinamide; NAG, niacinamide + n-acetyl glucosamine; PDT, photodynamic therapy; SD, seborrheic dermatitis; ssUV, solar simulated ultraviolet; TEWL, transepidermal water loss; TP, test preparation; UV, ultraviolet.

[a]As defined by authors.

Appendix 3.1. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you prescribe or administer any of the following as a compounded topical product? (please check all that apply)
    - ○ Betamethasone acetate
    - ○ Betamethasone dipropionate
    - ○ Betamethasone sodium phosphate
    - ○ Cholestyramine resin
    - ○ Cimetidine
    - ○ Clobetasol propionate
    - ○ Clotrimazole
    - ○ Cromolyn sodium
    - ○ Dexamethasone sodium phosphate
    - ○ Diclofenac sodium
    - ○ Finasteride
    - ○ Fluconazole
    - ○ Fluticasone propionate
    - ○ Hydrocortisone
    - ○ Itraconazole
    - ○ Ketoconazole
    - ○ Lidocaine hydrochloride
    - ○ Methylprednisolone acetate
    - ○ Metronidazole
    - ○ Mupirocin
    - ○ Niacinamide
    - ○ Phytonadione (vitamin K1)
    - ○ Prilocaine
    - ○ Spironolactone
    - ○ Sulfacetamide sodium monohydrate
    - ○ Terbinafine hydrochloride
    - ○ Tetracaine hydrochloride
    - ○ Triamcinolone acetonide
    - ○ Zinc oxide

- None of the above

3. Do you prescribe the compounded topical products that you selected in in combination with other active pharmaceutical ingredients as a multi-ingredient product?
    - Yes
    - No
    - I'm not sure
4. Why do you use the compounded topical products that you selected? (please check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
    - Patient allergies prevent me from using commercially available products (please explain) _____
    - Patient conditions prevent me from using commercially available products (please explain) _____
    - I am not aware of any commercially available products containing these products
    - Other (please explain) _____
5. Do you stock non-patient-specific compounded products at your practice?
    - Yes
    - No
    - I'm not sure
6. I obtain compounded products from the following: (please check all that apply)
    - Compound myself at my practice
    - Have the product compounded by an in-house pharmacy
    - Purchase, or have a patient purchase, from a compounding pharmacy
    - Purchase, or have a patient purchase, from an outsourcing facility
    - Other (please explain) _____
7. What is your practice setting? (please check all that apply)
    - Physician office/private practice
    - Outpatient clinic
    - Hospital/health system
    - Academic medical center
    - Emergency room
    - Operating room
    - Other (please describe) _____
8. What degree do you hold? (please check all that apply)
    - Doctor of Medicine (MD)
    - Doctor of Osteopathic Medicine (DO)
    - Doctor of Medicine in Dentistry (DMD/DDS)
    - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - Naturopathic Doctor (ND)
    - Nurse Practitioner (NP)
    - Physician Assistant (PA)
    - Other (please describe) _____

Appendix 3.2. Survey instrument for pharmacy roundtable prequestionnaire

1. Please select all that apply regarding the facility with which you are affiliated.
    - Academic medical center
    - Acute care hospital
    - Children's hospital
    - Community hospital
    - Critical access hospital
    - Dialysis center
    - Federal government hospital
    - Health system
    - Inpatient rehabilitation center
    - Long-term acute care hospital
    - Outpatient surgery center
    - Rural hospital
    - Skilled nursing facility
    - Specialty hospital, please identify specialty(ies)
    - Trauma center
    - Urban hospital
2. Please select the number of beds in the facility with which you are affiliated.
    - < 50
    - 50-99
    - 100-199
    - 200-299
    - 300-399
    - 400-599
    - > 600
3. Do you use an outsourcing facility (503b facility) to obtain any products used in your facility? A list of FDA registered outsourcing facilities can be found at https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilities.
    - Yes
    - No
4. Why do you use an outsourcing facility to obtain product(s)? Please select all that apply
    - Backorders
    - Convenience
    - Cost
    - Need for concentrations not commercially available
    - Need for preservative-free products
    - Need for ready-to-use products
    - No FDA-approved products available
    - No onsite compounding facility
    - Onsite compounding facility not equipped to compound all necessary products
    - Other, please explain _____
5. Please select the type(s) of products obtained from an outsourcing facility.
    - Nonsterile products
    - Sterile products
6. Please select the category(ies) of products obtained from an outsourcing facility.
    - Cardioplegic solutions
    - Dermatologic preparations
    - Dialysate solutions

- Fluids
- Ophthalmic preparations
- Patient-controlled analgesia
- Ready-to-use anesthesia syringes
- Ready-to-use antibiotic syringes and/or bags
- Ready-to-use electrolyte solutions
- Ready-to-use vasopressor solutions
- Total parenteral nutrition solutions
- Other, please identify _____

7. From the list below, please select the drug(s) that you obtain as either a single ingredient or multi-ingredient product from an outsourcing facility.
    - Acetylcysteine
    - Adenosine
    - Aluminum potassium sulfate
    - Aspartic acid
    - Atenolol
    - Atropine
    - Baclofen
    - Betamethasone
    - Biotin
    - Bupivacaine
    - Calcium chloride
    - Caffeine sodium benzoate
    - Cholecalciferol
    - Chromium chloride
    - Clonidine
    - Dexamethasone sodium phosphate
    - Diclofenac
    - Gentamicin
    - Glycerin
    - Hydroxyzine
    - Ketamine
    - Levocarnitine
    - Lidocaine
    - Lorazepam
    - Magnesium sulfate
    - Manganese chloride
    - Methylprednisolone
    - Midazolam
    - Mupirocin
    - Norepinephrine
    - Ondansetron
    - Phytonadione
    - Potassium chloride
    - Potassium phosphate
    - Prilocaine
    - Proline
    - Propranolol
    - Ropivacaine
    - Sodium chloride
    - Sodium citrate

- Sodium phosphate
- Tetracaine
- Triamcinolone acetonide
- Tropicamide
- None of the above

Appendix 4. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Anesthesiology	Society of Cardiovascular Anesthesiologists	Declined – failed to respond
Cardiology	American Academy of Cardiovascular Perfusion	Declined
	American Board of Cardiovascular Perfusion	Declined – failed to respond
	American Society of Extracorporeal Technology	Declined – failed to respond
Dermatology	American Academy of Dermatology	Declined – failed to respond
Naturopathy	American Association of Naturopathic Physicians	Agreed
Nephrology	American Society of Diagnostic and Interventional Nephrology	Declined
Ophthalmology	American Academy of Ophthalmology	Declined – failed to respond
	American Society of Cataract and Refractive Surgery	Agreed
	American Society of Retina Specialists	Declined
Podiatry	American Podiatric Medical Association	Agreed
Psychiatry	The International Society for Electroconvulsive Therapy and Neurostimulation	Agreed
Rheumatology	American College of Rheumatology	Agreed
Surgery	American Association of Neurological Surgeons	Declined – failed to respond
	American Association for Thoracic Surgery	Declined – failed to respond
	American College of Surgeons	Declined – failed to respond
	American Society for Reconstructive Microsurgery	Declined – failed to respond
Urology	Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction	Declined
Wound Care	Association for the Advancement of Wound Care	Declined – failed to respond

[a]Associations that declined in Year 1 and/or Year 2 were not contacted in Year 3.