MEMORANDUM

TO: File

FROM: Center for Drug Evaluation and Research

DATE: July 29, 2020

SUBJECT: Clinical need for glycolic acid in compounding under section 503B of the FD&C Act

This memorandum reflects the discussions of the 503B Working Group, comprised of representatives from the following: CDER Office of New Drugs, Office of Pharmaceutical Quality, Office of Regulatory Policy, Office of Compliance, and Office of Regulatory Affairs.

The Food and Drug Administration (FDA or Agency) is developing a list of bulk drug substances that can be used in compounding under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353b). Section 503B of the FD&C Act describes the conditions that must be satisfied for drug products compounded by an outsourcing facility to be exempt from requirements concerning FDA approval prior to marketing (section 505 (21 U.S.C. 355)); labeling of drugs with adequate directions for use (section 502(f)(1) (21 U.S.C. 352(f)(1))); and drug supply chain security requirements (section 582 (21 U.S.C. 360eee-1)).[1]

To qualify for the exemptions available in section 503B of the FD&C Act, a drug product must be compounded in an outsourcing facility that does not compound using bulk drug substances unless: (1) the bulk drug substance appears on a list established by the Secretary of Health and Human Services identifying bulk drug substances for which there is a clinical need (the 503B Bulks List), or (2) the drug compounded from such bulk drug substances appears on the drug shortage list in effect under section 506E of the FD&C Act (21 U.S.C. 356e) at the time of compounding, distribution, and dispensing.

This memorandum evaluates glycolic acid for the 503B Bulks List for the treatment of hyperpigmentation disorders and photodamaged skin under the "clinical need" standard in section 503B of the Act.

[1] In general, drug products compounded under the conditions in section 503B must meet current good manufacturing practice (CGMP) requirements in section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)). Outsourcing facilities are also subject to FDA inspections according to a risk-based schedule, specific adverse event reporting requirements, and other conditions that help to mitigate the risks of the drug products they compound. Outsourcing facilities may or may not obtain prescriptions for identified individual patients and can, therefore, distribute compounded drugs to healthcare practitioners for "office stock," to hold in their offices in advance of patient need.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

We evaluated glycolic acid for potential inclusion on the 503B Bulks List under the clinical need standard in section 503B, consistent with the interpretation and policies described in FDA's March 2019 guidance, "Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act" (the Clinical Need Guidance). Because glycolic acid is not a component of an FDA-approved drug, we did not ask the questions in the Part 1 analysis described in the Clinical Need Guidance. Consistent with the Part 2 analysis in the Clinical Need Guidance, we have considered data and information regarding the physical and chemical characterization of glycolic acid, safety issues raised by use of this substance in compounding, available evidence of effectiveness or lack of effectiveness, and historical and current use in compounding.[2] **For the reasons stated below, we conclude that the Agency should propose adding the bulk drug substance glycolic acid to the 503B Bulks List with a limitation for topical use in concentrations up to 70 percent.**

I. Background

A. Nominated Product

Sincerus Florida, LLC (Sincerus) nominated glycolic acid, 0.08 to 70 percent for topical use for the treatment of hyperpigmentation disorders and photodamaged skin (Docket No. FDA-2015-N-3469, document no. FDA-2015-N-3469-0035). (See Appendix A – Sincerus Nomination.)

The Outsourcing Facilities Association (OFA) nominated glycolic acid, 10 percent, in various topical dosage forms, for the treatment of hyperpigmentation disorders and photodamaged skin (Docket No. FDA-2015-N-3469, document no. FDA-2015-N-3469-0123).[3] (See Appendix B – OFA Nomination.)

B. Other Materials Reviewed

In addition to the nominations for the 503B Bulks List, the Agency considered data and information from its earlier evaluation regarding the use of glycolic acid for the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act (21 U.S.C. 353a) (the 503A Bulks List) (the 503A Evaluation). Glycolic acid was nominated for use in compounding drug products under section 503A to treat hyperpigmentation and photodamaged skin. FDA reviewed glycolic acid in a September 29, 2016 memorandum to the Pharmacy Compounding Advisory Committee (PCAC). (See Appendix C – September 29, 2016

[2] In particular, OPQ has reviewed the data and information regarding the physical and chemical characterization of glycolic acid, OND has reviewed safety issues raised by use of this substance in compounding and available evidence of effectiveness or lack of effectiveness, and Compliance has reviewed information about the historical and current use in compounding.

[3] The OFA nomination also states that prescribers may want glycolic acid compounds in other formulations to treat other conditions but does not identify the conditions or formulations. It also refers to the use of glycolic acid in combination with other ingredients and, in particular, to compounding a formulation containing hydroquinone 6 percent and tretinoin 0.1 percent. Information submitted with this nomination relevant to compounding with glycolic acid for the treatment of hyperpigmentation disorders and photodamaged skin was considered. This memo does not consider whether there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substances hydroquinone or tretinoin, or other bulk drug substances.

Memorandum.) At its meeting on November 3, 2016, the PCAC voted to include glycolic acid for topical use on the 503A Bulks List.[4] FDA also consulted with the United States Pharmacopoeia Convention (USP) as part of the Agency's consideration of glycolic acid for inclusion on the 503A Bulks List. FDA has proposed to add this substance to the 503A Bulks List with a limitation for topical use in concentrations up to 70 percent (84 FR 46688).[5]

FDA also considered the report provided by the University of Maryland Center of Excellence in Regulatory Science and Innovation (CERSI) (See Appendix D – CERSI Report on Glycolic Acid.), and conducted a search for relevant scientific literature and safety information, as described below in footnote 8, focusing on materials published or submitted to FDA since the503A Evaluation.

II. Evaluation

A. Physical and Chemical Characterization

We agree with the conclusion in the September 29, 2016 memorandum to the PCAC that glycolic acid, also known as hydroxyacetic acid, is a well-characterized small molecule, and it is likely to be stable under ordinary storage conditions.[6] It is easily characterized with various analytical techniques, and the preparation of glycolic acid has been well developed. Based on the available information, there are no concerns about whether glycolic acid can be identified or compounded consistently based on its the physical and chemical characteristics, when potential impurities in the drug substance, such as formaldehyde, are controlled at acceptable levels.

B. Safety Issues Raised by Use of the Substance in Compounding

We agree with the conclusions in the September 29, 2016 memorandum to the PCAC which reviewed nonclinical data and human safety data.

With regard to nonclinical data, we agree with the conclusion in the September 29, 2016 memorandum that, overall, the use of glycolic acid topically at low concentrations does not raise major safety concerns.[7] Glycolic acid in high concentrations is used as a chemical peel as it causes exfoliation of stratum disjunctum and epidermal remodeling. Glycolic acid in very high concentrations causes local effects that are typical of a strong acid, such as dermal and eye irritation. It also induces significant toxicity via inhalation (target organs: lung, liver, and thymus). However, its acute oral toxicity is considered low (LD50 ~2000 mg/kg). Repeat dose oral toxicity studies in rats showed that glycolic acid induced calculi formation (target organs: urinary bladder and kidney) after 4 weeks of dosing while such finding was not seen in dogs after 35 days of oral dosing of 1000 mg/kg/day glycolic acid. In a 13-week oral toxicity study in

[4] Materials from the PCAC's 2016 meetings are available on FDA's website at https://www.fda.gov/advisory-committees/pharmacy-compounding-advisory-committee/2016-meeting-materials-pharmacy-compounding-advisory-committee.

[5] The Agency has not finalized the rulemaking at this time, but we have reviewed the comments submitted to the docket on the proposed rule.

[6] See Appendix C – September 29, 2016 Memorandum, at Section II.A.

[7] See Appendix C – September 29, 2016 Memorandum, at Section II.B.1.

rats, renal toxicity was noted at 300 and 600 mg/kg/day (NOAEL identified as 150 mg/kg/day) while immunotoxicity or neurotoxicity was not seen at doses up to 600 mg/kg/day, the highest dose tested. Glycolic acid was not mutagenic or clastogenic in various genotoxicity assays. It is not a skin sensitizer in nonclinical studies. It has not demonstrated photocarcinogenic potential. In oral reproductive and developmental toxicity studies in rats, it induced developmental toxicity at high maternal toxic doses. In a pivotal study in rats, the NOAEL for developmental toxicity was identified as 150 mg/kg/day. There is lack of nonclinical data for the evaluation of chronic dermal toxicity and dermal carcinogenic potential of glycolic acid.

We also agree with the September 29, 2016 memorandum that the available information about human safety, including extensive clinical data accumulated since the 1990s, does not raise major safety concerns associated with the topical use of glycolic acid.[8] The available data suggest that topical use of glycolic acid is mainly associated with local irritancy (e.g., burning, erythema, swelling, and less commonly, vesiculation), although serious outcomes have been reported with use of products containing glycolic acid as one of several or many ingredients, or concomitant use of other topical products. Reported adverse reactions generally appeared to be readily manageable and temporary in duration. However, there were reports of post-inflammatory hyperpigmentation and rarely, scarring. No information is available on long-term outcomes. The reports of systemic reactions to products containing glycolic acid are also confounded by the presence of multiple other components in the products and/or the concomitant use of oral or topical agents.

C. Available Evidence of Effectiveness or Lack of Effectiveness

As discussed in the September 29, 2016 memorandum, there are no placebo-controlled trials for the use of glycolic acid in the treatment of melasma or other forms of hyperpigmentation. There are, however, controlled trials showing positive results in the treatment of epidermal melasma with glycolic acid, either as a peel or as a topical agent. There is a single vehicle-controlled clinical trial providing some evidence of effectiveness for the mitigation of manifestations of photodamaged skin. Many of these trials combined the use of glycolic acid with that of other topical medications like retinoids and/or hydroquinone. All of the trials used adjunctive measures like sun protection with sunscreens and protective clothing. There were some clinical trials with negative results; most of these trials were small and have been criticized in the literature for using low concentrations of glycolic acid or having too short a duration of treatment.

[8] See Appendix C – September 29, 2016 Memorandum, at Section II.B.2.

In February 2020, a search of the FAERS, CAERS, EMBASE, PubMed, TOXNET, and Google/Google Scholar databases was conducted focusing on materials published or submitted to FDA since the 503A Evaluation. Our determination is that glycolic acid's safety and efficacy profile is, indeed, unchanged. The February 2020 FAERS search identified only six new reports, all of which contained adverse reactions clearly unrelated to the product's use or already identified in our 2016 review. The February 2020 CAERS search identified only one additional report, but that report contains no new product safety or efficacy information. And, the other sources identified 14 new articles that were not previously considered, but revealed a safety and effectiveness profile consistent with our 2016 review (see Section IV- Bibliography).

We agree with the conclusion in the September 29, 2016 memorandum that there is clinical evidence that provides some support for the effectiveness of glycolic acid for the mitigation of manifestations of photodamaged skin and as a second line treatment for melasma that has failed standard therapy or as an adjunctive treatment to other commonly used topical medications.[9]

D. Historical and Current Use in Compounding

Historically, glycolic acid has been used for a number of dermatologic conditions. The substance has been used in pharmacy compounding in the United States and in other countries for several decades. The extent of use could not be precisely determined, but in addition to the United States, use has been reported in at least eight countries. Glycolic acid is listed in the British and the European Pharmacopeia but not the USP-NF or the pharmacopeia of Japan.

Information obtained by CERSI from its review of articles, other materials, and interviews supports our assessment of the historical use and suggests a similar profile for the current use of glycolic acid. Dermatologists interviewed described glycolic acid, at concentrations up to 70 percent, being used approximately every two weeks depending on the condition being treated. Dermatologists also reported glycolic acid being held as "office stock" in advance of patient need.

III. Recommendation

Glycolic acid was nominated as a bulk drug substance for the 503B Bulks List to compound drug products for topical use at concentrations ranging from 0.08 to 70 percent for the treatment of hyperpigmentation and photodamaged skin. [10] The nominated bulk drug substance is not a component of an FDA-approved drug product. We evaluated glycolic acid for potential inclusion on the 503B Bulks List under the clinical need standard in section 503B, considering data and information regarding the physical and chemical characterization of glycolic acid, safety issues raised by use of this substance in compounding, available evidence of effectiveness or lack of effectiveness, and historical and current use in compounding.

Glycolic acid, also known as hydroxyacetic acid, is physically and chemically well characterized. When used in high concentrations, glycolic acid causes local effects that are typical of a strong acid, such as dermal and eye irritation. Reported adverse reactions were generally limited in duration and readily manageable. There is no information available on long-term outcomes. The available data on short-term outcomes do not raise major safety concerns associated with the topical use of glycolic acid.

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[9] See Appendix C – September 29, 2016 Memorandum, at Section II.C, and footnote 7 above.

[10] See Docket No. FDA-2015-N-3469, document nos. FDA-2015-N-3469-0035 and FDA-2015-N-3469-0123. One of the nominations also states that prescribers may want glycolic acid compounds in other formulations to treat other conditions but does not identify the conditions or formulations. It also refers to the use of glycolic acid in combination with other ingredients and, in particular, to compounding a formulation containing hydroquinone 6 percent and tretinoin 0.1 percent. Information submitted with this nomination relevant to compounding with glycolic acid for the treatment of hyperpigmentation disorders and photodamaged skin was considered. FDA's evaluation does not consider whether there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substances hydroquinone or tretinoin, or other bulk drug substances.

Data from controlled clinical trials have shown consistently positive results in the treatment of epidermal melasma or other forms of hyperpigmentation. The available evidence suggests that there is a role for glycolic acid in the treatment of melasma, typically as a second line treatment. There is also some evidence indicating that glycolic acid may be effective for the mitigation of manifestations of photodamaged skin. Glycolic acid has been used for several decades to compound drug products for dermatologists and continues to be used for this purpose. Conclusions regarding each of these factors are for use at concentrations up to 70 percent; data and evidence regarding use of higher concentrations are very limited.

On balance, the physical and chemical characterization, safety, effectiveness, and historical and current use of glycolic acid weigh in favor of including this substance on the 503B Bulks List at concentrations up to 70 percent. Accordingly, we propose adding glycolic acid to the 503B Bulks List for topical dermal use in concentrations up to 70 percent. Nominators did not submit, and we have not identified, significant evidence to support use in other routes of administration or higher concentrations.

IV. Bibliography

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APPENDIX SECTION A

Sincerus

3265 W McNab Road
Pompano Beach, FL 33069
Phone: (561) 404-8885
Fax: (561) 503-4131

November 1, 2017

FILED ELECTRONICALLY
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, Maryland 20852

Re: Docket No. FDA-2015-N-3469 for Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act; Establishment of a Public Docket

Dear Sir or Madam:

Sincerus Florida, LLC, located in Pompano Beach, Florida submits the attached nominations in accordance with the Notice published in the Federal Register for Docket No. FDA-2015-N-3469 Bulk Drug Substance's That Can Be Used To Compound Drug Products in Accordance With Section 503B of the Federal, Food, Drug and Cosmetic Act; Establishment of a Public Docket. For reasons set forth in the attached Excel Spreadsheet that complies with the data requirements established by the FDA, Sincerus submits the 33 drug substances listed on Attachment 1: Nominated Drugs for inclusion on the list of bulk drug substances that may be used in compounding by an outsourcing facility pursuant to Section 503B(a)(2)(A)(i) of the Federal Food, Drug, and Cosmetic Act.

If any further information is required, do not hesitate to contact me at (800) 604-5032 or via email at jliu@sincerususa.com.

Sincerely yours,

Jenny Liu, Pharm. D.
Pharmacist in Charge

Attachments 1: Nominated Drugs

Bulk Drug Substance Nomination	
What is the name of the nominated ingredient?	Glycolic acid
Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in §207.3(a)(4)?	Yes
What is the chemical name of the substance?	Glycolic Acid $C_2H_4O_3$
What is the common name of the substance?	Glycolic Acid
Does the substance have a UNII Code?	No but in the USP: **Glycolic Acid,** $C_2H_4O_3$—**76.05** *[79-14-1]*—White crystalline powder or chunks
What is the chemical grade of the substance?	Reagent grade
What is the strength, quality, stability and purity of the substance?	0.08 percent to 70 percent. See https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM529467.pdf
How is the ingredient supplied?	White crystalline powder or chunks
Is the substance recognized in foreign pharmacopeias or registered in other countries?	Yes. British and European; see FDA PCAC 503A recommendation https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM529467.pdf
Has information been submitted about the substance to the USP for consideration of monograph development?	Yes, for 503A and the committee recommended that it be added to the list for bulk compounding. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM529467.pdf
What medical condition(s) is the drug product compounded with the bulk drug substances intended to treat?	Treatment of hyperpigmentation disorders and photodamaged skin
Are there other drug products approved by the FDA to treat the same medical condition?	A variety of topical treatments have been used to treat epidermal postinflammatory hyperpigmentation, with varying degrees of success. These agents include hydroquinone, tretinoin cream, corticosteroids, glycolic acid (GA), and azelaic acid. https://emedicine.medscape.com/article/1069191-treatment
If there are FDA approved drug products that address the same medical condition, why is there a clinical need for a compounded drug product?	The requested products are at strengths greater than the commercially available product. Accordingly, API is needed to concentrate or to compound at strengthens greater than those commercially available. In addition, the requesting physicians have determined that there is a clinical difference between whatever compounded drug is being requested and the comparable commercially available one.

	Al-Talib, H., Al-khateeb Alyaa, Hameed, A., & Murugaiah, C. (2017). Efficacy and safety of superficial chemical peeling in treatment of active acne vulgaris. *Anais Brasileiros de Dermatologia*, *92*(2), 212–216. http://doi.org/10.1590/abd1806-4841.20175273 Acne vulgaris is an extremely common condition affecting the pilosebaceous unit of the skin and characterized by presence of comedones, papules, pustules, nodules, cysts, which might result in permanent scars. Acne vulgaris commonly involve adolescents and young age groups. Active acne vulgaris is usually associated with several complications like hyper or hypopigmentation, scar formation and skin disfigurement. Previous studies have targeted the efficiency and safety of local and systemic agents in the treatment of active acne vulgaris. Superficial chemical peeling is a skin-wounding procedure which might cause some potentially undesirable adverse events. This study was conducted to review the efficacy and safety of superficial chemical peeling in the treatment of active acne vulgaris. It is a structured review of an earlier seven articles meeting the inclusion and exclusion criteria. The clinical assessments were based on pretreatment and post-treatment comparisons and the role of superficial chemical peeling in reduction of papules, pustules and comedones in active acne vulgaris. This study showed that almost all patients tolerated well the chemical peeling procedures despite a mild discomfort, burning, irritation and erythema have been reported; also the incidence of major adverse events was very low and easily manageable. In conclusion, chemical peeling with glycolic acid is a well-tolerated and safe treatment modality in active acne vulgaris while salicylic acid peels is a more convenient for treatment of darker skin patients and it showed significant and earlier improvement than glycolic acid
Are there safety and efficacy data on compounded drugs using the nominated substance?	****
	Faghihi, G., Taheri, A., Shahmoradi, Z., & Nilforoushzadeh, M. A. (2017). Solution of Azelaic Acid (20%), Resorcinol (10%) and Phytic Acid (6%) Versus Glycolic Acid (50%) Peeling Agent in the Treatment of Female Patients with Facial Melasma. *Advanced Biomedical Research*, *6*, 9. http://doi.org/10.4103/2277-9175.200784 **Background:** Melasma, a common acquired disorder of hyperpigmentation, especially in women, is often resistant to therapy. This study was aimed to evaluate the efficacy and safety of azelaic acid, resorcinol and phytic acid solution in chemical peeling of melasma in comparison to 50% glycolic acid. **Materials and Methods:** This clinical trial was performed, on 42 female patients with bilateral melasma. Severity of melasma was assessed by melasma area and severity index (MASI). Combination of (20% azelaic acid + 10% resorcinol + 6% phytic acid) was used as a new peeling agent on the right side of the face and 50% glycolic acid on the left side every 2 weeks for 6 times. Follow-up was carried out for 3 months after the last session. Any decrease in MASI score and unwanted complications following peeling were evaluated and compared during the trial. **Results:** Patients showed marked improvement as calculated with MASI score before and after treatment in both sides of the face. The efficacy of combination formula (azelaic acid, resorcinol and phytic acid) was similar to glycolic acid, but with fewer complications. There was no statistically difference in improvement between two groups ($P > 0.05$). However, the patient's discomfort following procedures was significantly lower with azelaic acid, resorcinol and phytic compared with the glycolic acid peels ($P < 0.05$) and there was the same duration in the beginning of the therapeutic response in both groups. **Conclusion:**

	Results showed that triple-combination was found to be an effective and safe peeling agent in the treatment of melasma and it was as effective as 50% glycolic acid peel.
If there is an FDA -approved product that includes the bulk drug substance nominated, is it necessary to compound a drug product from the bulk drug substance rather than from the FDA-approved drug product?	Yes. Percentage of active ingredient may vary from commercially available products and may be used with other excipients. For example, the requested products are at strengths greater than the commercially available product. Accordingly, API is needed to concentrate or to compound at strengthens greater than those commercially available. In addition, the requesting physicians have determined that there is a clinical difference between whatever compounded drug is being requested and the comparable commercially available one.
What dosage form(s) will be compounded using the bulk drug substance?	Creams, pads and lotions
What strength(s) will be compounded from the nominated substance?	0.08 to 70 percent for topical use (see FDA PCAC recommendation https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM529467.pdf
What are the anticipated route(s) of administration of the compounded drug product(s)?	Topical
Has the bulk drug substance been used previously to compound drug product(s)?	Yes. See FDA PCAC recommendation https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM529467.pdf

APPENDIX SECTION B

SAFE ▪ EFFECTIVE ▪ SOLUTIONS
OFA
OUTSOURCING FACILITIES ASSOCIATION

Lee H. Rosebush
Chairman | OFA
Partner | BakerHostetler
1050 Connecticut Avenue, NW
Suite 1100
Washington, D.C. 20036-5403

July 20, 2018

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2015-N-3469 for *Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act, Concerning Outsourcing Facilities; Request for Nominations*

This submission is for the nomination of a bulk drug substance in accordance with the Notice published in the Federal Register Docket No. FDA 2015-N-3469-Bulk Drug Substances that can be used to compound drug products in accordance with section 503B of the Federal Food, Drug, and Cosmetic Act; Establishment of a public docket; 80 Federal Register 65770 (Oct. 27, 2105).

We hereby nominate the bulk drug substance in the attached nomination for FDA's consideration as a bulk drug substance that may be used by outsourcing facilities to compound drug products under Section 503B.

	Bulk Drug Substance Nomination	
1	What is the name of the nominated ingredient?	Glycolic acid
2	Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in §207.3(a)(4)?	Yes
3	What is the chemical name of the substance?	Glycolic Acid, $C_2H_4O_3$
4	What is the common name of the substance?	Glycolic Acid
5	Does the substance have a UNII Code?	0WT12SX38S
6	What is the chemical grade of the substance?	Reagent grade
7	What is the strength, quality, stability and purity of the substance?	Refer to enclosed Certificate of Analysis labeled as "Exhibit A"
8	How is the ingredient supplied?	Solution
9	Is the substance recognized in foreign pharmacopeias or registered in other countries?	Yes. British and European
10	Has information been submitted about the substance to the USP for consideration of monograph development?	Yes, for 503A and the committee recommended that it be added to the list for bulk compounding. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM529467.pdf
11	Is the nominated bulk substance component of an FDA approved drug product?	None found
12	Are there any other products approved by FDA to treat the same medical condition?	Yes
13	Is there basis to conclude, for each FDA approved product that includes the nominated bulk drug substance, that: (i) an attribute of an FDA approved product makes it medically unsuitable to treat certain patients for the condition that FDA is evaluating, and (ii) the drug product proposed to be compounded is	As with any drug product patients respond differently. The compounded drug product listed in "Exhibit B" containing this nominated ingredient may be the only formulations to effectively treat the indication for which it is intended to treat.

	intended to address that attribute?	
14	Is there basis to conclude that the drug product proposed to be compounded must be produced from a bulk drug substance rather than from an FDA approved drug product?	Yes. There are no FDA approved drugs containing this Active Pharmaceutical ingredient (API). In addition, Compounding from bulk drug substances means using only the ingredients necessary to achieve the desired clinical outcome. That means starting with the API in its purest form without any fillers, excipients, fillers, binders, dyes, preservatives or other materials. Use of the bulk will ensure that no irritating, hazardous or allergen ingredients are included. Another reason for using a bulk drug substance instead of a finished product is the need for accuracy. Individual finished products have a considerable variance in the actual API and the use of a finished product has the potential to introduce unacceptable inaccuracies into the compounded medication.
15	What medical condition(s) is the drug product compounded with the bulk drug substances intended to treat?	Compounded drugs are requested by prescribers to treat the individual needs of prescriber's patients. The exact medical condition for which the compounded drug is being requested to treat is generally unknown to 503Bs. However, the nominated ingredient is generally used to treat: • hyperpigmentation disorders and photodamaged skin
16	Are there safety and efficacy data on compounded drugs using the nominated substance?	Please see the enclosed list of studies that include data on the nominated substance as an active pharmaceutical ingredient labeled as "Exhibit C". Also, please refer to the enclosed data on 336 compounded medications by formulation using the nominated ingredient labeled as "Exhibit D". There are no reported incidents.
17	What dosage form(s) will be compounded using the bulk drug substance?	Based on prescriber's request, various topical dosage forms may be compounded including: creams, pads and lotions
18	What strength(s) will be compounded from the nominated substance?	Strength is based on prescriber's request. Therapeutic dose: 10%
19	What are the anticipated route(s) of administration of the compounded drug product(s)?	Topical
20	Has the bulk drug substance been used previously to compound drug product(s)?	Yes. The nominated substance has been used in the products listed on enclosed list labeled as "Exhibit B".

Exhibit A
Certificate of Analysis

MEDISCA®
YOUR TRUSTED PARTNER IN COMPOUNDING

CERTIFICATE OF ANALYSIS

GLYCOLIC ACID SOLUTION (70%) (High Purity)

Batch/Lot Number : 120054

Manufacturing Date : 01/16/2015

Expiration Date : 12/31/2016

Retest Date : NOT APPLICABLE

CAS Number : N/A

† All dates in this document are in format mm/dd/yyyy unless otherwise specified

TESTS	SPECIFICATIONS	RESULTS
ASSAY	70 - 72 % (as Glycolic acid)	72 %
DESCRIPTION	Clear liquid, free of visible suspended matter.	CONFORMS
SOLUBILITY	Soluble in water.	CONFORMS
pH	0.4 - 0.8	0.8
IRON	<= 10 ppm	0.1 ppm
FORMALDEHYDE	<= 0.5 ppm	< 0.1 ppm
HEAVY METALS	<= 10 ppm	1 ppm
SPECIFIC GRAVITY	1.24 - 1.29	1.26
COLOR ALPHA	<= 20	10
PACKAGING AND STORAGE	Preserve in tight containers.	

Lot number has been changed from GX7015-A1 to 120054.

The above mentioned product conforms to the manufacturer's specifications.

The above test results are a direct transcription of information provided to Medisca Inc. from the Certificate of Analysis provided by the manufacturer / supplier. Additional testing conducted by Medisca Inc. is represented by an asterisk.

Dated: 2/11/2015

Exhibit B
Proposed Formulas

Formula
GLYCOLIC ACID 10% / HYDROQUINONE 6% / TRETINOIN 0.1%

Exhibit C

Studies

Glycolic Acid

Chandrashekar, B. S., et al. "Retinoic acid and glycolic acid combination in the treatment of acne scars." *Indian dermatology online journal* 6.2 (2015): 84.
https://www.ncbi.nlm.nih.gov/pubmed/25821727

Chaudhary, Savita, and Surabhi Dayal. "Efficacy of combination of glycolic acid peeling with topical regimen in treatment of melasma." *Journal of drugs in dermatology: JDD* 12.10 (2013): 1149-1153.
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Draelos, Zoe Diana, et al. "Evaluation of a kojic acid, emblica extract, and glycolic acid formulation compared with hydroquinone 4% for skin lightening." *Cutis* 86.3 (2010): 153-158.
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https://www.ncbi.nlm.nih.gov/pubmed/10906645

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doi: 10.4103/2229-5178.153007
PMCID: PMC4375771
PMID: 25821727

Retinoic acid and glycolic acid combination in the treatment of acne scars

BS Chandrashekar, KR Ashwini, Vani Vasanth, and Shreya Navale

Department of Dermatology, CUTIS, Academy of Cutaneous Sciences, Bengaluru, Karnataka, India
Address for correspondence: Dr. BS Chandrashekar, CUTIS, Academy of Cutaneous Sciences, 5/1, 4th Main, MRCR Layout, Vijayanagar, Bengaluru - 560 040, Karnataka, India. E-mail: cutisclinic@gmail.com

Abstract

Go to:

Introduction:

Go to:

Acne is a prevalent condition in society affecting nearly 80-90% of adolescents often resulting in secondary damage in the form of scarring. Retinoic acid (RA) is said to improve acne scars and reduce postinflammatory hyperpigmentation while glycolic acid (GA) is known for its keratolytic properties and its ability to reduce atrophic acne scars. There are studies exploring the combined effect of retinaldehyde and GA combination with positive results while the efficacy of retinoic acid and GA (RAGA) combination remains unexplored.

Aim:

Go to:

The aim of this study remains to retrospectively assess the efficacy of RAGA combination on acne scars in patients previously treated for active acne.

Materials and Methods:

Go to:

A retrospective assessment of 35 patients using topical RAGA combination on acne scars was done. The subjects were 17-34 years old and previously treated for active acne. Case records and photographs of each patient were assessed and the acne scars were graded as per Goodman and Baron's global scarring grading system (GSGS), before the start and after 12 weeks of RAGA treatment. The differences in the scar grades were noted to assess the improvement.

Results:

Go to:

At the end of 12 weeks, significant improvement in acne scars was noticed in 91.4% of the patients.

Conclusion:

Go to:

The RAGA combination shows efficacy in treating acne scars in the majority of patients, minimizing the need of procedural treatment for acne scars.

Keywords: Acne scars, glycolic acid, retinoic acid, retinoic acid and glycolic acid

INTRODUCTION

Go to:

Acne is a prevalent condition in society affecting nearly 80% of adolescents and often results in secondary damage in the form of scarring. Although these lesions can be treated in a number of ways, they are often physically and emotionally troublesome.[1,2]

Retinoic acid (RA) improves acne scars and postinflammatory hyperpigmentation (PIH),[3,4] while glycolic acid (GA) has keratolytic properties and reduces atrophic acne scars. GA is beneficial in treating PIH and melasma.[5,6,7] Though the efficacy of retinaldehyde and GA (RALGA) combination has been well explored in treating acne scars,[8] the efficacy of RA and GA (RAGA) combination has not been recorded. In addition, RA is more readily available than retinaldehyde in India and therefore, we did the following retrospective assessment to study the efficacy of topical RAGA combination in the treatment of acne scars.

MATERIALS AND METHODS

Go to:

A retrospective assessment was done at Cutis academy of Cutaneous Sciences, Bengaluru to study the efficacy of topical RA 0.025% and GA 12% (RAGA) combination in treating acne scars and PIH (postacne).

The patients previously treated for active acne and reporting with acne scars at our center were prescribed 0.025% RA and 12% GA. They were advised to mix half a fingertip unit of each and apply evenly over full face sparing 1 cm area around eyes, nostrils and mouth.

The duration of application was escalated gradually from half an hour in the evening to few hours to overnight depending on patient's tolerance to the application. A moisturizer was prescribed to ensure least irritation.

The case records and photographs of 35 patients (12 males and 23 females), who were on topical RAGA treatment for acne scars, were assessed. The patients were 17-34 years (mean age = 26.11 years). Photographs taken at the start of acne scar treatment (baseline) and at the end of 12th week were assessed and case records were reviewed for any history of irritation and noncompliance. The patients had not been on any other treatment for acne scars and PIH.

The acne scars were graded according to Goodman and Baron's quantitative global scarring grading system (GSGS)[9] at baseline and after 12 weeks of topical RAGA treatment [Table 1] by an independent observer. The first point on this grading system is “macular erythematous pigmented” scars and the difference in these grades were considered to measure improvement in PIH.

Table 1

Goodman and Baron's quantitative global acne scarring grading system

Grade or type	Number of lesions 1 (1-10)	Number of lesions 2 (11-20)	Number of lesions 3 (>20)
Milder scarring (1 point each)	1 point	2 points	3 points
Macular erythematous pigmented			
Mildly atrophic dish-like			
Moderate scarring (2 points each)	2 points	4 points	6 points
Moderately atrophic, dish-like			
Punched out with shallow bases small cars (<5 mm)			
Shallow but broad atrophic areas			
Severe scarring (3 points each)	3 points	6 points	9 points
Punched out with deep but normal bases, small scars (<5 mm)			
Punched out with deep but abnormal bases, small scars (<5 mm)			
Linear or troughed dermal scarring			
Deep, broad atrophic areas			
Hyperplastic	2 points	4 points	6 points
Papular scars	Area <5 mm	Area 5-20 mm^2	Area >20 cm^2
Keloidal/hypertrophic scars	6 points	12 points	18 points

The differences in the acne scar grades before and after the treatment were noted. The improvement status was categorized into a 5-point scale depending on the reduction in the GSGS scores as depicted in Table 2. When difference between the GSGS scores of a patient before the treatment and after RAGA treatment is 0, the improvement status would be categorized as no improvement (when scar grades remained the same). Similarly when difference is 1-5 points then the improvement is categorized as mild, moderate improvement when scar grades reduced between 6 and 10 points, good improvement when scar grades decreased by 11-15 points and very good improvement when scar grades reduced by more than 15 points [Table 2].

Table 2

Improvement status

Reduction in GSGS scores	Improvement status
0-5	Minimal Improvement
5-10	Moderate Improvement
10-15	Good Improvement
>15	Very good Improvement

GSGS: Global scarring grading system

Open in a separate window

While considering only macular erythematous pigmented lesions, the improvement was categorized according to Table 3 as no improvement (no change in 3 points score), mild improvement (1 point reduction), moderate improvement (2 point reduction in score), and good improvement (3 point reduction in score).

Table 3

Improvement status of postinflammatory hyperpigmentation

Reduction in macular erythematous pigmented lesions	Improvement status	Number of patients
3	Good Improvement	20
2	Moderate Improvement	8
1	Mild Improvement	2
0	No Improvement	5

RESULTS

Go to:

Of the 35 patients, three showed no improvement in scar grades at the end of 12 weeks, while 16 patients demonstrated a mild improvement in their scars that is, the acne scar grades reduced to up to 5 points [Figure 1a and b]. Thirteen patients had moderate improvement in their acne scars [Figure 2a and b], two had good improvement [Figure 3a and b] and one patient demonstrated 21 points reduction in the appearance of his acne scars and had very good improvement [Figure 4a and b]. The overall improvement in acne scars is shown graphically in Figures 5 and 6.

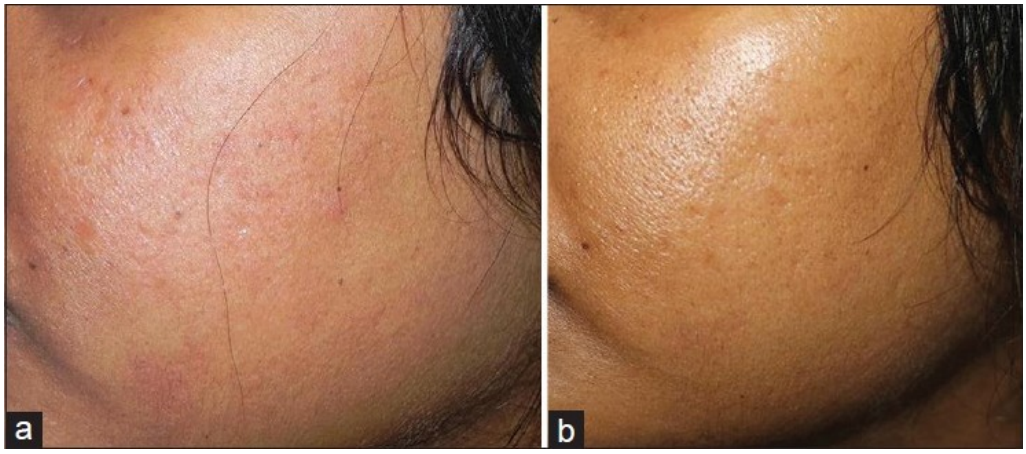

Figure 1

(a) Acne scars with global scarring grading system score of 6 before starting of retinoic acid and glycolic acid treatment (b) Acne scars after 12 weeks of retinoic acid and glycolic acid treatment showing mild improvement with a global scarring grading system score of 3

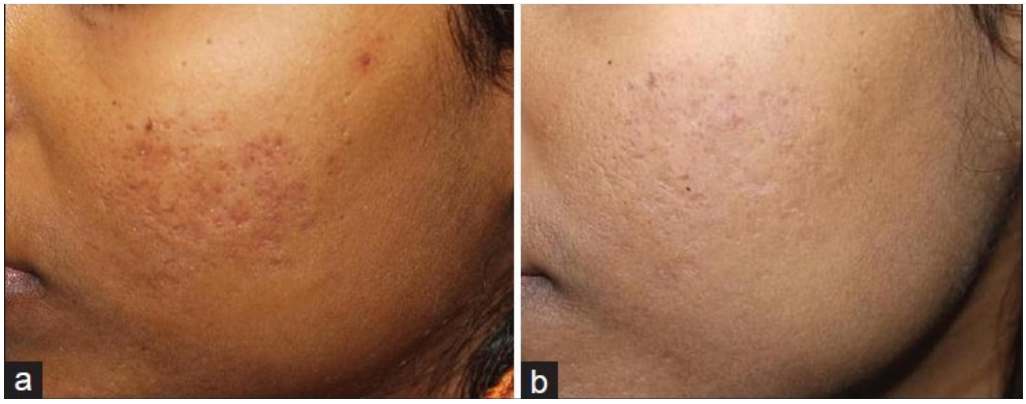

Figure 2

(a) Acne scars with global scarring grading system score of 15 before starting of retinoic acid and glycolic acid treatment (b) Acne scars after 12 weeks of retinoic acid and glycolic acid treatment showing moderate improvement with a global scarring grading system score of 9

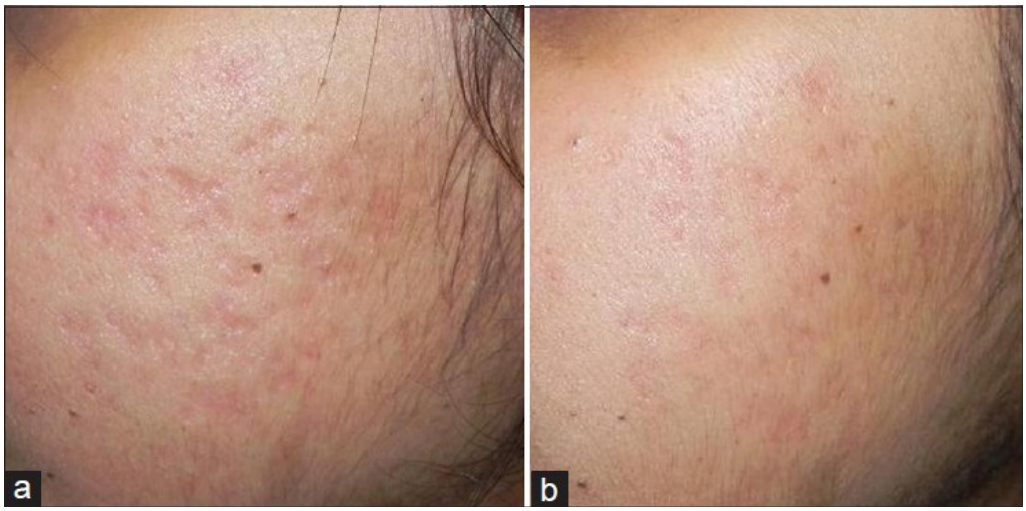

Figure 3

(a) Acne scars with global scarring grading system score of 28 before starting of retinoic acid and glycolic acid treatment (b) Acne scars after 12 weeks of retinoic acid and glycolic acid treatment showing good improvement with a global scarring grading system score of 17

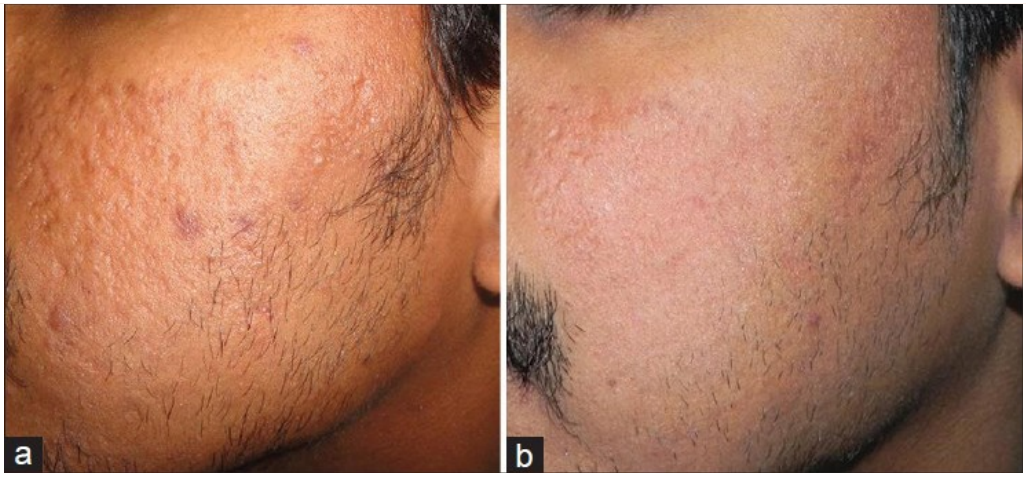

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Figure 4

(a) Acne scars with global scarring grading system score of 37 before starting RAGA treatment (b) Acne scars showing very good improvement with global scarring grading system score of 16

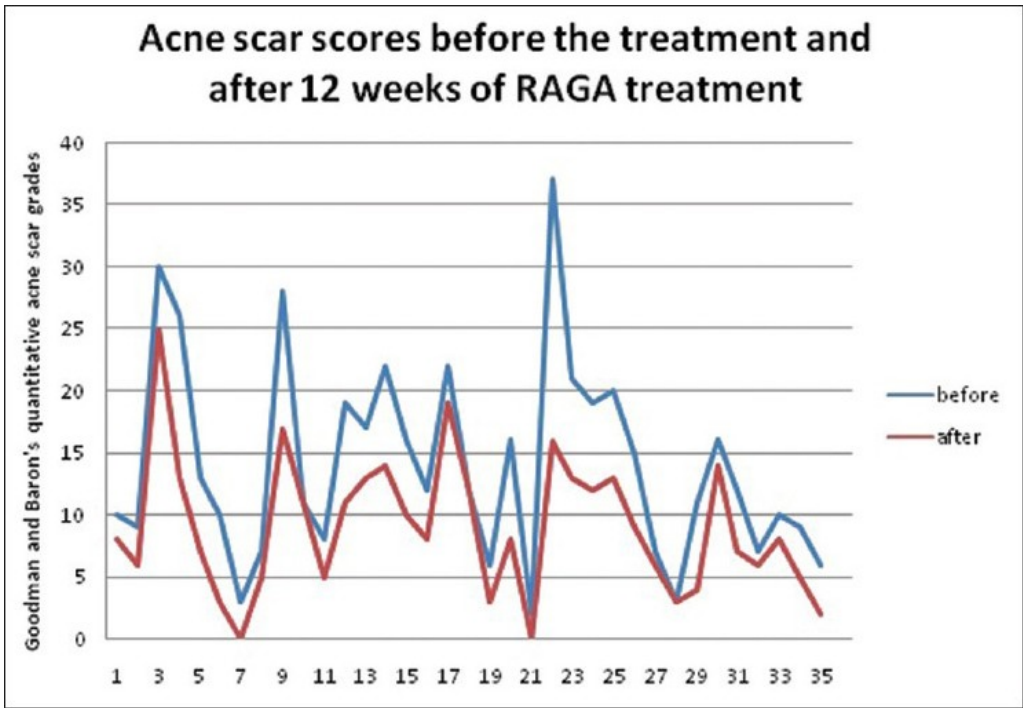

Figure 5

Line graph depicting the acne scar grades before starting retinoic acid and glycolic acid (RAGA) treatment (blue) and after 12 weeks of RAGA treatment (red)

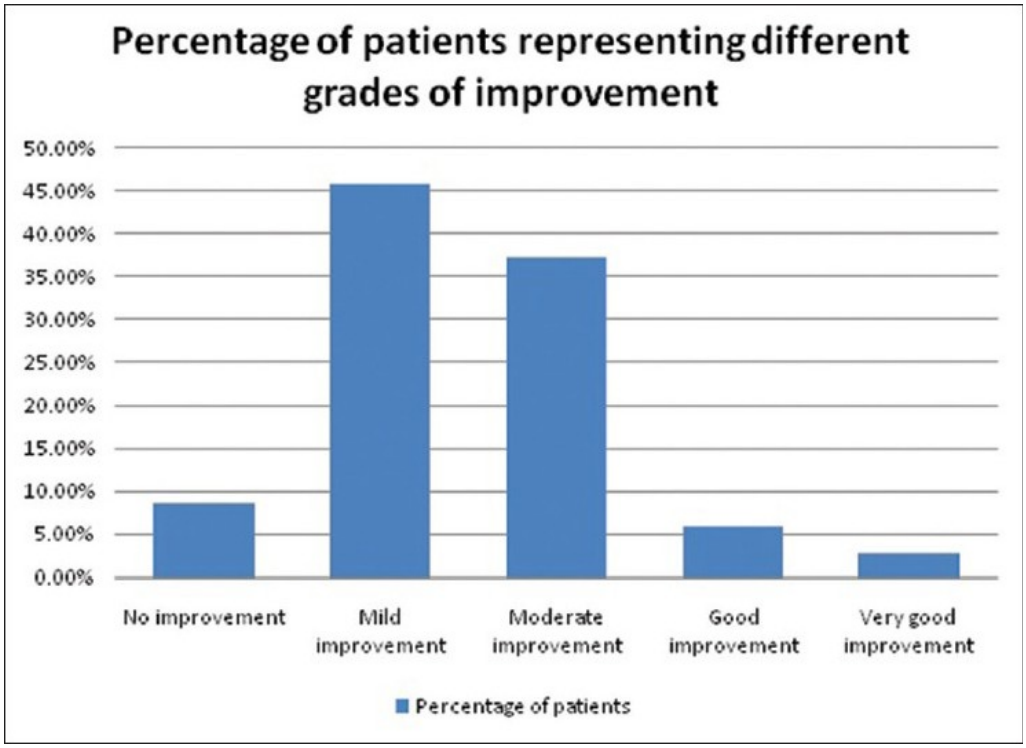

Figure 6

Bar graph representing the number of patients with different improvement grades on taking retinoic acid and glycolic acid treatment on acne scars

Among macular pigmentary lesions, 20 patients showed a 3-point reduction in macular lesions [Figure 7a and 7b], while eight of them had a reduction of 2 points and 2 patients showed a reduction of 1 point. Overall 85.71% of the patients had an improvement in the appearance of their pigmented macules. The improvement is depicted in Figure 8 and Table 3. None of the patients complained of erythema or burning.

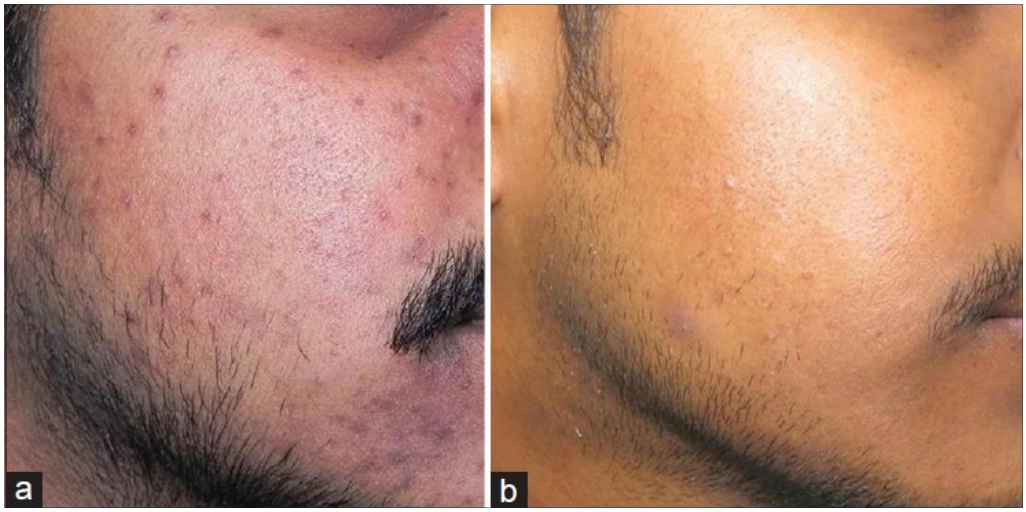

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Figure 7

(a) Picture showing postinflammatory hyperpigmentation as a sequelae to acne before starting retinoic acid and glycolic acid treatment (b) Photograph showing 3 points improvement in postinflammatory hyperpigmentation

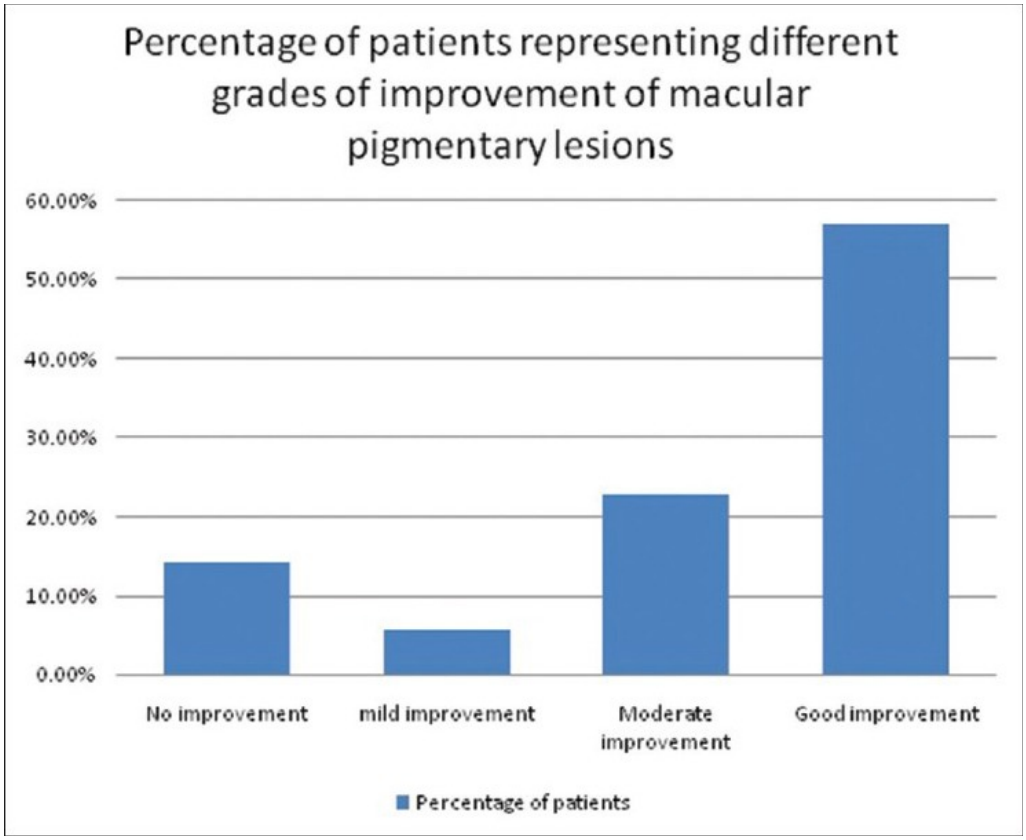

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Figure 8

Graphical representation of the percentage of patients with different grades of improvement of macular pigmentary lesions

DISCUSSION

Go to:

On an average 80-90% of people with acne scars have atrophic scars associated with a loss of collagen compared to a minority who show hypertrophic scars and keloids.[2] Scars originate at the site of tissue injury (during healing of active acne) and the wound healing process progresses through three stages: (1) inflammation; (2) granulation and tissue formation; and (3) matrix remodeling.

1. During inflammation, vasoconstriction for homeostasis results in blanching. After the blood flow has been stopped, vasodilatation and resultant erythema replace vasoconstriction. Melanogenesis

may also be stimulated. This step plays an important role in the development of postacne erythema and hyperpigmentation.

2. During granulation and tissue formation stage the damaged tissues are repaired and new capillaries are formed. New production of collagen by fibroblasts begins approximately 3-5 days after the wound is created.
3. The matrix remodeling stage is associated with production of enzymes, by fibroblasts and keratinocytes, that determine the architecture of the extracellular matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs. This results in an imbalance in the ratio of MMPs to tissue inhibitors of MMPs leading to the development of atrophic or hypertrophic scars. Inadequate response results in diminished deposition of collagen and formation of an atrophic scar while, if the healing response is exuberant, a raised nodule of fibrotic tissue forms hypertrophic scars.[2,10]

Topical retinoids such as tretinoin have been shown to decrease the synthesis of MMPs and increase dermal procollagen and collagen synthesis and hence may provide some benefits in preventing scar development and potentially reduce the extent of scar formation that is in progress.[10,11] Schmidt *et al*. in their study showed that tretinoin-iontophoresis significantly decreased the depth of atrophic scars in 94% of the study subjects.[3]

Topical retinoids improve several features of photoaging that include dispigmentation and wrinkling (fine and coarse). The clinical improvement is accompanied by the reversal of epidermal atrophy and dysplasia along with increased collagen synthesis.[10] This is supported by the study conducted by Schwartz *et al*. which stated that retinoic acid stimulates collagen synthesis *in vivo*.[11]

Glycolic acid is a naturally occurring alpha-hydroxy acid and has been well-established in dermatological practice for its cosmetic benefits when used on skin. The mechanism of its effect might be due to epidermal remodeling and accelerated desquamation, which would result in quick pigment dispersion on pigmentary lesions. It also directly reduces melanin formation in melanocytes by tyrosinase inhibition.[12,13]

Erbağci and Akçali in their study titled “biweekly serial GA peels versus long term daily use of topical low-strength GA in the treatment of atrophic acne scars” showed that long term daily use of GA is effective on scars and may be recommended for patients who cannot tolerate the peeling procedure.[14]

Studies conducted by Dreno *et al*. showed that RALGA combination can efficiently treat acne scars and PIH.[8] However, the combination of RAGA had not yet been studied. Both RA and GA play an active role in scar remodeling, their combination can work synergistically in enhancing and hastening improvement in acne scars.

In our study, we noticed that 91.4% showed improvement in their acne scars and of these 85.71% of patients showed a definite reduction in PIH. All the patients were previously treated for active acne and perhaps the scar formation was still in the early stages. The improvement in the acne scars might be attributed to the increased MMPs and collagen synthesis brought about by retinoic acid and epidermal remodeling and pigment dispersion brought about by GA in the RAGA combination. None of the patients complained of erythema.

Limitations

This retrospective assessment was conducted in a small sample size of patients and there was no interaction with the patients during this assessment. A prospective study of the same with a larger study group is intended in the future.

Go to:

CONCLUSION

This study shows that the RAGA combination can be considered as a topical treatment for early acne scars including PIH, thereby minimizing the need of procedural treatment for acne scars. However, more studies are required to optimize the ideal concentration of each ingredient, viability of combined formulations in a single tube, frequency of application, and duration of treatment.

Footnotes

Go to:

Source of Support: NFunded by the CUTIS Academy of Cutaneous Sciences, Bengaluru, Karnataka, India

Conflict of Interest: None declared.

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PubMed

Format: Abstract

Full text links

JDD Full-Text Article on JDDonline

J Drugs Dermatol. 2013 Oct;12(10):1149-53.

Efficacy of combination of glycolic acid peeling with topical regimen in treatment of melasma.

Chaudhary S, Dayal S.

Abstract

BACKGROUND: Various treatment modalities are available for management of melasma, ranging from topical and oral to chemical peeling, but none is promising alone. Very few studies are available regarding efficacy of combination of topical treatment with chemical peeling. Combination of chemical peeling and topical regimen can be a good treatment modality in the management of this recalcitrant disorder.

OBJECTIVE: To assess the efficacy of combination of topical regimen (2% hydroquinone, 1% hydrocortisone and 0.05% tretinoin) with serial glycolic acid peeling in the treatment of melasma in Indian patients.

METHODS: Forty Indian patients of moderate to severe epidermal variety melasma were divided into two groups of 20 each. One Group i.e. peel group received topical regimen (2% hydroquinone, 1% hydrocortisone and 0.05% tretinoin) with serial glycolic acid peeling and other group i.e. control group received topical regimen (2% hydroquinone, 1% hydrocortisone, 0.05% tretinoin).

RESULTS: There was an overall decrease in MASI from baseline in 24 weeks of therapy in both the groups (P value < 0.05). The group receiving the glycolic acid peel with topical regimen showed early and greater improvement than the group which was receiving topical regimen only.

CONCLUSION: This study concluded that combining topical regimen (2% hydroquinone, 1% hydrocortisone and 0.05% tretinoin) with serial glycolic acid peeling significantly enhances the therapeutic efficacy of glycolic acid peeling. The combination of glycolic acid peeling with the topical regimen is a highly effective, safe and promising therapeutic option in treatment of melasma.

PMID: 24085051

[Indexed for MEDLINE]

PubMed

Format: Abstract

Cutis. 2010 Sep;86(3):153-8.

Evaluation of a kojic acid, emblica extract, and glycolic acid formulation compared with hydroquinone 4% for skin lightening.

Draelos ZD[1], Yatskayer M, Bhushan P, Pillai S, Oresajo C.

Author information

Abstract

Hydroquinone has been the standard prescription agent for skin lightening; however, its use recently has become controversial. Hydroquinone is banned in Europe and parts of Asia because of potential long-term consequences, including carcinogenesis when orally consumed. These concerns have stimulated research to develop alternative skin lightening agents with efficacy comparable to hydroquinone but with a better safety profile. This double-blind study examined the skin lightening ability of a topical formulation containing kojic acid, emblica extract, and glycolic acid compared with prescription generic hydroquinone cream 4%. Eighty multiethnic participants with mild to moderate facial dyschromia were randomly assigned to use the study product or hydroquinone 4% twice daily for 12 weeks to evaluate product efficacy, tolerability, and safety using investigator assessment, participant assessment, and dermospectrophotometry. Study results demonstrated efficacy parity between the study product and hydroquinone 4%. Thus this novel skin lightening preparation is an alternative to hydroquinone 4% for participants with mild to moderate facial dyschromia.

PMID: 21049734

[Indexed for MEDLINE]

Publication types, MeSH terms, Substances

LinkOut - more resources

Dermatologic Surgery. 22 (5):435–437, MAY 1996
DOI: 10.1111/j.1524-4725.1996.tb00343.x
, PMID: 8634805
Issn Print: 1076-0512
Publication Date: 1996/05/01

Photoprotective and Antiinflammatory Effects of Topical Glycolic Acid

NICHOLAS V. PERRICONE; JOSEPH C. DiNARDO

+ Author Information

Abstract

BACKGROUND
Concerns about photosensitizing potential of alpha hydroxy acids have been expressed. A previous study, however, reported topical glycolic acid showing the opposite potential, that is, photoprotective. This study was designed to test the antiinflammatory and photoprotective capabilities of glycolic acid.

OBJECTIVE

The effects of short-wave ultraviolet light (UVB) on skin treated with glycolic acid were evaluated in two different studies at two different locations.

METHODS

In the first study the antiinflammatory potential of topical glycolic acid was tested on erythematous templates on the backs of human volunteers. Erythema was induced by exposure to three times the minimum erythema dose (MED) of UVB. Glycolic acid cream in an oil-in-water vehicle at 12% partially neutralized with ammonium hydroxide to a pH of 4.2 was applied to the template beginning 4 hours post irradiation four times a day. A second template on the same subject was used as a vehicle control. After 48 hours a marked reduction of erythema was noted when compared with the vehicle control site. In the second study, four test sites were exposed to UVB light in the following manner. Site 1 was a nontreated control site and was used to establish the MED for the subjects being tested; site 2 was also exposed to a MED series but was treated 24 hours postirradiation for 7 days with two glycolic acid–based products (cleanser and oil-free moisture lotion, both containing 8.0% glycolic acid at a pH of 3.25); site 3 was treated first with the two glycolic acid–based formulas for 3 weeks prior to being exposed to UVB light; and site 4 was treated as outlined in site 3, with the inclusion that the site was chemically peeled for 6 minutes (with a 50% glycolic solution at a pH of 2.75) 15 minutes prior to UVB exposure.

RESULTS

When UVB-burned skin was treated with glycolic acid daily for 7 days (site 2), a 16% reduction in irritation was observed compared to nontreated skin (site 1), implying that skin healed sooner when treated with glycolic acid. When a comparison of nontreated skin was made to skin treated with glycolic acid for 3 weeks prior to UVB exposure (site 1 vs site 3), a sun protection factor (SPF) of 2.4 was achieved. When a comparison of skin treated for 3 weeks was made to skin treated for 3 weeks and chemically peeled (site 3 vs site 4) the data implied that the chemical peel reduced the SPF value of skin treated with glycolic by approximately 50%, however, an SPF

trend of 1.7 was still obtained when compared with untreated skin.

CONCLUSIONS

The studies demonstrated that topical glycolic acid provides a photoprotective effect to pretreated skin yielding an SPF of approximately 2.4. In addition, when glycolic acid is applied to irradiated skin, it accelerates resolution of erythema. The data obtained from both studies support the hypothesis that glycolic acids acts as an antioxidant.

Article

June 1996

Topical 8% Glycolic Acid and 8% L-Lactic Acid Creams for the Treatment of Photodamaged Skin

A Double-blind Vehicle-Controlled Clinical Trial

Matthew J. Stiller, MD; John Bartolone, PhD; Robert Stern, MD; et al

Arch Dermatol. 1996;132(6):631-636. doi:10.1001/archderm.1996.03890300047009

Abstract

Objective: To evaluate the efficacy and tolerability of 2 widely used topical α-hydroxy acids at low concentrations, 8% glycolic acid and 8% lactic (L-isoform) acid creams, in the treatment of photodamaged skin.

Design: A single-center, 22-week, double-blind, vehicle-controlled, randomized clinical trial assessed the overall severity of photodamage on the faces and forearms of volunteers, based on 7 individual clinical components of cutaneous photodamage.

Setting: The study was performed in an outpatient clinical research unit at the Massachusetts General Hospital, Boston.

Patients: Seventy-four women, aged 40 to 70 years, with moderately severe photodamaged facial skin were enrolled in the study. One subject withdrew from the study early because of skin irritation, and 6 subjects withdrew from the study for personal reasons.

Interventions: Glycolic acid, L-lactic acid, or vehicle creams were applied twice daily to the face and outer aspect of the forearms.

Main Outcome Measures: Improvement in α-hydroxy acid—treated photodamaged skin as determined by patient self-assessments and physician evaluations of efficacy and irritancy.

Results: The percentage of patients using either 8% glycolic acid or 8% L-lactic acid creams on the face achieving at least 1 grade of improvement (using a scale from 0 through 9) in overall severity of photodamage was significantly greater than with the vehicle cream (76% glycolic acid, 71% lactic acid, and 40% vehicle; $P<.05$). On the forearms, after 22 weeks, treatment with glycolic acid cream was superior to the vehicle in improving the overall severity of photodamage and sallowness ($P<.05$). L-Lactic acid cream was significantly superior to the vehicle in reducing the overall severity of photodamage ($P<.05$), mottled hyperpigmentation ($P<.05$), sallowness ($P<.05$), and roughness on the forearms ($P<.05$) at week 22.

Conclusions: Topical 8% glycolic acid and 8% L-lactic acid creams are modestly useful in ameliorating some of the signs of chronic cutaneous photodamage. These agents are well tolerated and available without prescription.(Arch Dermatol 1996;132:631-636)

Full Text

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Effects of glycolic acid on light-induced skin pigmentation in Asian and Caucasian subjects☆

Tsen-Fang Tsai, MD[a, b], Paul H. Bowman, MD[b], Shiou-Hwa Jee, MD[a], Howard I. Maibach, MD[b]
Taipei, Taiwan, and San Francisco, California
From the Department of Dermatology, National Taiwan University Hospital, Taipei,[a] and the Department of Dermatology, University of California, San Francisco.[b]

DOI: https://doi.org/10.1067/mjd.2000.104894

Abstract

Background: Topical use of α-hydroxy acid (AHA) may increase skin photosensitivity, as demonstrated by increased numbers of sunburst cells. However, effects of AHA on tanning have not been studied. **Objective:** Our purpose was to study whether short-term use of glycolic acid hastens resolution of pre-existing light-induced pigmentation and whether the skin becomes tan more easily in Asian and Caucasian subjects after such treatment. **Methods:** Six Asian and six Caucasian volunteers received separate irradiations of UVB and UVA to both sides of the lower back. In a double-blind fashion, patients then applied a 10% glycolic acid gel, pH 3.52, to one side of the back, including the irradiated area, and the contralateral extensor forearms once daily for 7 days and then twice daily for 2 weeks. A placebo gel, pH 5.75, was applied to the opposite sides. The subjects returned for measurement of residual tanning with a colorimeter and received additional irradiation to forearms and a second site on the back. Resulting pigmentation was measured immediately after irradiation, at 2 hours, and at 1 week. **Results:** Increased UVB-induced skin tanning occurred on the forearm and the lower back in both races in areas pretreated with glycolic acid. UVA also caused increased tanning, but only on the extensor forearms in Asian subjects. Treatment with glycolic acid for 3 weeks had no effect on pre-existing light-induced pigmentation. **Conclusion:** Short-term topical treatment of glycolic acid caused an increase in UVB tanning as well as in UVA tanning in some subjects, even in the absence of overt irritation. The inclusion of UVB, and even UVA, sunscreen in AHA products may be warranted. (J Am Acad Dermatol 2000;43:238-43.)

Exhibit D
Enclosed Data

Units Sold	Adverse Reactions Reported	Formula
336	0	GLYCOLIC ACID 10% / HYDROQUINONE 6% / TRETINOIN 0.1%

APPENDIX SECTION C

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: September 29, 2016

FROM: Ben Zhang PhD
ORISE Fellow, Office of New Drug Products, Office of Pharmaceutical Quality

Jianyong Wang, PhD
Pharmacology/Toxicology Reviewer, Division of Dermatology and Dental Products, Office of Drug Evaluation III

Doanh Tran, PhD
Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3, Office of Clinical Pharmacology

Jane Liedtka, MD
Clinical Reviewer, Division of Dermatology and Dental Products, Office of Drug Evaluation III

Hon-Sum Ko, MD
Clinical Reviewer, Division of Dermatology and Dental Products, Office of Drug Evaluation III

THROUGH: Ramesh K. Sood, PhD
Senior Scientific Advisor (acting), Office of New Drug Products, Office of Pharmaceutical Quality

Barbara Hill, PhD
Pharmacology/Toxicology Supervisor, Division of Dermatology and Dental Products, Office of Drug Evaluation III

Edward D. Bashaw, PharmD
Division Director, Division of Clinical Pharmacology 3, Office of Clinical Pharmacology

Kendall A. Marcus, MD
Director, Division of Dermatology and Dental Products, Office of Drug Evaluation III

Julie Beitz, MD
Director, Office of Drug Evaluation III

Frances Gail Bormel, RPh, JD
Director, Division of Prescription Drugs, Office of Unapproved Drugs and Labeling Compliance

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Glycolic Acid for Inclusion on the 503A Bulk Drug Substances List

I. INTRODUCTION

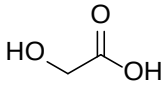
Glycolic acid, 0.08% to 70%, has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for topical use in the treatment of hyperpigmentation and photodamaged skin. It was also nominated for subcutaneous injection and topical use as an anesthetic and in the treatment of keratosis and warts. This review will focus only on topical use in hyperpigmented and photodamaged skin because adequate support was not provided for the other nominated uses.

We have reviewed available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. For the reasons discussed below, we believe the evaluation criteria ***weigh in favor*** of placing glycolic acid, 0.08% to 70%, for topical use on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act (503A Bulks List).[1]

II. EVALUATION CRITERIA

A. Is the substance well characterized, physically and chemically, such that it is appropriate for use in compounding?

Glycolic acid, also known as hydroxyacetic acid, is a small organic molecule with the following molecular structure:



This substance is currently marketed in cosmetics in various dosage forms, including creams, pads, and lotions.

Databases searched for information on glycolic acid in regard to Section II.A of this review included PubMed, SciFinder, Analytical Profiles of Drug Substances, the European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and US Pharmacopeia/National Formulary.

[1] Inclusion on the list of bulk drug subtances that can be used to compound drug products in accordance with section 503A of the FD&C Act (503A Bulks List) should not, in any way, be equated with or considered an FDA approval, endorsement, or recommendation of any drug compounded using the substance. Nor should it be assumed that a drug compounded using a substance included on the list has been proven to be safe and effective under the standards required to receive Agency approval. Any person who represents that a compounded drug made with a bulk drug substance that appears on the 503A Bulks List is FDA approved, or otherwise endorsed by FDA generally or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the FD&C Act (21 U.S.C. 352(a), (bb)).

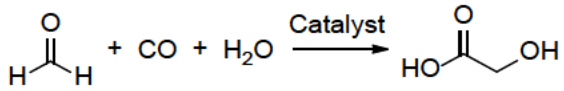
1. Stability of the API and likely dosage forms

No stability issues have been reported for glycolic acid in the literature. It is very likely to be stable either as a solid or in aqueous solutions, especially at low pH values, since glycolic acid is usually self-preserving (Villiers et al., 1997). Therefore, this compound is very likely to be stable under ordinary storage conditions in the proposed dosage forms, such as lotions and gels.

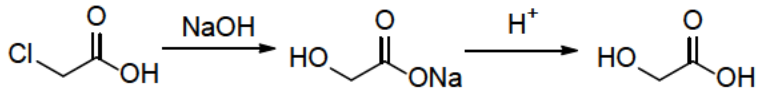
2. Probable routes of API synthesis

There have been various synthetic routes to prepare glycolic acid. The two methods most commonly used are shown below.

Route 1: Industrial synthesis of glycolic acid in the United States is based on the reaction between formaldehyde with carbon monoxide and water in the presence of catalyst at > 30 MPa (John 1939).



Route 2: Glycolic acid is also produced in large quantities by treating monochloroacetic acid with sodium hydroxide (or other bases) followed by acidification (Witzemann 1917; Ebmeyer et al., 1998). This method usually results in products with higher purity compared with route 1, described above.



3. Likely impurities

Likely impurities may include:

- Residual starting materials, such as formaldehyde in route 1 and monochloroacetic acid in route 2
- Residual catalysts or reagents used in the reaction
- Side products, byproducts or reaction intermediate from the reaction, such as sodium chloride in route 2 or formic acid and methoxyacetic acid in route 1

4. Toxicity of those likely impurities

Formaldehyde and formic acid from synthetic route 1 and monochloroacetic acid from route 2 can have toxicities depending on the exposure level. Further toxicity issues are discussed in section B.

5. Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism

Glycolic acid is a colorless crystalline solid that is highly soluble in water. No further information on the influence of particle size and polymorphism on bioavailability was found in the literature.

6. Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize

Glycolic acid is easily characterized with proton nuclear magnetic resonance (^{1}H NMR) spectroscopy, Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy, Fourier transform infrared spectroscopy (FT-IR), and mass spectrometry (MS).

Conclusions: Glycolic acid is a well-characterized small molecule, and it is likely to be stable under ordinary storage conditions. It is easily characterized with various analytical techniques, and the preparation of glycolic acid has been well developed. Based on the available information, there are no concerns about the physical and chemical characterization of glycolic acid as a bulk drug substance that can be used for compounding under section 503A of the FD&C Act, when potential impurities in the drug substance, such as formaldehyde, are controlled at acceptable levels.

B. Are there concerns about the safety of the substance for use in compounding?

1. Nonclinical Assessment

The following public database(s) were consulted in the preparation of this review: PubMed, TOXNET, and Google/Google Scholar.

a. Pharmacology of the drug substance and its likely impurities (see II.A.3 above)

Glycolic acid, an alpha-hydroxyl acid (AHA), has been widely used in cosmetic and skin care products. In low concentrations (4 to 10%), it has been used to ameliorate the appearance of skin aging. In higher concentrations (> 20%), it has been used as a chemical peel in conditions such as calluses, keratoses, acne, psoriasis, and photoaging (Kornhauser et al., 2010). Glycolic acid is believed to facilitate progressive weakening of cohesion of the intercellular material of the stratum corneum, resulting in uniform exfoliation of its outermost layers (the stratum disjunctum). A study in human volunteers with a 4% glycolic acid formulation indicated that the mechanism of action of glycolic acid on the stratum corneum appears to be a targeted desmosomal action (restricted to the stratum disjunctum) without disrupting the barrier structures of the stratum corneum (Fartasch et al., 1997).

Wang (1999) proposed the following theory for the mechanism of action of AHAs: AHAs reduce the calcium ion concentration in the epidermis and remove calcium ions from the cell adhesions by chelation. This causes a loss of calcium ions from the cadherins of the desmosomes and adherens junctions, from the tight junctions, and possibly also from other divalent metallic cation-dependent cell adhesion molecules. The cell adhesions are thereby disrupted, resulting in desquamation.

In a study using human skin biopsy specimens, epidermal and dermal hyaluronic acid content and collagen gene expression were all increased in glycolic acid-treated skin as compared to vehicle-treated controls (Bernstein et al., 2001). Another study conducted by Olkano et al. (2003) showed that glycolic acid not only directly accelerated collagen synthesis by fibroblasts, but that it also modulated matrix degradation and collagen synthesis through keratinocyte-

released cytokines. Usuki et al. (2003) showed that glycolic acid directly suppressed melanin formation in melanocytes by inhibiting tyrosinase activity.

b. Safety pharmacology

The effect of 0.35 to 0.8 mmol/kg glycolic acid on cyclopropane/epinephrine-induced cardiac arrhythmias was examined in dogs (White and Stutzman, 1950). Intravenous doses of 0.35 to 0.5 mmol/kg glycolic acid increased the duration of arrhythmias whereas doses > 0.5 mmol/kg decreased or totally eliminated the arrhythmias. Central nervous system depression was observed at higher doses. Glycolic acid, 1000 mg/kg given intraperitoneally, was a potent inhibitor of oxygen consumption and glucose metabolism in rat liver and myocardium in vivo, but it did not have an effect on brain oxygen consumption (Lamothe et al., 1971).

c. Acute toxicity

The oral LD_{50} of glycolic acid was 1950 and 1920 mg/kg in rats and guinea pigs, respectively (Smyth et al., 1941). The oral LD_{50} of glycolic acid was 2000 mg/kg in mice (Perier et al., 1988). The inhalation LC_{50} of glycolic acid in rats was 7.1 mg/L/4h (Kennedy and Burgess, 1997).

Single topical doses of 50% and 70% glycolic acid were applied to a 2 cm x 2 cm area of the back of two minipigs for 15 min (Moy et al., 1996). Epidermal and dermal necrosis was induced by 70% glycolic acid after 1 day. Some inflammatory infiltrate and dermal growth were observed with 50% and 70% glycolic acid after 7 and 21 days, respectively.

Glycolic acid in high concentrations (70% technical grade solution and pure) causes local effects that are typical of a strong acid, such as dermal and eye irritation. Skin contact may cause severe skin irritation with discomfort or rash. Prolonged exposure may cause skin burns or ulceration. Eye contact may cause eye corrosion with corneal or conjunctival ulceration. Permanent eye damage, even blindness, can occur (Material Safety Data Sheet (MSDS) from ScienceLab.com, 2013).

In a modified Draize test (species and number of animals not stated) in which 3% glycolic acid was used for the intradermal injection challenge and 60% glycolic acid was used for the topical application challenge, glycolic acid was not shown to be a sensitizer (Cosmetic Ingredient Review Expert Panel (CIREP), 1998).

d. Repeat dose toxicity

Topical doses of 3 mg/cm^2 of 0 (control: Vaseline), 5% or 10% glycolic acid (pH 3.0) were administered to two prewashed 5 cm x 8 cm areas on the back of hairless guinea pigs once daily for 3 weeks. Some erythema and/or flaking of the skin were noted in the two dose groups. At microscopic examination, treated skin had a thickening of the epidermis after treatment with 5% or 10% glycolic acid. Up to a 4-fold increase in viable epidermal thickness was observed for the glycolic acid-treated skin as compared to the Vaseline-treated or untreated skin. Although these

epidermal changes were observed in glycolic acid-treated skin, the barrier integrity of glycolic acid- and control-treated skin was not significantly different (CIREP 1998).

Groups of 10 male Wistar rats were fed a basal diet or the basal diet with 3% glycolic acid for 4 weeks to examine the effects of glycolic acid on calculi formation (Chow et al., 1978). The addition of glycolic acid to a basal diet resulted in decreased body weight gain and increased water intake. Glycolic acid was a potent calculi inducer, with deposits being observed in the ureters, urinary bladder, renal tubules, and/or renal pelvis, and papilla of all 10 rats.

Oral doses of 97 and 194 mg/kg/day glycolic acid were given to cats for 7 to 48 and 28 to 59 days, respectively (Krop and Gold 1944). In the low-dose group, signs of toxicity appeared after 7 to 20 days of dosing: urinary and blood changes were observed, and 4 of the 6 animals had weight loss (7% to 24%). In the high-dose group, signs of toxicity appeared after 4 to 17 days of dosing and weight loss ranged from 9% to 30%. One of 6 animals of the low-dose group and all 8 animals of the high-dose group died during the study.

Dogs (number and sex not specified) were given daily oral doses of 1000 mg glycolic acid for 35 days. No abnormal secretions of oxalic acid were found, and no damage to the gastrointestinal tract or kidneys was reported (CIREP 1998).

Groups of male rats were exposed by inhalation to 0 (control), 0.16, 0.51, or 1.4 mg/L glycolic acid, 6 hours/day, 5 days/week for 2 weeks (Kennedy and Burgess, 1997). The high dose was not well tolerated, with treatment being discontinued after 8 exposures, and 7 rats were terminated following labored breathing, lung noise, nasal and ocular discharge, and severe weight loss. Clinical pathology changes included decreases in serum protein, increases in both ALT and ALP, and decreases in urine volume and pH. These changes were reversible in the 3 surviving rats after a 10-day recovery period without treatment. Histopathological changes in this group included diffuse hepatocellular degeneration and thymus atrophy. One rat administered mid-dose died after 10 exposures. In animals exposed to mid-dose, clinical and microscopic pathology indicated liver and thymus damage, with clinical pathology changes being reversible. The tissues of the upper respiratory tract appeared normal at sacrifice but were not examined microscopically. The only effect seen at low dose was a very mild, diffuse hepatocellular degeneration seen in one of 10 rats examined 14 days post-exposure.

Oral (gavage) doses of 0, 150, 300 and 600 mg/kg/day glycolic acid (diluted in water) were administered to SD rats (40/sex/group). Ten animals/sex/group were designated for the evaluation of subchronic toxicity, immunotoxicity, neurotoxicity, or reproductive toxicity. In the subchronic toxicity and neurotoxicity studies, animals were treated for 13 weeks. The immunotoxicity assessment was performed by injecting sheep red blood cells (SRBC) in the tail vein of the assigned animals on day 23 and euthanizing the animals on day 29. For the evaluation of subchronic toxicity, outcomes assessed included: survival, body weight, food consumption, food efficiency, ophthalmic examination, clinical signs, organ weights, hematology, urinalysis, clinical chemistry, and histopathology. For the evaluation of neurotoxicity, outcomes assessed included a functional observational battery (FOB) and motor activity evaluations. Complete histopathological examination was performed for the control and high-dose groups; only liver, kidney, lung, and gross lesions were examined for the mid-dose

group; and no tissues were examined for the low-dose group. Two compound-related deaths occurred at high dose. Decrease in mean body weight, overall body weight gain, food consumption, and food efficiency occurred in males and females at mid-dose and high-dose. These effects were considered adverse in the high-dose group only (no further details provided). Toxicologically significant increases in blood neutrophils, urea nitrogen, phosphorous, and creatinine, and decreases in urine concentration were noted at mid dose and high dose. Mean absolute and relative kidney weights increased in male rats administered the mid dose or high dose. Gross findings of renal pelvis dilation, microscopic findings of oxalate crystal nephrosis and unilateral hydronephrosis, and hyperplasia of the transitional epithelium of the renal pelvis (considered secondary to irritation) were also observed (in males only) at these dose levels. No organ weight, gross or microscopic findings indicative of systemic toxicity were observed in female rats administered mid-dose or high-dose. Finally, microscopic findings (not specified) were observed in the respiratory tract (upper airways and lungs) of all treated animals and were thought to be a result of irritation from aspiration of glycolic acid following exposure via gavage. The immune response of the treated animals was not apparently affected by the treatment. The neurotoxicity study did not reveal any treatment-related neurobehavioral or neuropathological effects. The no-observed-adverse-effect level (NOAEL) for subchronic toxicity was identified as 150 mg/kg/day in this study. The NOAEL for immunotoxicity or neurotoxicity was identified as 600 mg/kg/day, the highest dose tested in this study (Non-human toxicity experts for glycolic acid/HSDB/TOXNET and CalEPA, 2001). For reproductive toxicity findings, see section II.B.1.f.

Albino rats were fed 0.5%, 1%, and 2% glycolic acid for ~200 to 250 days in a 1943 General Foods Corporation study. Decreased growth weight, an increase in renal oxalate, and nephrotoxic effects were observed in male rats fed 1% or 2% glycolic acid. No effects were observed in female rats or in male rats fed 0.5% glycolic acid. Mortality was 60% and 70% for the 1% and 2% dose groups, respectively, with deaths beginning at day 89 (CIREP 1998).

e. Mutagenicity

An Ames test was conducted with 20% glycolic acid, using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, with and without metabolic activation. Doses of 10 to 5000 µg/plate were tested in the main assay. The pH of the test article was 4.0. No positive responses were observed with or without metabolic activation in any of the test strains, and no precipitate or appreciable toxicity was observed. Glycolic acid was not mutagenic in this Ames test (CIREP 1998).

Another Ames test was conducted with 70% glycolic acid, using *S. typhimurium* strains TA97a, TA98, TA100, TA1535, and *E. coli* strain WP2 *uvr*A, with and without metabolic activation. Doses of 1 to 5000 µg/plate were tested in this study. Glycolic acid was negative for mutagenicity in this Ames test (CalEPA 2001).

A mouse lymphoma assay was conducted with 70% glycolic acid, using L5178Y $TK^{+/-}$ Mouse Lymphoma cell line, with and without metabolic activation. Doses of 39.3 to 5000 µg/mL were tested in the initial assay and doses of 250 to 5000 µg/mL were tested in the confirmatory assay. An increase in mutant frequency (> 2-fold of the control value) was evident for the activated

samples at doses > 2500 mg/mL. However, because the dose level was in excess of the treatment concentration limit of 10 mM, such increase is not considered to be a positive response (CalEPA 2001).

A chromosome aberration assay using CHO-K1 cells was conducted with 20% glycolic acid, with and without metabolic activation. The doses tested in the main assay were 625 to 5000 µg/mL. Test article pH was adjusted to ~ 6.5. At the highest dose, 5000 µg/mL, toxicity (mitotic inhibition) was approximately 10% and 43% with and without metabolic activation, respectively. The percentage of cells with structural aberrations in the test groups, both with and without metabolic activation, were not significantly increased as compared to the solvent control. Glycolic acid was negative for clastogenicity in this assay (CIREP 1998).

In a mouse bone marrow micronucleus assay, 5 CD-1 mice/sex/time point were dosed orally by gavage with 0, 1200 (males), or 1600 (females) mg/kg glycolic acid (70% solution) and euthanized at 24 and 48 hours after dosing. In addition, 5 mice/dose were dosed with 300 or 600 (males) mg/kg, or 400 or 800 (females) mg/kg glycolic acid and euthanized at 24 hours after dosing. To ensure that 5 animals/sex/dose were available for analysis, 5 additional males were dosed with 1200 mg/kg and 3 additional females with 1600 mg/kg glycolic acid because 5 males administered high doses and 3 females administered high doses died over the course of the study. Clinical signs included lethargy, moribundity, and abnormal gait. Bone marrow samples from the femur were examined and the percentage of polychromatic erythrocytes (PCE) with a micronucleus and the ratio of PCE to normochromatic erythrocytes were determined. No treatment-related increase in the number of micronucleated PCEs was noted. Glycolic acid was negative for clastogenicity in this assay (CalEPA 2001).

f. Developmental and reproductive toxicity

Oral (gavage) doses of 0, 150, 300 and 600 mg/kg/day glycolic acid (diluted in water) were administered to SD rats (10/sex/group) for 13 weeks. Animals were allowed to mate within their treatment group starting on day 97. It is not clear if the animals were exposed to glycolic acid during the reproductive portion of the study. There were significant decreases in body weights among parental females in the mid-dose and high-dose groups during gestation and in the females administered high-dose on day zero of lactation. The only parameter in which statistical significance was demonstrated was the smaller litter size of the high-dose group. However, the mean value was within the historical control range and thus was considered to be of minimal consequence. The NOAEL for reproductive and developmental toxicity was 600 mg/kg/day under the study conditions (Non-human toxicity experts for glycolic acid/HSDB/TOXNET and CalEPA 2001).

In a pilot developmental toxicity study in female Crl:CD BR rats, oral gavage doses of 0, 125, 250, 500, and 1000 mg/kg/day glycolic acid were administered to rats (8/group) on gestation days 7 to 21. Surviving dams were sacrificed on day 22 and the fetuses were examined. Maternal toxicity was observed at doses of 500 and 1000 mg/kg/day. Wet chin and lung noise were noted in females of the 500 mg/kg/day group. Abnormal gait and mobility, lung noise, salivation, and stained and wet haircoats were observed for dams given high dose. Maternal body weights for animals of this dose group were significantly reduced (88% of control) on day

22. One moribund high-dose female was terminated early. Ulcerations of the gastric mucosa, distended intestine, and mottled kidneys were observed at necropsy. Fetuses of the 500 mg/kg/day group had significantly decreased mean fetal weight, and the incidence of retarded sternebral ossification was increased. Fetuses of the 1000 mg/kg/day group had significantly decreased mean fetal body weight, and the incidence of early resorptions, specific malformations [gastroschisis, hydrocephaly, fused ribs, fused vertebra(e), and hemivertebra(e)], and specific variations [misaligned sternebra(e) and retarded vertebral and sternebral ossification] were significantly increased. The maternal and developmental NOAEL was 250 mg/kg/day in this study (CIREP 1998).

Oral (gavage) doses of 0, 75, 150, 300, and 600 mg/kg/day glycolic acid were administered to female Crl:CD BR rats (25/group) during gestation days 7 to 21. The dams were euthanized on day 22, and the fetuses were weighed, sexed, and examined for external, visceral, and skeletal alterations. Clear evidence of maternal toxicity was demonstrated at 600 mg/kg/day (wheezing/lung noise, abnormal gait/staggering, lethargy). In addition, maternal body weights, weight changes, and food consumption were significantly reduced at this dose level. Marginal evidence of maternal toxicity was demonstrated at 300 mg/kg/day (wheezing/lung noise observed in two of 25 dams). There was marked evidence of developmental toxicity at 600 mg/kg/day. Mean fetal weight was significantly reduced while the incidences of skeletal (ribs, vertebra, and sternebra) malformations and variations were significantly increased. At 300 mg/kg/day, there was a slight (two affected fetuses from two litters) increase in the incidence of two skeletal malformations: fused ribs and fused vertebrae. Although these increases were not statistically significant, they were consistent with findings seen at 600 mg/kg/day and thus were considered relevant. There was no other evidence of developmental toxicity at 300 mg/kg/day nor was any developmental toxicity seen at 150 or 75 mg/kg/day. Thus, the maternal and developmental NOAEL was considered to be 150 mg/kg/day (Munley et al., 1999).

g. Carcinogenicity

Male and female Crl:SKH-1 hairless mice were topically exposed to glycolic acid (0%, 4%, or 10% cream, pH 3.5, applied at 2 mg/cm^2) with simulated solar light (SSL) radiation [0, 0.3, 0.6, or 0.9 minimal erythema dose (MED)] using a filtered 6.5 kW xenon arc light source for 40 weeks, and the mice were held an additional 12 weeks after the treatment. The addition of glycolic acid (4% or 10%) did not affect the time to tumor formation in male or female mice at either SSL dose when compared to mice receiving the control cream. Glycolic acid did not affect the photocarcinogenesis of simulated solar light in this study (National Toxicology Program (NTP) 2007).

Hong et al., (2001) also conducted a photocarcinogenicity study in SKH-1 hairless mice with glycolic acid. Female hairless mice (15/group) were irradiated for 5 days per week at a total dose of 74.85 J/cm^2 UVA and 2.44 J/cm^2 UVB for 22 weeks. Glycolic acid [30 mg in a cream base made with PEG 400 and 8000 (1:2), pH 3.0] combination was applied topically twice a week at a dose of 8 mg/cm^2 immediately after UV irradiation. In this study, glycolic acid reduced UV-induced skin tumor development. The protective effect of glycolic acid was a 20% reduction of skin tumor incidence, a 55% reduction of tumor multiplicity (average number of tumors/mouse), and a 47% decrease in the number of large tumors (larger than 2 mm). Glycolic

acid also delayed the first appearance of tumor formation by about 3 weeks. It should be noted that there were many differences between this study and the NTP study described above, which may account for the result difference. The light source was different (UV vs. SSL); the test formulation was different; the topical dose of glycolic acid was different; and there was no vehicle control group in the study conducted by Hong et al.

h. Toxicokinetics

No information found.

Conclusions: Glycolic acid in high concentrations is used as a chemical peel as it causes exfoliation of stratum disjunctum and epidermal remodeling. Glycolic acid in very high concentrations causes local effects that are typical of a strong acid, such as dermal and eye irritation. It also induces significant toxicity via inhalation (target organs: lung, liver, and thymus). However, its acute oral toxicity is considered low (LD_{50} ~2000 mg/kg). Repeat dose oral toxicity studies in rats showed that glycolic acid induced calculi formation (target organs: urinary bladder and kidney) after 4 weeks of dosing while such finding was not seen in dogs after 35 days of oral dosing of 1000 mg/kg/day glycolic acid. In a 13-week oral toxicity study in rats, renal toxicity was noted at 300 and 600 mg/kg/day (NOAEL identified as 150 mg/kg/day) while immunotoxicity or neurotoxicity was not seen at doses up to 600 mg/kg/day, the highest dose tested.

Glycolic acid was not mutagenic or clastogenic in various genotoxicity assays. It is not a skin sensitizer in nonclinical studies. It has not demonstrated photocarcinogenic potential. In oral reproductive and developmental toxicity studies in rats, it induced developmental toxicity at high maternal toxic doses. In a pivotal study in rats, the NOAEL for developmental toxicity was identified as 150 mg/kg/day. There is lack of nonclinical data for the evaluation of chronic dermal toxicity and dermal carcinogenic potential of glycolic acid.

Overall the nonclinical data of glycolic acid do not raise serious safety concerns when it is used topically at low concentrations.

2. Human Safety

The following databases were consulted in the preparation of this review: PubMed, the Cochrane Library, and EMBASE.

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for glycolic acid through December 14, 2015, and retrieved 45 cases.

The Center for Food Safety and Nutrition (CFSAN) collects reports of adverse events involving food, cosmetics, and dietary supplements in the CFSAN Adverse Event Reporting System (CAERS). A search of CAERS was conducted for adverse events associated with glycolic acid on December 30, 2015, and retrieved 19 cases.

Glycolic acid's topical application enhances photoirritation by ultraviolet light. Because of the potential to enhance sensitivity to sunburn, a CFSAN guidance for industry[2] recommends that labeling for cosmetics containing AHAs intended for topical application to the skin or mucous membranes include the following statement:

> *Sunburn Alert: This product contains an alpha hydroxy acid (AHA) that may increase your skin's sensitivity to the sun and particularly the possibility of sunburn. Use a sunscreen, wear protective clothing, and limit sun exposure while using this product and for a week afterwards.*

a. Reported adverse reactions (FAERS, CAERS, Clinical Trials and Case Reports)

Of the 45 cases retrieved from the FAERS search, none specified the use of a compounded product. Of the 43 cases that could be evaluated, 38 reported the use of commercial products and 5 did not specify the glycolic acid product used. Patient age, reported in 40 cases, ranged from 16 to 70 years. Acne was the most frequently reported indication for use, reported in 33 cases. Thirty-nine reported serious outcomes,[3] and no deaths were reported. However, the majority of cases are confounded due to the presence of ingredients like benzoyl peroxide, salicylic acid, witch hazel, and/or others in the products used, or concomitant use of other topical products.

Thirty-two of the cases reported adverse events associated with the use of Proactiv or Proactiv Plus over-the-counter (OTC) multi-product acne treatment regimens. The cases primarily reported application site reactions, events suggestive of hypersensitivity reactions, or both. The application site reactions included erythema, dryness, peeling, burns, swelling, tingling, pruritus, pain, and contact dermatitis. Symptoms suggestive of hypersensitivity reactions included generalized itching, generalized hives or rash, tongue swelling, throat tightness, inability to swallow, and difficulty breathing. Other events included seizures in a patient with a seizure history, and photopsia in a patient evaluated by an ophthalmologist and general practitioner, with no cause identified. Each case reported the use of at least one product formulated with glycolic acid, but the majority of cases reported the use of five or more products, not all of which contained glycolic acid. The other active ingredients for the products included benzoyl peroxide, salicylic acid, sulfur, and hydroquinone.

One case, published in the medical literature, reported severe painful erythema, hyperpigmentation of the face and neck, and erosions in a 34-year-old female 3 days following a chemical peel with glycolic acid 70% (Gerber et al., 2014). Subsequently, she experienced post-inflammatory hyperpigmentation and scarring that persisted 2 months later. She had received glycolic acid peels at unspecified intervals for the past several months without problems. Her skin was prepared for the peel using 8% glycolic acid, and emollients and sunscreens were used

[2] Guidance for industry: *Labeling for Cosmetics Containing Alpha Hydroxy Acids*, available online at www.fda.gov/cosmetics/GuidanceRegulatory/GuidanceDocuments/ucm090816 htm.

[3] Serious outcomes are defined as death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

after the peel. At the initial referral, it was noted that for the preceding 10 weeks, she had taken self-prescribed isotretinoin 10 mg 3 times weekly for the treatment of coarse-pored skin. She had discontinued the isotretinoin for 3 weeks before at least one of the peels.

The following is a report of a systemic reaction to a product that contained multiple components, one of which was glycolic acid.

One case reported difficulty in breathing, swollen tongue, elevated blood pressure, erythema, and involuntary movement of the extremities and jaw 15 minutes following application of a chemical peel of "Alpha-Beta Solution" to the face of a 61-year-old female. The product was reported to include salicylic acid and a combination of AHAs, including glycolic acid. She had received injections of onabotulinumtoxinA six days previously for the treatment of migraines. Concurrent medications included alendronate, aspirin, oral and vaginal estradiol, and polyethylene glycol 3350. She was allergic to dogs and cats, and reported sensitivity to foods containing tyramine. One year previously, she had received the same chemical peel without adverse effects. She was treated with oral and intravenous diphenhydramine, and was discharged after being observed in the Emergency Room. Subsequently, she had allergy testing, which was negative for onabotulinumtoxinA, positive for the histamine control, and not reported for glycolic acid.

The following describes a systemic reaction reported to FDA to a product containing glycolic acid in conjunction with concomitant oral treatment with a monoamine oxidase inhibitor. The case reported palpitations, dizziness, tongue and generalized numbness, and difficulty in breathing within 15 minutes following the use of a commercial product reported as "Wrinkles," containing an unspecified concentration of glycolic acid, in a 34-year-old female. Her blood pressure increased to 160/95 mm Hg (from a baseline of 104/72). Concurrent medications included phenelzine (Nardil), a monoamine oxidase inhibitor for 3 years for the treatment of depression, and esterified estrogens/methyltestosterone. She was allergic to mold and ragweed. She was treated with nitroglycerin and recovered in approximately 40 minutes. The reporting physician suspected a drug interaction between the phenelzine and glycolic acid.

Of the 19 cases retrieved by the CAERS search, 8 were associated with the use of Proactiv or Proactiv Plus OTC multi-product acne treatment regimens. The other 11 cases involved a variety of OTC topical products, not compounded products, containing glycolic acid. In 4 cases it was unclear whether glycolic acid was a component, and if so, at what strength. Reported application site reactions included burned skin, development of keloids, puffiness, swelling, dryness, white discoloration, peeling, intense redness, itchy eyes and facial scarring. Reported systemic complaints included palpitations, hives, throat closing, shortness of breath, panic attack and seizure.

The following paragraphs discuss some representative adverse events reported from the clinical trials of glycolic acid in the treatment of melasma, a type of hyperpigmentation.[4]

[4] The majority of clinical studies of glycolic acid use in hyperpigmentation identified in the search are in patients with melasma.

Bari et al., (2002) reported “transient adverse reactions like burning, stinging and erythema” and noted that they were seen in most of the patients after the use of 40% to 60% glycolic acid and 20% to 30% salicylic acid (split-face study) following 2 weeks of “priming” both sides with 0.1% tretinoin cream.

Erbil et al., (2007) reported that “moderate to severe epidermolysis appeared in three patients with consequent mild post-inflammatory hyperpigmentation” after a combined treatment regimen including serial glycolic acid peels, topical azelaic acid cream, and adapalene gel in the treatment of 28 subjects with recalcitrant melasma. However, complete regression of these adverse effects was achieved in the 20-week treatment period.

Garg et al., (2008) reported: “All patients developed mild cutaneous erythema and superficial desquamation. Postpeel hyperpigmentation was seen in 20% of the patients receiving glycolic acid peels only while in patients using tretinoin and hydroquinone, 14.3% and 5.5% developed this side effect, respectively. In patients receiving glycolic acid peels only, milia developed in 26.6% of patients and nodulocystic acne in 5.5%. Persistent erythema was seen in a single patient who was put on hydroquinone. None of these side effects merited the stoppage of treatment.”

Park et al., (2011) in a comparision of 1064-nm Q-switched neodymium-doped yttrium-aluminum-garnet (Nd:YAG) laser alone vs laser plus 30% glycolic acid peels reported: “The main AEs were erythema, transient burning and slight edema of the face after treatment, which were generally mild and disappeared within 3 h. Superficial desquamation was treated with emollients, and no further intervention was required.”

Sarkar et al., (2002) in a comparision of triple combination cream (TCC- hydroquinone 5%, tretinoin 0.05%, hydrocortisone acetate 1%) alone vs TCC plus 30% to 40% glycolic acid peels, reported: “The patients in the peel group experienced focal erythema and mild burning during the peels. Two patients in the peel group developed focal superficial vesiculation which left behind post-inflammatory hyperpigmentation that subsided with the regular application of betamethasone dipropionate 0.05% cream twice a day… A persistent erythema was observed in two patients in the peel group and the patients were asked to use sunscreens and topical corticosteroids.”

A similar profile of adverse events was seen in the clinical trials in which glycolic acid was used on photodamaged skin.

Goldman et al., (2010) in a comparision of Vivite (a partially neutralized glycolic acid compound with natural antioxidants) vs Cetaphil moisturizing regimen, stated: “Four subjects in the Vivite group (15.4%) reported adverse events. Of these, the most common were erythema and dryness”.

Stiller et al., (1996) studied 67 subjects with photodamaged skin comparing 8% glycolic acid vs 8% L-lactic acid vs vehicle, and reported that “only erythema differed significantly between the α-hydroxy acid creams and the vehicle. Overall, all 3 test

creams were well tolerated. Only 1 patient withdrew as a result of facial irritation owing to the 8% L-lactic acid cream. Twenty-two subjects (30%) experienced some degree of erythema at 1 or more treatment sites at 1 time. Significant increases in erythema with 8% L-lactic acid and 8% glycolic acid were observed on the forearms at week two. However, at no time did the average change in erythema for any treatment increase 1 full grade from baseline."

b. Clinical trials assessing safety

We found no clinical trials that were specifically undertaken to assess safety. Safety assessments were among the study procedures in multiple clinical trials as noted in the examples above in section II.B.2.a.

c. Pharmacokinetic data

There are no reports of human pharmacokinetic studies following topical application of glycolic acid. Jiang and Qureshi (1998) reported percutaneous absorption results following in vitro topical application of glycolic acid to human skin using a flow-through diffusion cell system. Application of 4% glycolic acid formulated at pH 2.0 for 24 hours resulted in 13.46 ± 7.44% and 12.22 ± 9.03% of the applied dose recovered in the viable skin and the receptor fluid, respectively. When the product was formulated at pH 3.8, the amount absorbed significantly reduced to 2.23 ± 1.51% and 1.42 ± 0.77% in the viable skin and the receptor fluid, respectively. When solutions containing 4 to 60% glycolic acid at their native pH values between 2.0 and 0.67 were applied for 24 hours, the fraction of dose recovered in the receptor fluid increased with the increase in strength (and corresponding decrease in pH) with more than 80% of the dose penetrated into the receptor fluid for the 60% strength solution. The authors also reported that percutaneous absorption of glycolic acid is time-dependent, with greater fraction recovered in the receptor fluid following 24 hours of application compared to 6 hours of application. The data suggest that glycolic acid can be absorbed following topical application if formulated at its low native pH. The percutaneous absorption is reduced if formulated at higher pH such as pH 3.8 and duration of contact is shortened.

d. The availability of alternative approved therapies that may be as safe or safer

- Melasma

  Fluocinolone acetonide, hydroquinone, and tretinoin Cream, 0.01%/4%/0.05% (Tri-Luma), is indicated for the short-term treatment of moderate-to-severe melasma of the face in the presence of measures for sun avoidance, including the use of sunscreens.

- Photoaging

  There are numerous topical retinoids (e.g., tretinoin and tazarotene products) approved as "an adjunctive agent for use in the mitigation (palliation) of fine facial wrinkles in patients who use comprehensive skin care and sunlight avoidance programs."

There are numerous injectable botulinum toxin type A products "indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients."

Botox Cosmetic is also "indicated for the temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients."

Procedural (non-drug) therapies such as laser, microdermabrasion, and intense pulsed light are also available for the treatment of melasma and improving the manifestations of photodamaged skin.

Conclusions:

The available data suggest that topical use of glycolic acid is mainly associated with local irritancy (e.g., burning, erythema, swelling, and less commonly, vesiculation), although serious outcomes have been reported with use of products containing glycolic acid as one of several or many ingredients, or concomitant use of other topical products. Reported adverse reactions generally appeared to be readily manageable and temporary in duration. However, some authors did report post-inflammatory hyperpigmentation and rarely, scarring. No information is available on long-term outcomes.

The reports of systemic reactions to products containing glycolic acid are also confounded by the presence of multiple other components in the products and/or the concomitant use of oral or topical agents.

The available information, including extensive clinical data accumulated since the 1990s, does not raise major safety concerns associated with the topical use of glycolic acid.

C. Are there concerns about whether a substance is effective for a particular use?

1. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

A literature search revealed 25 reports of studies involving the use of glycolic acid for the treatment of melasma and other forms of hyperpigmentation. There were no placebo controlled trials. There were 23 clinical trials, which included 14 active controlled trials: 10 involving the addition of glycolic acid peels to a regimen of topical therapy and 4 involving a comparision (split face design) of glycolic acid peels versus other products. There were an additional 3 trials involving combination products that included glycolic acid as a component and 2 open-label trials. Some of the above trials included endpoints traditionally associated with photoaging studies. In addition, there were 4 systematic reviews of treatment of melasma including a Cohcrane review from 2010 that included glycolic acid in the list of products recommended for the treatment of melasma.

Two clinical trials specifically addressed manifestations of photoaging changes: one comparing glycolic acid to lactic acid and one comparing a combination crème containing glycolic acid and antioxidants

with an emollient. The following are some representative reports from the clinical trials of glycolic acid in the treatment of melasma and post-inflammatory hyperpigmentation.

Bari et al., (2002) reported a comparison of the use of 40% to 60% glycolic acid (right side of face) to 20% to 30% salicylic acid (left side of face) following 2 weeks of "priming" both sides of the face with 0.1% tretinoin cream in 40 subjects with mixed and epidermal type of melasma. In this 12-week trial, both regimens (glycolic acid and salicylic acid) resulted in a statistically significant improvement from baseline using the Melasma Area and Severity Index (MASI), percent change in lesional area, and photos as outcome measures. In group I (pre-treated with tretinoin), the mean MASI score at baseline was 13.30 (range 3.60 to 28.20), which was reduced to 5.72 (range 1.2 to 11.70) at 12 weeks ($p<0.001$). In group II (with no pre-treatment), the respective mean MASI scores were 12.41 and 6.44 ($p< 0.001$). With regard to percent reduction in lesional area, in group I on the right half of the face (glycolic acid) the improvement was 45.7%, and on the left half (salicylic acid) it was 49.8% ($p>0.05$). In group II, the right half showed 37.1%, and the left half 43% improvement ($p>0.05$). There was no statistically significant difference between the peeling agents or the primed versus unprimed subjects.

Burns et al., (1997) reported a comparison of topical therapy with 2% hydroquinone/10% glycolic acid gel bid + 0.05% tretinoin cream qhs alone vs the same topical therapy plus 6 serial glycolic acid peels (50% to 68%) q 3 weeks in 19 African American women with post-inflammatory hyperpigmentation for a duration of 22 weeks. Evaluation was performed based on the Hyperpigmentation Area and Severity Index (HASI). The mean HASI score decreased by 50% (from 10.22 to 5.12) for the peel group and by 42% (from 8.70 to 5.00) for the control group at 22 weeks. The difference was not statistically significant.

Erbil et al., (2007) reported a prospective, randomized comparison of a combined treatment regimen including serial glycolic acid peels, topical azelaic acid cream and adapalene gel vs the topical azelaic acid cream and adapalene gel alone in the treatment of 28 subjects with recalcitrant epidermal melasma over a 20-week duration. In the chemical peel group, a percentage change of 83.08% in mean MASI scores was observed at week 20, compared with a 69.34% decrease in the control group ($p=0.001$ and $p=0.005$, respectively; Wilcoxon signed ranks test). The results were statistically significant in favor of the peel group at weeks 12 ($p=0.013$), 16 ($p=0.035$) and 20 ($p=0.048$).

Garg et al., (2008) reported a prospective, single-blind comparison of 60 subjects with melasma (any type) randomly assigned to 3 groups for a duration of 6 months:

- Group I: glycolic acid peels (20 to 45%) q 2 weeks X 6 then q 4 weeks X 3
- Group II: glycolic acid peels (20 to 45%) q 2 weeks X 6 then q 4 weeks X 3 + 0.025% tretinoin
- Group III: glycolic acid peels (20 to 45%) q 2 weeks X 6 then q 4 weeks X 3 + 2% hydroquinone

Fifty subjects completed the trial, and all 3 groups had a statistically significant response with decreased MASI of 30%, 38% and 52% for groups I, II, and III, respectively. Thus, it was concluded that the hydroquinone was the most effective priming agent, followed by the tretinoin.

Hurley et al., (2002) reported a prospective, investigator-masked, split-face comparison of 21 subjects with epidermal or mixed melasma randomly assigned to glycolic acid peels (20% to 30%) q 2 weeks to

one side of the face while both sides of the face received 4% hydroquinone cream BID for 8 weeks. Physician Global evaluation showed that 8 patients had more improvement on the peeled side, and 7 were thought to have more improvement on the non-peeled side compared with baseline photgraphs. Two patients were thought to have no difference between the two sides. Both sides showed a statistically significant improvement from baseline, but there was not a statistically significant difference between the treatments.

Park et al., (2011) reported a randomized, observer-blinded, split-face comparision of 1062-nm Q-switched Nd:YAG laser alone vs laser plus 30% glycolic acid peels q 2 weeks X 3 in 16 Korean subjects with resistant, mixed-type melasma over 6 weeks. After treatment, significant improvements from baseline were seen in Mexameter and modified Melasma Area and Severity Index (mMASI) on both sides of the face. The combined therapy side achieved an average 32.6% improvement in Mexameter readings and 37.4% improvement in mMASI, compared with 22% and 16.7%, respectively, on the side treated with laser only ($p \leq 0.05$).

The following describe some examples of clinical trials on glycolic acid in the treatment of manifestations of photodamaged skin.

Goldman et al., (2010) reported a randomized, investigator-masked comparison of Vivite Skin Care System ("partially neutralized glycolic compounds with natural antioxidants") vs. Cetaphil cleanser and moisturizer in 36 subjects with photoaging in a 60 day trial. A similar proportion of subjects in each group had a 1-point improvement on the hyperpigmentation scale (42% of Vivite subjects, 44% of Cetaphil subjects). There were no statistically significant between-group differences in investigator rating of wrinkles. Subject assessments favored the Vivite group for improvement in wrinkling and texture change.

Stiller et al., (1996) reported a randomized, double-blind, vehicle-controlled comparison of 8% glycolic acid vs. 8% L-lactic Acid (LA) vs. vehicle cream in women with moderate to severe photodamaged skin over 22 weeks (74 enrolled; 67 completed). Outcome measures included a 9-point Investigator's global assessment scale (IGA) and a similar 9-point scale for each of 7 clinical signs of photodamage (mottled hyperpigmentation, fine wrinkling, coarse wrinkling, laxity, sallowness, telangiectasia, and tactile roughness) as well as 3 signs and symptoms of irritation or intolerance to study medication (erythema, dryness, and scaling). The percentage of patients using either 8% glycolic acid or 8% LA creams on the face achieving at least 1 grade of improvement (on the IGA) in overall severity of photodamage was significantly greater than that using the vehicle cream (76% glycolic acid, 71% lactic acid, and 40% vehicle; $p<0.05$). On the forearms, treatment with glycolic acid was superior to the vehicle in improving the overall severity of photodamage and sallowness ($p<0.05$). LA was significantly superior to the vehicle in reducing the overall severity of photodamage ($p<0.05$), mottled hyperpigmentation ($p<0.05$), sallowness ($p<0.05$), and roughness on the forearms ($p<0.05$).

The table below displays results for the clinical trials described above and additional clinical trials for the use of glycolic acid in the treatment of melasma and other types of hyperpigmentation, as well as manifestations of photodamaged skin.

Table 1: Clinical Trials for the Use of Glycolic Acid

Author/ Year/Rx Duration	Arms/Design	# of Subjects per arm	Indication	Outcome measures	Results
Bari 2002 12 weeks (wks)	• Group1=tretinoin X 2 weeks pretreatment • Group 2=no pretreatment Split-face, 6 peels (q 2 wks) Right side (R)=40-60% GA Left side (L)=20-30% Salicylic Acid (SA) Prospective (P), Randomized (R)	20 20	Melasma-all types	Melasma Area and Severity Index (MASI), Lesional area, photos	Moderate to excellent response on both sides, no statistically significant (SS) differences between sides
Burns 1997 22 wks	• hydroquinone 2% (HQ) + tretinoin 0.05% (T) + GA 10% • HQ + T + GA 10% + GA peels: 6 peels (50-68% GA q 3 wks) P, R	9 10	Post-inflammatory hyperpig-mentation (PIHP) in African American subjects	Hyperpig-mentation Area + Severity Index (HASI), Chromameter, photos	Significant overall lightening in both groups, no SS differences between groups
Erbil 2007 20 wks	• Azaleic Acid 20% cream (AA) + Adapalene 0.1% gel (AG) qhs • AA + AG + GA peels (20-70% X 8 peels) P, R	12 16	Epidermal Melasma-Resistant	MASI, photos	MASI scores↓ significantly on both sides, SS difference in favor of peel group at 12-20 wks
Faghihi 2011 12 wks	• 70% GA peels • 1% tretinoin peels Split-face, 4 peels (q 2 wks) R, double-blind (DB)	63 (total)	Epidermal and mixed melasma	MASI, photos, tolerance, patient satisfaction	MASI scores↓ significantly on both sides, no SS difference
Garg 2008 6 months	• GA peels (Group I) • GA peels + tretinoin 0.025% cream (Group II) • GA peels + HQ 2% (Group III) Peels=GA 20-45% q 2 wks X 6 then q 4 wks X 3 R, single-blind (SB)	20 20 20	Melasma-all types	MASI, photos, patient assessment	MASI scores↓ significantly in all groups, Group III SS better than Group I at 6 months

Goldman 2010 60 days	• Vivite Skin care ("partially neutralized glycolic compounds with natural antioxidants") • Cetaphil R, investigator-masked (IM)	27 9	Photo-aged skin	9-point IGA, Wrinkle scale, patient ratings	No SS difference except for patient ratings
Guevara 2003 12 wks	• 4% HQ+10%GA+Vit C, E+ sunscreen • Sunscreen alone IM	20 15	Epidermal melasma	Mexameter, MASI, Patient Global Assessment (PGA), Investigator Global Assessment (IGA)	SS decrease using study cream ($p<0.0001$)
Hurley 2002 8 wks	• 4% HQ + GA peels (20-30% q 2 wks) • 4% HQ alone Split-face, P	21 (total)	Epidermal and mixed melasma in Hispanic women	MASI, linear analog scale, PGA, photos, mexameter	MASI scores↓ significantly on both sides, no SS difference
Ilknur 2010 6 months	• GA peels (20-70% q 2 wks X 12) • Amino Fruit Acid (AFA) peels (20-60% q 2 wks X 12) Split-face, R, SB	31 (total)	Epidermal melasma	MASI, photos, tolerance, patient assessment (PA)	MASI scores↓ significantly on both sides, no difference in PA
Kar 2012 12 wks	• A: Low fluence Q-switched Nd:YAG laser/wk X 12 wks • B: GA peels (35-70%) q 2 wks X 12 wks • C: High fluence Q-switched Nd:YAG laser/2 wks X 12 wks	25 25 25	Melasma – all types in Indian subjects	MASI, photos	MASI scores↓ significantly in all groups, A was SS better than B which was SS better than C
Khunger 2004 12 wks	• 1% tretinoin peel • 70% GA peel Split-face Peels q wk X 12 weeks	10 (total)	Epidermal and mixed melasma in dark-skinned women	MASI, photos, tolerance, PA	MASI scores↓ significantly on both sides, no SS difference
Kumari 2010 12 wks	• GA 20–35% peels/2 wks X $\geq$4 peels • trichloroacetic acid (TCA) 10–20% peels/2 wks X $\geq$4 peels R	20 20	Epidermal and mixed melasma in Indian women	MASI, photos, tolerance, PA	MASI scores↓ significantly in both treatment groups, no SS difference

Lawrence 1997 3 months	• 70% GA peel • Jessners peel Peels q month X 3 Split-face	16 (total)	Melasma – all types	MASI, photos, chromameter	MASI scores↓ significantly on both sides, no SS difference
Macedo 2006 7 months	• 10%GA+4% HQ plus vehicle peel • 10%GA+4% HQ plus 70% GA peel Split-face q15 d x 4 peels; 30 d rest; treatment reversal to opposite side, also q15 d x 4 peels	8 (total)	Melasma	photos	No SS
Oresajo 2008 12 wks	• Capryloyl salicylic acid peels 5–10% • GA peels 20–50% q 2 wk X 6 Split-face, R, SB	50 (total)	Facial hyper-pigmentation + fine lines	6 grade scale for both facial hyper-pigmentation + fine lines	Significant reduction of pigmentation compared to baseline on both sides, no SS difference
Park 2011 6 weeks	• Q-switched Nd:YAG laser alone • same laser + 30% GA peels q 2 wk X 3 Split-face, R, SB	16 (total)	Melasma-mixed type resistant in Korean women	Mexameter, MASI, PA	MASI scores↓ significantly in both groups; combined Rx was SS better than laser alone
Rendon 2008 12 wks	• Fluocinolone acetonide 0.01%, HQ 4%, tretinoin 0.05% + 5 GA peels (% and time between peels not described), Open label	20	Moderate to Severe Melasma	IGA, Success = clear or almost clear	65% (13/20) achieved success at wk 12 P≤0.001 vs baseline
Sarkar 2002 18 wks	• Triple-combination (TC) cream (hydrocortisone acetate 1%, HQ 5%, tretinoin 0.05%) • TC cream + GA peels (30-40% q 3 wks X 6)	20 20	Epidermal melasma in dark-skinned subjects	MASI, photos, tolerance, PA	MASI scores↓ significantly in both groups; combined Rx was SS better than TC cream alone
Seghal 2003 24 weeks	• 10% GA gel qhs + 20-50% GA peels q 3-4 weeks Open-label	50	Melasma-4 freckles-4 wrinkles-2 scars- 40	Poor, moderate, good or excellent response	Excellent response in 1, Good in 2 with epidermal melasma

Sobhi 2012 Study duration not specified	• GA 70% peel X 6 • topical nanosome vitamin C ionto-phoresis X 6 (time between sessions not described) Split-face design, SB	14 (total)	Melasma in Type IV-V skin	MASI, photos, PA	MASI scores↓ significantly in both groups; Vit C was SS better than glycolic acid peels
Stiller 1996 22 wks	• GA 8% • L-Lactic Acid 8% • vehicle R, DB, Vehicle-controlled	21 24 22	Moderate photodamage on face + forearms	9 point PGA, PA, tolerance	Significant improvement in both active arms, no SS difference between acids
Teng 1997 26 wks	• GA 10% + HQ 2% • GA 10% + HQ 2% + GA peels (20-70% q 3 wks) Split-face	10 (total)	Moderate to severe epidermal melasma in Asian women, fine wrinkling	Photos, PA, Clinician assessment, Munsell color chart	Significant improvement on both sides, no SS difference between sides
Teng 1999 12 wks	• GA 10% + HQ 2% + Kojic acid 2% • GA 10% + HQ 2% Split-face, R	40 (total)	Epidermal melasma in Chinese women	Photos, PA, Clinician assessment of % improvement	Significant improvement on both sides, no SS difference between sides
Vachiramon 2015 12 wks	• Low fluence Q-switched Nd:YAG laser q wk X 5 • Same Laser Rx + 30% GA peels Split-face, SB, R	15 (total)	Melasma in men - mixed type	Colorimeter, mMASI	mMASI ↓ 38% on combined side vs 17% on laser alone side at wk 4, but then both sides worsened (not back to baseline) at wk 8 and wk 12

Source: Reviewer's Table

2. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

Melasma, hyperpigmentation, and photodamaged skin are not serious or life-threatening diseases/conditions.

3. Whether there are any alternative approved therapies that may be as effective or more effective.

Yes, there are approved drug therapies for these conditions that have been shown to be effective. See Section II.B.2.a.

Conclusions:

There are no placebo-controlled trials for the use of glycolic acid in the treatment of melasma or other forms of hyperpigmentation. There are, however numerous active controlled trials showing consistently positive results in the treatment of epidermal melasma with glycolic acid, either as a peel or as a topical agent. There is a single vehicle-controlled clinical trial providing some evidence of effectiveness for the mitigation of manifestations of photodamaged skin.

Many of these trials combined the use of glycolic acid with that of other topical medications like retinoids and/or hydroquinone. All of the trials used adjunctive measures like sun protection with sunscreens and protective clothing. There were some clinical trials with negative results; most of these trials were small and have been criticized in the literature for using low concentrations of glycolic acid or having too short a duration of treatment.

Overall, the evidence suggests a role for glycolic acid as a second line treatment for melasma that has failed standard therapy or as an adjunctive treatment to commonly used topical medications. There is also clinical evidence that provides some support for the effectiveness of glycolic acid for the mitigation of manifestations of photodamaged skin.

D. Has the substance been used historically as a drug in compounding?

1. Length of time the substance has been used in pharmacy compounding

Glycolic acid has been used in clinical practice in the United States since at least the mid 1990s (Stiller et al., 1996).

2. The medical condition(s) it has been used to treat

Glycolic acid has been used to ameliorate the appearance of skin aging and to treat various conditions including melasma, other disorders of hyperpigmentation, calluses, keratoses, acne, and psoriasis (Rajaratnam et al., 2010).

3. How widespread its use has been

The precise extent of use cannot be determined from the available information. However, in addition to the United States, use has been reported in Brazil, Mexico, France, Singapore, Thailand, Korea, India and Turkey (Rajaratnam et al., 2010).

4. *Recognition of the substance in other countries or foreign pharmacopeias*

Glycolic acid is listed in the British and the European Pharmacopeia. It was not found in the USP-NF or the pharmacopeia of Japan.

Conclusions:

Glycolic acid has been used for a number of dermatologic conditions. The substance has been used in pharmacy compounding in the United States and in other countries for several decades. The extent of

use could not be precisely determined, but in addition to the United States, use has been reported in at least eight countries in disparate parts of the world.

III. RECOMMENDATION

We have balanced the criteria described in section II above to evaluate glycolic acid, up to 70%, for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs in favor*** of glycolic acid, up to 70%, being placed on that list for topical use based on the following:

1. Glycolic acid is well characterized in its physical and chemical properties.

2. The safety profile of glycolic acid shows that reported adverse reactions generally appeared to be local, readily manageable, and temporary in duration. The topical use of glycolic acid is mainly associated with burning, erythema, swelling and less commonly, vesiculation, although serious reactions have been reported with the use of products in which glycolic acid was one among several or many components, or concomitant use of other topical products. and some authors did report post-inflammatory hyperpigmentation and rarely, scarring. No information was available on long-term outcomes.

   The reports of systemic reactions to products containing glycolic acid were also confounded by the presence of multiple other components in the products and/or the concomitant use of oral or topical agents.

   The available information including extensive clinical data accumulated since the 1990s have not raised major safety concerns associated with the use of glycolic acid.

3. There is some evidence available from active controlled clinical trials on the effectiveness of glycolic acid for melasma. There is a single vehicle, controlled clinical trial that provides some evidence of effectiveness for the mitigation of manifestations of photodamaged skin.

4. Glycolic acid has been compounded for use in melasma, other disorders of hyperpigmentation, and photodamaged skin for several decades, and use has been reported in disparate parts of the world.

Based on this information, a balancing of the four evaluation criteria weighs in favor of glycolic acid, up to 70%, for topical use, be added to the list of bulk drug substances that can be used in compounding under 503A of the FD&C Act. Standard of care for use of higher concentrations (20% to 70%) is in-office application by a licensed health care professional.

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APPENDIX SECTION D

Summary Report

Glycolic Acid

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 2U01FD005946

Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
University of Maryland School of Pharmacy

January 2020

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REVIEW OF NOMINATION

Glycolic acid (UNII code: 0WT12SX38S) was nominated for inclusion on the 503B Bulks List by Sincerus Florida, LLC for treatment of hyperpigmentation disorders and photodamaged skin via topical creams, pads, and lotions from 0.08-70%. The reason provided for nomination to the 503B Bulks List is that the requested products are in greater strengths than the commercially available products.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of glycolic acid products in the United States (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 glycolic acid; name variations of glycolic acid 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; 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 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing glycolic acid. 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

Two databases (PubMed and Embase) were searched including any date through July 27, 2018. The search included a combination of ("glycolic acid"[TIAB] OR "hydroxyacetic acid"[TIAB]) AND (therapy[TIAB] OR therapeutics[TIAB] OR clinical[TIAB] OR pigmentation[TIAB] OR pigment[TIAB] OR hyperpigmentation[TIAB] OR "photodamaged skin"[TIAB] OR skin[TIAB] OR photodamage[TIAB] OR warts[TIAB] OR keratosis[TIAB]) AND (humans[MeSH Terms] AND English[lang]). Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to Covidence®, merged, and sorted for removal of duplicate citations.

Study selection

Articles were not excluded on the basis of study design. Articles were considered relevant based on the identification of a clinical use of glycolic acid or the implementation of glycolic acid in clinical practice. Articles were excluded if not in English, a clinical use was not identified, incorrect salt form, or if the study was not conducted in humans. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

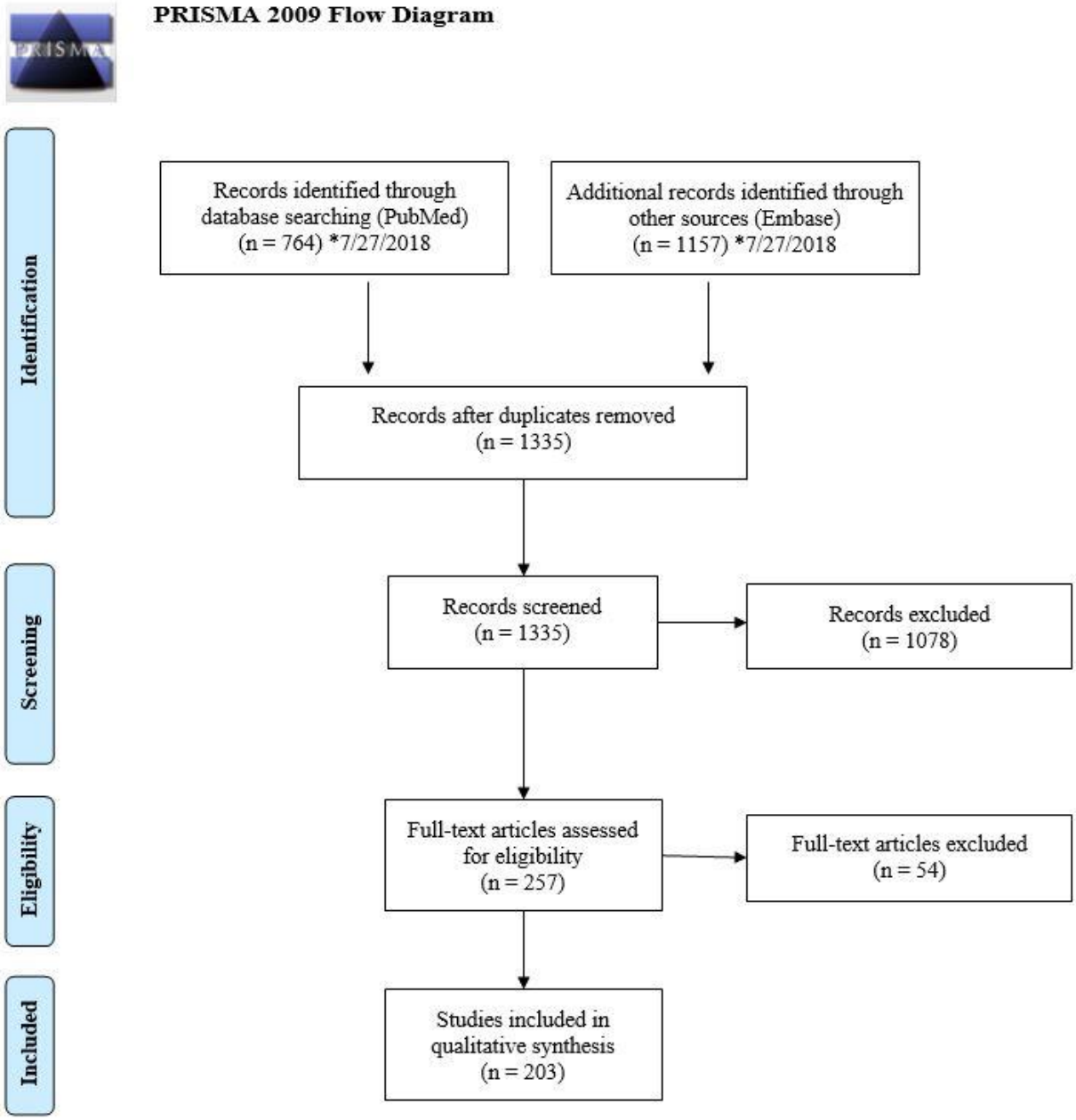
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for glycolic acid use; dose; strength; dosage form; ROA; frequency and duration of therapy; any combination therapy utilized; if applicable, formulation of compounded products; study design; and any discussion surrounding the use of glycolic acid compared to alternative therapies.

Results

Please refer to Figure 1.

Figure 1. Summary of literature screening and selection (PRISMA 2009 Flow Diagram)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Outreach to medical specialists and specialty organizations

Using the indications from the nomination and the results of the literature review, two (2) medical specialties that would potentially use glycolic acid were identified: dermatology and oncology. Semi-structured interviews were conducted with subject matter experts within these specialties. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. Three (3) experts were contacted for interviews, of which two (2) accepted and one (1) failed to respond to the interview request. The interviews were recorded and transcribed via ©Rev.com. QSR International's Nvivo 12 software was utilized for qualitative data analysis. The University of Maryland, Baltimore IRB and the Food & Drug Administration RIHSC reviewed the study and found it to be exempt. Subject matter experts provided their oral informed consent to participate in interviews.

Survey

General professional medical associations and specialty associations for dermatology and oncology, identified from the nomination, literature review, and interviews, were contacted to facilitate distribution of an online survey. A Google™ search was conducted to identify relevant professional associations within each specialty. Associations were included if their members are predominantly practitioners, national associations, and organizations focused on practice within the US. Organizations without practicing physicians and state or regional organizations were excluded. The association's website was searched in order 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 online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to five (5) associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

Participation was anonymous and voluntary. The estimated time for completion was 30 minutes with a target of 50 responses per survey. The Office of Management and Budget (OMB) approved this project.

Table 1. Participating associations

Specialty	Association
Dermatology	American Academy of Dermatology (AAD)
	American Society for Dermatologic Surgery (ASDS)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Oncology	American Society of Clinical Oncology (ASCO)	Declined, "they are unable to share survey with members"

CURRENT AND HISTORIC USE

Summary of background information

- Glycolic acid is not available as an FDA-approved product.
- Glycolic acid is available in various topical dosage forms as an OTC product in the US.
- There is no current United States Pharmacopeia (USP) monograph for glycolic acid. However, there is a current reagent monograph.
- Glycolic acid is not available in any of the foreign medicine registries searched.

Table 3. Currently approved products – US

No approved products in the US

Table 4. Currently approved products – select non-US countries and regions

No approved products in the selected non-US countries and region

Summary of literature review

- Total number of studies included: 203 studies (57 descriptive, 138 experimental, and 8 observational).
- Most of the studies were from the US (67).
- The most common indications for the use of glycolic acid in both the US and non-US countries were for skin rejuvenation, skin hyperpigmentation, and acne vulgaris/scarring.
- Compounded products were identified from both US (solution 12-70%) and non-US (10% cream, 7.15-20% gel, and 2% solution) studies.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive[1-57]	57
Experimental[58-195]	138
Observational[196-203]	8

Table 6. Number of studies by country

Country	Number of Studies
Australia[187]	1
Bangladesh[75]	1
Belgium[101,153]	2
Brazil[8,15,29,134,156,175,190,196]	8
Canada[32,42]	2
Chile[44]	1
China[201]	1
Colombia[161]	1
Egypt[21,82,127,183,194]	5
France[68,88,171,172]	4
Germany[4,25,59,60]	4
Greece[41,57,116,117]	4
Hong Kong[9]	1
India[5,26,31,37-39,49,52,64,74,77,78,93,94,97,107,114,118,129,135,157-159,162,177-180,182,186,191]	31
Iran[86,145]	2
Italy[3,12,14,22,67,108,137,138,140-142,148,155,160,164,166-170,173]	21
Japan[24,33,35,36,91,103,110-113,130,188,197,200,203]	15
Lebanon[7]	1
Malaysia[2]	1

The Netherlands[16]	1
Pakistan[58,99,198]	3
Poland[128,195]	2
Portugal[11]	1
Singapore[34,132,133]	3
South Korea[106,119,120,149]	4
Spain[47,165]	2
Switzerland[1]	1
Taiwan[192]	1
Thailand[189]	1
Turkey[56,71,84,85,104,105,174,181]	8
UK[48]	1
US[6,10,13,17-20,23,27,28,30,40,43,45,46,50,51,53-55,61-63,65,66,69,70,72,73,76,79,81,83,87,89,90,92,95,96,98,100,102,109,115,121-126,131,136,139,143,144,146,147,150-152,163,176,184,185,193,199,202]	67
Multiple Countries • Belgium, France[154] • France, Greece, Italy[80]	2
	Total US: 67 Total non-US Countries: 136

Table 7. Number of studies by combinations

No combination products were nominated

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Skin rejuvenation[6,10,20,27,30,43,45,46,54,61,62,65,70,73,81,83,87,89,95,96,100,121-123,125,139,143,144,146,147,152,176,185,199]	–	2-15%	Cleanser, cream, lotion, serum	Topical	2-30 weeks
	–	20-70%	Peeling solution, gel		1-8 treatments
Skin hyperpigmentation[10,20,30,45,50,70,72,76,79,92,98,102,109,115,131,147,150,163,193]	–	5-20%	Cream, gel, lotion	Topical	2-24 weeks
	–	20-70%	Gel, peeling solution		1-12 treatments
Acne vulgaris and scarring[20,23,30,45,53,54,66,69,70,184,202]	–	5-10%	Foam, gel, lotion	Topical	6-12 weeks
	–	20-70%	Peel		–
Actinic keratosis[13,17,18,28,136]	–	20-70%	Gel, solution	Topical	Once-8 weeks
Rosacea[20,54,70]	–	70%	Peel	Topical	6 months
Abnormal keratinization[40]	–	8-70%	Lotion, solution	Topical	–
Impacted cerumen[90]	–	–	–	Otic	Once or twice
Laser skin resurfacing[19]	–	–	Cream	Topical	–
Lichen planus pigmentosus[55]	–	35-50%	Peel	Topical	16 weeks
Pseudofolliculitis barbae[151]	–	8%	Lotion, soap	Topical	8 weeks
Scalp psoriasis[51,126] and seborrheic psoriasis[126]	–	10%	Lotion, shampoo	Topical	8 weeks
Striae alba[63]	–	20%	Cream	Topical	12 weeks
Xerotic skin[124]	–	15%	Lotion	Topical	6 weeks

Abbreviations: "–", not mentioned; ROA, route of administration.

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Skin hyperpigmentation[1,5,9,26,31,32,35-37,39,47,48,52,56-58,64,74,75,77,78,85,86,93,97,99,101,104,107,110,112,114,118,127,129,130,132-135,149,154,157-159,161,168,174,177-181,183,186,189,194,198,201]	–	2-20%	Cream, gel, lotion, serum	Topical	4-26 weeks
	–	10-70%	Peeling solution		3-12 treatments
Acne vulgaris and scarring [2-4,8,9,12,14,16,24,31,34,38,39,41,52,57,59,60,71,80,82,84,94,103,105,106,108,113,116,117,119,120,130,137,142,162,170,182,188,192,197,200]	–	1-15%	Cream, emulsion, gel, serum	Topical	1 week-24 weeks
	–	10-70%	Peeling solution		1-18 treatments
Skin rejuvenation[4,12,15,21,22,25,29,44,67,68,88,91,111,128,140,141,148,153,156,164,167,169-173,187,190,191,203]	–	3-50%	Cream, gel, lotion serum	Topical	2-12 weeks
	–	40-70%	Gel, peeling solution	Topical	2 days-6 weeks
	–	20-70%	Peeling solution	Topical	1-5 treatments
Warts[33,49,165]	–	15-50%	Gel	Topical	3 months
	–	35%	–		12 weeks
Actinic keratosis[160,196]	–	4%	Gel	Topical	3 months
	–	70%	Solution		–
Striae distensae[138,145]	–	10%	Cream	Topical	4 weeks
	–	70%	Cream		6 months
Plaque psoriasis[12] and scalp psoriasis[166]	–	–	Shampoo	Topical	12 weeks
	–	70%	Solution		–

Burn sequelae[175]	–	5-7%	Cream, gel	Topical	3 months
Congenital Hemidysplasia with Ichthyosiform nevus and Limb Defects (CHILD) syndrome[7]	–	12%	Cream	Topical	–
Dandruff[155]	–	–	Shampoo	Topical	Once
Keratosis pilaris[9]	–	20-70%	Solution	Topical	3-4 treatments
Minute digitate hyperkeratosis[11]	–	15%	Lotion	Topical	–
Molluscum contagiosum[42]	–	–	–	Topical	–
Squamous cell carcinoma[195]	–	5%	Ointment	Topical	–

Abbreviations: "–", not mentioned; ROA, route of administration.

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Skin rejuvenation[83]	1993	• Medical grade 70% glycolic acid partially neutralized with ammonium hydroxide	Peeling solution	12-70%

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Skin rejuvenation[140,141,148]	• Glycolic acid partially neutralized with sodium hydroxide or glycine and arginine	Gel	20%
	• Glycolic acid partially neutralized with either glycine and arginine or glycine and lysine in a cream vehicle	Cream	10%
	• Glycolic acid in a cream vehicle	Cream	10%
	• Gelification of glycolic acid 70% in water	Gel	7.15%
	• Glycolic acid with hydroxyethylcellulose, methylparaben, and glycerin	Peel	70%
Acne vulgaris and scarring[119,142]	• Glycolic acid with lactic acid and carbonated water	Peeling solution	2%
	• Glycolic acid buffered with chlorexidine digluconate and salicylic acid in a soybean liposome vehicle	Cream	–

Abbreviation: "–", not mentioned.

Summary of focus groups/interviews of medical experts and specialty organizations

Two (2) interviews were conducted. One (1) medical expert specializing in oncology failed to respond to the interview request.

Table 12. Overview of interviewees

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Glycolic Acid	Interview Summary Response
DER_01	MD	Dermatology	Academic medical institution Faculty at a School of Medicine	Yes	• Currently buys different concentrations in big bottles and stocks it in the office • Commonly used for many indications – personally uses this every to every other week
DER_03	MD	Dermatology Dermatology/Immunology	Independent consultant	Yes	• There is a need for office stock for convenience and those who want to have tailored formulations. • Glycolic acid has been around for a long time and has a reasonable safety profile.

Abbreviation: MD, Doctor of Medicine.

Indications:

- Disorders in which there is a need to exfoliate the skin
- Acne
- Post-inflammatory hyperpigmentation
- Wrinkles
- Melasma
- Treating lichenification

Administration and dosing considerations:

- The glycolic acid concentration depends on how deep of a peel the provider wants to induce.
    - Concentrations between 30-50% are very superficial peels.
        - One interviewee stated that glycolic acid is the most common superficial peel.
    - Concentrations that are greater than 70% are medium-depth peels.
        - Interviewee stated that most dermatologists are usually "at the 70% place. They're not messing around with the lower concentrations, in general." This is because they are using it for therapeutic reasons for diagnosis as opposed to the more superficial peeling.
- Glycolic acid is applied to the skin as a topical product and is almost always used with other agents.
- Duration of use
    - Very superficial peels are left applied for 1-2 minutes. Whereas deeper peels can be applied for up to 3-15 minutes.
- Frequency of use depends on the condition being treated
    - One interview reported they have a colleague that sees a patient every two weeks for repeated peels as treatment for acne.
    - Another interviewee says, "we have people on a regimen where they're repeating it every two weeks."
- Patient considerations
    - Some patients are more sensitive.
        - Fitzpatrick skin type – how dark somebody's skin is can determine the concentration of glycolic acid and duration of use.
    - Pediatric acne patients are less likely to be treated with glycolic acid in adolescence.
    - There is a potential concern for higher exposure for patients with genetic disorders that relate to protein B6 in their skin. This would leave them susceptible to increased absorption of topical preparations. Examples include kids who have gotten salicylism and a disease called Netherton's.

Need for office stock/bulk compounding

- NeoStrata are dermatologist-grade substances. They have varying concentrations but several people the interviewee has spoken to are "actually more used to ordering it in a bulk compounding space because they want to tailor that particular formulation, whether it's buffered or non-buffered and what other excipients are in there."
- Providers develop a familiarity and like the ability to order what they want to use.
    - "People who have a lot of experience and can manage them are gonna be using the liquids or the gel, will have a sort-of slower onset of action and maybe be used in a different context. So, they really like the ability to order up what they want to use. And, they've developed a familiarity with it and will use it."
- For providers who use glycolic acid on a regular basis, office stock would be convenient to have. However, one interviewee also stated that there is another option on the market if they became unable to stock bulk compounded glycolic acid.
- An interviewee stated that many dermatologists like "controlling a lot more than just what percent glycolic acid they have."
- Dermatologist do a lot of in-office detailing.

- One interviewee currently gets different concentrations (anywhere from 20 to 70%) in big bottles and stocks it in the office.

Other options

- Glycolic acid is viewed as a safer alternative to phenol and Jessner peels.
  - Jessner peels tend to be harder to control.
  - Phenol peels used in the old days, hard to control and could be devastating if left on for too long.
- Fraxel and related fractioned laser type therapy – the interviewee did not know as much about this but stated that these have taken over that space for the peels.

Summary of survey results

Table 13. Characteristics of survey respondents [1 person responded to the survey]

Board Certification	No Response
No Response	1

Table 14. Types of products used, prescribed, or recommended

Types of Products	Respondents, n (N=1[a])
Compounded	0
FDA-approved	1
Over-the-counter	1
Dietary	0
Unsure	0
No Response	0

[a]Out of one (1) respondent, one (1) reported using, prescribing, or recommending multiple types of glycolic acid product.

Table 15. Compounded use of glycolic acid in practice

No survey respondents provided this information

Table 16. Indications for which glycolic acid is considered a standard therapy

Indication	Standard Therapy	
	Compounded, n (N=0)	**Non-compounded, n (N=2[a])**
Acne	0	1
Anti-aging	0	1
Sun damage	0	1
No response	0	0

[a]The respondent reported more than one indication.

Table 17. Reasons for using compounded product instead of the FDA-approved products

No survey respondents provided this information

Table 18. Change in frequency of compounded glycolic acid usage over the past 5 years

No survey respondents provided this information

Table 19. Do you stock non-patient specific compounded glycolic acid in your practice?

No survey respondents provided this information

Table 20. Questions related to stocking non-patient specific compounded glycolic acid

No survey respondents provided this information

CONCLUSION

Glycolic acid (UNII code: 0WT12SX38S) was nominated for inclusion on the 503B Bulks List by Sincerus Florida, LLC for treatment of hyperpigmentation disorders and photodamaged skin via topical creams, pads, and lotions from 0.08-70%. Glycolic acid is available in various topical dosage forms as an OTC product in the US; there is no current USP monograph. Glycolic acid is not approved in any of the foreign medicine registries searched.

From the literature review, the most common indication in the US in both the US and non-US countries were for skin rejuvenation, skin hyperpigmentation, and acne vulgaris/scarring. Compounded products were identified from both US (solution 12-70%) and non-US (10% cream, 7.15-20% gel, and 2% solution) studies.

From the interviews, one (1) interviewee expressed a need for office stock, and one (1) interviewee currently stocks glycolic acid in the office. Glycolic acid is commonly used for a variety of indications and has a reasonable safety profile.

From the survey, the one (1) respondent used glycolic acid as a FDA-approved and OTC product. This respondent reported that glycolic acid is standard therapy for acne, anti-aging, and sun damage.

APPENDICES

Appendix 1. References

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Appendix 2. Transcripts from focus groups/interviews

INTERVIEW 1 DER_01

Interviewer 1: And then the last substance that we have was glycolic acid. And it seems like anything under the sun, you can use glycolic acid for, so I don't know exactly how to start asking some of these questions in terms of indications, but I guess from your practice setting, and your experience and background, what would be your reasoning for using glycolic acid, primarily?

DER_01: We use it a lot for disorders where there is a need to exfoliate the skin, in particular. So that could be for anything from [inaudible 00:29:34], could be keratosis that you're trying to dislodge, to somebody who has something that might be perceived as more cosmetic, like fine lines and wrinkles, and just that skin that's looking yucky and you want to get rid of this. And this is a substance that I would say I use, I think I can honestly say I use it every week. It's extremely commonly used. It exists in various substances in some take-home products, too, but in general, the higher percentages of glycolic acid, like I know in some states, like aestheticians are allowed to 10-15% glycolic acid for various indications and topical use on the face and elsewhere, but sometimes the higher concentrations, like 30, 40, 50, we have up to 70%, are available more for physician use in an office setting.

DER_01: It's basically a peeling agent. So glycolic acid is a common, superficial peeling agent. Peels come in three different major categories: there's superficial peels, there's medium-depth peels, and then there's deep chemical peels. There are all kinds of chemical peels, but there's only medium and deep. And superficial chemical peels mostly go on the epidermis, through the stratum corneum, that's where they're operating. Medium-depth chemical peels would be like 35% TCA peels, perhaps, trichloroacetic acid, and those would go through to the superficial dermis, and then you would have deep chemical peels, which are things like phenol peels, which go to the reticular dermis. Those are not done so much anymore, but superficial peels are done most of all, and glycolic peels are probably the most common superficial peels. I think there's a lot of indications for having those on bulk, because that's exactly what we do. We have a supply of it, and everybody needs about- like if you were peeling someone's face, you need about 5 cc of it, so you have a larger container from which you carefully pour out 5 cc into a little sterile cup, and then you use something that looks like a large cotton tip to apply it to people's faces, and then you have a timer, which tells you how long you've done that. And usually after three or four minutes, you neutralize it with a base, and the person's a little red when you treated them, then they go home.

Interviewer 1: You had mentioned that you could go up to 70% strength?

DER_01: At least in my practice. And maybe there's some higher percentages, but I know we have 20, 30, 40, 50, 60, and 70.

Interviewer 1: You said there are multiple reasons that you might want to do the peel. Would you say that there's one indication that seems to be more frequent, or is it just kind of a hodgepodge of things that would need this particular peel for?

DER_01: I think very commonly, anything for which you can use superficial peels. So I think that will remove, fix the stratum corneum, and whatever has thickened, for whatever reason, it's a mechanical way of removing it. You're not removing it permanently, it could happen again, but think of it as an exfoliating agent, if that makes- that's what you're kind of doing, exfoliating the skin chemically.

Interviewer 1: We're trying to categorize how these substances are used, and it just seems like there's so many different options and so many different reasons, so I'm just trying to figure out how we compile all this information together into something that makes some sense.

DER_01: I think the most common indication, by far, would be exfoliating the stratum corneum. I would guess that's more than half the glycolic acid use by dermatologists.

Interviewer 1: And you said that it is something that, you're not removing it permanently, so is this something that would be kind of a, you do it once, and then you repeat it every so many weeks or months, or something along those lines?

DER_01: Exactly. We have people on a regimen where they're repeating it every two weeks, so they come and want me to do it.[crosstalk 00:34:29].

DER_01: There's one other common indication, it's late in the day, I'm not thinking, another common use for it, that common disease process, very commonly, would be acne.

Interviewer 1: Is it treated the same way as you do the peel, you use the q-tip to kind of put it on the face, leave it, and then neutralize it in the same sort of process for acne, as well?

DER_01: Yes. Exactly right. And it does treat active acne.

Interviewer 1: So you mentioned that you have this kind of stocked in your office. Is this something that you get from an outsourcing facility, or is this something that you can purchase, or make yourself?

DER_01: We get it from somewhere. I don't know exactly where we get it from, I might have to look it up, but we don't make it ourselves. We have somebody make it, then we buy it from them in larger bottles, and when we use the bottles that we have- there are different concentrations that we purchase, so it's not as if we are diluting 70% to 60%, we just try to get the concentrations that we need, which is like a round number from 20 to 70.

Interviewer 1: Would you say, is there an FDA-approved product that would meet the need that glycolic acid is fitting?

DER_01: I don't think so. I'm not aware of- I know there are a number of different places you can buy this from, but I'm not aware that there is an FDA-approved product, because usually if there is an FDA-approved product, I think without exception, if there is one, we didn't buy it. Because we're at a university, so we're not trying to cut any corners, but if there isn't one, and we have to get it kind of as a [inaudible 00:36:32].

Interviewer 1: I wasn't sure if there is, in term of treatment options, if there's multiple options, and this just happens to be the one that is preferred or kind of where this fits in everything.

DER_01: I'm not aware of any branded pharmaceuticals that glycolic acid [inaudible 00:36:55].

Interviewer 1: I think you have answered most of the questions that I had. Is there anything that you think that we missed in terms of glycolic acid or DPCP, that you think would be relevant for us as we're kind of collecting all of this information?

DER_01: I don't think so. I think you were pretty thorough.

Interviewer 1: Alright. Well, thank you so much for taking the time this evening to talk with this, and sorry if we disrupted your dinnertime.

DER_01: It's all good, and I apologize for chewing at the same time.

Interviewer 1: We appreciate it. We're kind of progressing through, and I know when we talked at the meet-and-greet, we had our initial ten substances, and now we've got our full 75 that we're going to be doing over the course of the year, so I'm sure we will probably be in touch with you as we work through, because it seems like a lot of the substances that we're reviewing do have an indication in dermatology. But, we would hope that you'd be able to help us out as we move throughout this process.

DER_01: Sure. You have a lot work ahead of you.

Interviewer 1: It's going to be a long process, but I think it will be really useful information at the end, and I think our biggest concern is missing something, so we're trying to make sure we're collecting as much information as we possibly can, because we don't want to limit the ability of compounded products, so we want to make sure we get all those indications that we can. So we appreciate you taking the time to talk with us about it all.

DER_01: Same here. Nice talking with you.

Interviewer 1: Alright. Well, thank you, and enjoy the rest of your evening.

INTERVIEW 2 DER_03

Interviewer 1: Okay.

DER_03: I'm way more excited about glycolic acid than I was about the-

Interviewer 1: Oh good.

DER_03: -the dyeing agent.

Interviewer 1: Oh good. So I guess just really generically, how do you utilize glycolic acid in your practice?

DER_03: So, we have to go back to that positioning which is that I'm not currently seeing patients at this time, but I take care of patients usually in this context of clinical trials in groups of a couple hundred at a time. But I have reached out to colleagues who have been involved in the glycolic acid alpha hydroxy acid state and had conversations with them. Alpha hydroxy acids, in general, are broadly recognized as an effective keratolytic agent. So, they help to lubricate the interstitial spaces between cornea sites and allow them to then exfoliate. And, in conditions such as acne, plasma, post-inflammatory hyper-pigmentation, wrinkling, and other indications which I actually haven't been aware of. But, glycolic acid is a well-deployed tool in the hands of these dermatologists.

Interviewer 1: Okay. So, in terms of ... and, this is kind of where some of our confusion I think might be coming, so we'll get to the indications in a minute, but ... so, glycolic acid seems like it's a really commonly used substance in both dermatology and even if you go get a facial, they might do a glycolic acid peel or something.

DER_03: Correct.

Interviewer 1: So, it seems like it's a relatively common agent. So, where does compounding fit into this? Because, as a dermatologist, are you able to just purchase, you know, 70% glycolic acid and just have it at your practice site?

DER_03: Yeah. So, there's a company called NeoStrata, which you're probably aware of. And they are the big-wigs in having it available. And it's dermatologist-grade stuff. And, they're well known in the dermatology space. They will have varying concentrations that you can get, but several of the people that I spoke with are actually more used to ordering it in a bulk compounding space, because they want to tailor that particular formulation, whether it's buffered or non-buffered and what other excipients are in there.

Interviewer 1: Oh, okay.

DER_03: So, generally, you know, liquids are a little bit harder to control. People who have a lot of experience and can manage them are going to be using the liquids or the gel, will have a sort-of slower onset of action and maybe be used in a different context. So, they really like the ability to order up what they want to use. And, they've developed a familiarity with it and will use it. So, for example, one of the dermatologists that I spoke with is a woman named [redacted], who's well known in the [redacted] area. She has been here for, you know, 20, 30 years and runs a very high-end boutique dermatology practice. She uses repeat glycolic acid peels to manage acne. She thinks it's the most effective acne treatment that she's ever used.

Interviewer 1: Okay.

DER_03: I'm more familiar with seeing it in context of melasma, post-inflammatory pigment. Interestingly, one of the women who wrote one of the chapters on this product, a woman who's now retired but was active for a long time, she told me that she uses it to manage eczema patients. And then, I realized that what she's doing is she's using it to control the ischiatic component, where people have lichenification and lots of scratching and they develop these thickened plaques and she's doing repeat peeling to try to get those patients' skin back to a baseline level that she thinks is actually going to alleviate some of the symptoms of the atopic dermatitis. That's the disease we call “the itch that rashes”. Whenever you have a disease where there's 20 things that are used, it's because none of them really work very well. Mostly it's topical steroids, but calcineurin inhibitors, the PDE-4 inhibitor, Eucrisa are used there. But, this woman swore by using glycolic acid peels to help get her patients back to baseline-state. Which, I thought was like whoa, that was different.

Interviewer 1: Yeah, yeah. Okay, so in terms of the application and the dosage form, could you kinda walk through, you know, how would you utilize it. You mentioned it has a liquid, how long do you apply it, and those types of things?

DER_03: Sure. Did you see the review article that was in Clinical, Cosmetic, and Investigational Dermatology by Sharad, published in 2013?

Interviewer 1: Is that one of the ones that ... hang on, we're checking to see if that's one of the ones that's on our list.

DER_03: Oh, I can send it to you. It's open access through Dove Press. The point is that, you know, depending on the concentration, you're going to get varying levels of peel. So, in this particular article, they talked about any concentration that was in the 30 to 50% range as a very superficial peel, particularly if you left it on for short contact and didn't neutralize it. Whereas if you used a higher concentration it would be superficial and then you'd get a medium-depth peel as anything over 70%. Most of the people that I was talking with,

when they're doing this as dermatologists, they're usually at the 70% place. They're not messing around with the lower concentrations, in general.

Interviewer 1: Okay.

DER_03: It's just because they're using it for therapeutic reasons for diagnosis as opposed to more superficial peeling, the quote-unquote lunch-time peel. And, I was sort-of surprised too, cause, you know, when lunch-time peels were really popular- this is just a little history- it was before we had Fraxel, which is a fractionated laser. Remember, when lasers first came out, they were much more ablative. It was only when they got to these ultra-pulse, really short time, small units of energy that they were better able to control the depth of penetration of how much energy they were delivering to the skin. So, Fraxel and some of its cousins- and I'm not a laser jock so I don't do a lot of this, know exactly what's happening in that field right now as well as people who spend all their time in the laser field ... those peels were being used before we had the Fraxel. Now that we've got Fraxel, my guess is that some of that market has shifted and people who have lasers find ways to use them, because if you spent a lot of money for that device, you're going to continue to employ it.

Interviewer 1: Yeah.

DER_03: So, if you have it, you use it. If you don't have it, you're gonna use glycolic acid. I don't know how much people are still using Jessner peels, which is the other one you probably have come across. It's often talked about in the same breath, it tends to be a little bit harder to control. In the old days, people used to use phenol peels. Those are really hard to control and really could be quite devastating if you left it on too long.

Interviewer 1: Okay.

DER_03: So, I think glycolic acid was viewed as a safer alternative to the phenol and the Jessners as better controlled. But, to one extent, Fraxel and some of its other cousins have taken over that space ... I don't really know. If you want, I can call people, cause I know people.

Interviewer 1: Yeah, yeah.

DER_03: We can find out.

Interviewer 1: Yeah, that would be good. So, I guess in terms of, you know, for the dermatology purposes, you primarily would be using the 70%. Is it generally only applied to the face or could you apply it to other parts of the body?

DER_03: Yeah. So, the woman who's using to control AD would be using it in other places as well. So, if you have a lichenified spot on the back of the hands or wrists or in the antecubital fossa. And, she would have to go slowly with her patients and build up tolerance. I didn't go into all of the details with her ...

Interviewer 1: Yeah.

DER_03: ... I can certainly call her back. She's a friend, she'll talk to me. She's retired, but she was one of the authors who did some of the writing about glycolic acid peels and that's why I reached out to her for this call.

Interviewer 1: Okay. So, you would apply it to the skin. What would be the time frame in which you would leave it on the skin?

DER_03: So, it varies between the short-contact, the very superficial peels, is 1 to 2 minutes and the others would be up to 3 to 15 if you were going for a bigger, deeper peel.

Interviewer 1: Okay. Then you would wipe it off of the face and then the patient would come back, what, a week later, two weeks later? Or just depending on the condition?

DER_03: Yeah, it would depend on the condition. So, the acne lady, [redacted], she's seeing these patients about every 2 weeks and she tells them, "I'm gonna make you better, but you have to commit and it's gonna take us awhile, and I'm gonna see you every 2 weeks, and you're gonna need a series of these". And, actually this Dove Press paper has some of the data in there about people who were doing repeat peels.

DER_03: You know, you gotta remember, I'm a clinical trialist, so this data is not the kind of data that I like where it's a randomized, double-blind, placebo control trial, because people know what they're getting and it's harder to really assess exactly how good they were. With the exception of people with nodular cystic disease, I think there was like 1 patient, these are like really small numbers, don't do well. But I wouldn't expect them to. And, frankly, from an FDA perspective, the FDA doesn't look at nodular cystic acne as belonging in the other space with acne vulgaris. They consider that a separate disease.

Interviewer 1: Okay.

DER_03: But, in general, with repeat peels, as people were tolerating it, people were getting better. But, again, it's extended case-report type of data from an evidence perspective.

Interviewer 1: Okay, so in terms of applications. So, this happens in a dermatologist's office?

DER_03: Yes.

Interviewer 1: Would you ever have a patient perform this at their own home?

DER_03: Well, that's a different issue. So, there are products that you can get and if you put glycolic acid in on your favorite search engine, as I'm sure you already have, you'll see there's a huge variety of what you can get and you can get it by yourself. You're not going to get the NeoStrata 70%, hopefully, you're gonna get something else. You're gonna get lower concentrations, and the lower concentration glycolic acid could be used like a retinol. Right?

Interviewer 1: Yeah.

DER_03: So, retinols are also keratolytic or low-concentration salicylic acid, which is a member of OTC acne products. One's an alpha hydroxy, one's a beta hydroxy.

Interviewer 1: Okay. So, potential ... in terms of a compounded product, I guess at least with the 70% that as a dermatologist you would be using, would it make sense to write a prescription, send it to a pharmacy, pharmacy sends you ... I assume that you're not using a very large quantity of this to put on the face, so would that make sense to get a patient-specific prescription, or is it something that you would just have in the office, available when these patients come in.

DER_03: Yeah, it's much more likely that they want to be able to have it available for that particular patient when they come in. For the people who are using this and doing enough of it, having it available on a regular basis, I think, would be preferable for them. They would look at it as a barrier to care if they had to get the patient prescription that needed

to be sent. The bigger question for me, and I don't know the answer to this one, Ashlee, is; so, if a company like NeoStrata is making that for the physician and that's already, essentially compounded, so we know something about the quality and the stability, and it's available and they can buy it and have it in their office, do we also then need it in another direction? That's sort of a philosophical issue, beyond the scope of you know, are we using it, do derms need it, are they still looking for it?

Interviewer 1: Well, I think that's also part of the question that the FDA is wanting to know, is if, as a dermatologist, you can go buy 70% glycolic acid, well then, why does the outsourcing facility need to make it if it's available for purchase? So, I think, that's kind of the question of ... I don't have the formulations for the glycolic acid that the outsourcing facilities are making, they generally are relatively secretive about what they use.

DER_03: You bet.

Interviewer 1: That would be interesting it see, you know, what's the difference between the two products. I haven't looked at the commercially available one to see if there's any ingredient in there that might cause allergy or whatever it may be to a patient to warrant the need for it. I don't know how familiar you are with the product but is there anything in it that would concern you about using the commercially available one?

DER_03: Yeah. Because it's proprietary, they're selling it. I mean, I could probably, as a dermatologist could get some additional information about what it is. I didn't go there until I had this conversation with you, but I don't know. In general, I expect that if I'm the dermatologist and I ask, they're gonna tell me all of the excipients that are available. Simply because, I do care a lot about what excipients are there and what influence those may have on ... you know, what are you using as the preservative, is there fragrance? The things that are most common contact allergens in dermatology, as you know, one is fragrance and the second one are the preservatives. So, we care about those a lot, and my friend [redacted] was just talking about the preservative review. We come up with a new preservative, we put it in stuff, and the next thing you know it's now causing more trouble than we had anticipated.

Interviewer 1: Yeah.

DER_03: But, I'm happy to get more information on it just to get more of a sense of what the range is. But, again, because it's sort of that cosmeceutical space, I don't even know from a regulatory perspective how it is actually made available. So, generally, these things ... it's a topical, it's an alpha hydroxy acid, I don't know the restriction on somebody else can come in with a competitor.

Interviewer 1: Yeah, see, that I'm not entirely ... the cosmetic is a little bit different of a beast. So, I don't know. So, in terms of dermatology, as we're looking through this and, if, by chance, we're able to come across the different formulations, are there particular preservatives or fragrances that we should be on alert for to say, "oh, that would be a preservative of concern or this would be a fragrance of concern", or would just any fragrance in general be of concern?

DER_03: Yeah. It's fragrance in general. The challenge is that, you know the difference between unscented and fragrance-free?

Interviewer 1: No.

DER_03: There technically is a difference.

Interviewer 1: Oh, okay.

DER_03: Okay, so this is outside of the glycolic acid thing. So, fragrance free, when you walk down the aisle and you see a product and it says, 'fragrance-free', then by law there is no fragrance that has been added to it.

Interviewer 1: Okay.

DER_03: In contrast, something that is unscented may have a masking perfume that's been added to it so that it hides the chemical smell. You don't detect the scent, but in fact, there may still be scent there. So, if you are truly allergic to something, you as a person who's sensitive to it, can actually still break out. And, this is, good example, down the laundry detergent aisle you can look at Cheer, Cheer Free, Tide has a fragrance-free variant. So, when they say fragrance-free that means they did not add any. The problem is, that the ability to detect fragrance in patch testing is pretty ... the word I think may be 'dismal'. Because, there's not really been good standardization about all of the fragrances. There's a product called Balsam of Peru, which is an extract and a lot of fragrances have components that are in Balsam of Peru, but the North American Contact Dermatitis kit, which is what we use as a screening tool, uses this Balsam of Peru to look for fragrance allergy. But, it's sort of a [inaudible 00:18:01] of a lot of other stuff and it doesn't really help detect it.

Interviewer 1: Okay.

DER_03: Anyway.

Interviewer 1: That's interesting. My mom is very sensitive to smells, so I feel like that's a good bit of trivia when I go back for the holidays to be like, "hey, mom, did you know?".

DER_03: Yeah, the difference between fragrance free and unscented. People don't look at that, they look at it and they go, "but it says unscented on there". Yeah, but if you actually go read what's in there, you'll find that there's up to 0.5% of fragrance can be added.

Interviewer 1: Okay.

DER_03: You just can't detect it. If you're allergic, you're allergic. It doesn't matter. I mean, 0.25 or 0.5, 0.05, doesn't matter. You're allergic. So these products, if you want, I'm happy to get more information. I also heard from [redacted] that [redacted] who's another big-named, famous dermatologist, [redacted] is going to be doing something at the upcoming [redacted] meeting about peels. But, that's early March, so it's a bit of a way. But I know [redacted], I'm happy to reach out to her and say, "hey, what are you doing on peels".

Interviewer 1: Yeah.

DER_03: We can look. I think some of this goes back to that issue, though, about what people want ... I'll tell you. A lot of dermatologists are frustrated pharmacists. They like being able to make that solution and put it at this vehicle and know what the pH is going to be or qs to or buffer it to a pH of Y and they feel like that's what they're used to using. Whether they're able to get it for a cheaper price than what NeoStrata's selling it for, I don't know.

Interviewer 1: Okay, that's interesting.

DER_03: They're controlling a lot more than just what percent glycolic acid they have.

Interviewer 1: Yeah, yeah. Definitely. I mean, it does allow for kind-of that more specialization, so I'm sure, as a dermatologist, you probably have your, like you said, your particular formulas that you like.

DER_03: The reality, though, is if it went away, if bulk compounding went away, there is a product on the market that is at least, one that considered could meet their need. I would hazard that because it's not protected by patent at this junction, glycolic acid's been known since Eugene Van Scott in the 1950's, there will be other companies that will have it. There also are a lot of old compounding companies that do work for dermatologists, like, will make stuff for them and you can have [redacted] brand something or other and sell in your office. Dermatology is one of those fields where there is a lot of in-office detailing. Most other specialties don't do that, but derm does. It's controversial.

Interviewer 1: Okay, yeah. So, one of the things we're trying to do is we're trying to, kinda, obviously you've already mentioned that when you pull up glycolic acid, there's all sorts of things that come up and, we're trying to kinda categorize the indications to make it into a little bit more of a stream-lined table, if you will, so that as we're presenting the information, we have it as condensed as we can make it to where it's still readable and the public is able to understand what we're doing. So, I was wondering if you would be able to help us as we're categorizing some of these indications to see would they be things that we could include as one overarching theme for glycolic acid, or does each one of these indications need to be its own separate entity? Melissa, do you have the ...

DER_03: Well, for me, I mean, the bottom line is if they're keratolytic. Right, so we're using it as a way to enhance taking off the superficial scale and enhance epidermal turnover. So, under that umbrella, you know, acne, melasma, post-inflammatory hyperpigmentation, wrinkles, and even treating lichenification are all embedded underneath that.

Interviewer 1: Okay, so kind of the overarching theme is that it's a keratolytic, to peel the layer, and then all of these indications kind of fall under that category of keratolytic. So, is there ...

DER_03: Well, keratolytic is the mechanism of action. The other diseases are specific disorders. So, you're using a mechanism of action as the bucket.

Interviewer 1: So, in terms of all the various indications, you know, acne, wrinkles, and all of those, is the dosing the same or would the dosing vary depending on the reason why you're having to do the peel.

DER_03: Yeah. I think it's gonna vary depending on why you're doing the peel.

Interviewer 1: Okay.

DER_03: So, from [redacted] is a woman who used it for her atopic dermatitis patients. She was apparently starting at a lower concentration and working her way up. So, it wasn't even standard across a patient. But, these are patients who can be very sensitive to anything you put on their skin. With [redacted], who's doing the acne peels and the repeat applications, in general she's using the 70%. She may not put it on for the same duration in every patient, and that's part of the art, before she neutralizes it, but I would think, generally ... so there will be differences, depending on the depth of what you're trying to take off. It also depends on ... one of the problems and one of the concerns with these agents and the concern with doing a lot of things on people who have darker pigmented skin ... have you come across the term Fitzpatrick skin type yet?

Interviewer 1: Yes. Yes, we have.

DER_03: So, the chair at the department at Harvard, long ago, was this guy, Thomas B. Fitzpatrick, who wrote a big textbook of dermatology and also established a categorization that goes from 1 to 6 about how dark is somebody's skin. So, type 1 people are really fair, blue-eyed, fair-haired. The minute they go outside, they're gonna get pink and red and they're gonna peel. Type 6 are the really darker, African American, other people from Saharan and South American regions, the really darkest of the dark who could go out in the sun and if they stayed out forever, they would burn, but in fact, they're really darker pigmented. And then, 2's, 3's are mostly Northern European, 3, 4, 5 is getting to southern, Mediterranean, and Hispanics and lighter-skinned African Americans. So, this whole spectrum. And, the things we worry about is how much melanin you have in your skin, and whether when I do something to it, are you going to have more problem with post-inflammatory pigment changes, either darkening or lightening. So, that also was a play. The article, I'll send you, which was an Indian woman who was talking about glycolic acid because she was talking in the context of what was known about these different pigment types. In Asians, for example, another good group where you can get a lot of post-inflammatory pigment. So, that's part of why people would use different concentrations of glycolic acid and why they'll leave it on for different amounts of time.

Interviewer 1: Okay, what range ... oh sorry, go ahead.

Interviewer 2: So, like a quick question on that. Cause, I saw that like that skin type was mostly in the melasma ...

DER_03: Sorry, you're fading. Can you get closer to the microphone?

Interviewer 1 2: Can you hear me better now? Is this better?

DER_03: Yeah.

Interviewer 2: So, that Fitzpatrick skin type, I saw it mostly in the melasma indication, so can those be grouped together or should I separate them out in that case?

DER_03: Well, the Fitzpatrick skin type is ... everybody has a Fitzpatrick skin type and in patients who have melasma, it becomes particularly important. It's important for acne and every other skin condition. African Americans who get acne have a lot of more post-inflammatory pigment changes. Glycolic acid's been used to try to address some of that. One, to help improve the acne, but two, to actually get rid of some of that pigment by turning over the skin. The canard is, that all we're really doing when we do this is we theoretically are only lifting the epidermal layers and the pigment is dermal, it's not in the epidermis. Once it goes to superficial skin spots, those are epidermal, seborrheic keratosis are mostly epidermal, but the pigment changes you see with melasma and with post-inflammatory pigment is more of a dermal process. But it seems to work. So, we have to not worry too much about that the mechanism of action is not always well understood.

Interviewer 2: So, would you recommend that if the articles do mention the skin type to separate them out.

DER_03: I wouldn't, I think if you try to get into separating them out, it's going to start to get ugly.

Interviewer 2: I think most don't, so ...

DER_03: The article just makes the point that in fact while we worried a lot more about somebody and how dark their skin was and whether glycolic acid peels were a good idea, there's enough literature that's been published to say that it works in darker skin patients, and it's been less of a concern. Same thing's going on with laser right now where there's an article coming out from University of Miami talking about darker skinned patients can be treated with laser with less concern than we used to have about treating those patients.

Interviewer 2: Thank you.

DER_03: No problem.

Interviewer 1: So in terms of, I guess, stocking in your office, you would want concentrations going up to 70% and kind of, are there particular increments of, you know, 65, 70, or would you need to get even more specific as a difference between 1 or 2 percentages?

DER_03: I don't think you'd have to get more specific than that. I think it's broader like, 30, 50, 70. But, again, I don't have my hands on these products right now. I'm not doing this type of work. I'm happy to get more information from people who are. And, again, if you look at that NeoStrata website, what we'll see is they're not quite as discriminating in all of these varying with a large number.

Interviewer 1: So, in terms of place and therapy, I know you already touched on this a little bit, where ... it would depend obviously on the indication, but in terms of this being the standard therapy to treat particular indications, would this be the standard therapy that you would utilize for any of the indications?

DER_03: So, in general, in dermatology it's not a single product. It's usually a combination of approaches. Right? So, if you're treating a patient with melasma, a fundamental to that is including a good regimen for sun protection. There may be other components like you're going to use maybe hydroquinone and glycolic acid peels. Usually by the time a patient arrives at a dermatologist's office, they've tried the stuff that's available over the counter, there's other stuff that they're probably using. Our goal is typically to try the target things from several angles in order to optimize the results for an individual patient. Part of that is none of these treatments that we have work particularly well as sole agents. Think of cancer chemotherapy. It's almost always a cocktail. And dermatology is the same way.

Interviewer 1: Okay. Is there any concerns about using these substances in various patient populations?

DER_03: Great questions. Getting back to that question we had about kids and alopecia areata and unapproved uses and the ethics of things for which there's no data to say they really work. I think the data on glycolic acid is probably stronger, in general.

DER_03: I don't think people are using glycolic acid in kids, you know, if acne patients show up at adolescence. The youngest patients, nowadays, from the FDA perspective, their expectations are that clinical trials in acne go down to age 9. So, we routinely see 9-year-olds being enrolled in clinical trials, but there's not a lot of them at that age group. If they're 9 and they've got acne, they've usually got it because they're already pubescent, they're already well into their adolescence. And, it takes about 6 months before they're even eligible to be in a trial. So, the younger kids are not quite as likely to have been treated with it.

DER_03: I think the place where I would be worried would be in patients who have genetic disorders where they've got protein B-6 in their skin that leaves them susceptible to

increased absorption of anything you put on topically. The classic example is salicylates and kids have gotten salicylism who have some of these genetic disorders. There's one called Netherton's, which is a trans-glutaminase 5 deficiency that leads to a barrier defect. So, essentially their skin is like a kitchen sink sponge. Anything you put on topically goes right through and gets into their blood stream. Normally, bioavailability of topically applied products is less than 1%, usually closer to 0.05. So, if I put a gram of a drug on, I get small amounts in. With kids who have these barriers, because they've got ichthyosis or they got epidermolysis bullosa or some other god-awful disease where they don't have the barrier in place, they can potentially get higher exposure.

DER_03: But nobody using glycolic acid in that setting. We've seen it with salicylates, but that's because some of these disorders are characterized by plaque-like scales. But less likely if they use glycolic acid here. So, when you call me about salicylic acid ... I really like having this conversation ... those are the ones that theoretically are a concern, but it's not done in practice. In the dermatology community they know, they know these patients. Part of the problem is they'll look like a regular atopic dermatitis patient, and if you're not looking at them carefully you may miss the fact that it's really something else. But that is the only place where there's a theoretical risk.

Interviewer 1: Okay. I think those were all the questions. Do you all have any other questions?

Interviewer 1: Do you have anything else that you would like to add in regard to glycolic acid?

DER_03: No. This one's been around a long time. I think it has a reasonable safety profile. I think the people who are doing it do a fair amount of it and are experienced enough with it that it’s not ... that the risks are somewhat minimized. But I'm happy to do more to help your team along the way. So, I'll send you the article that I described that talks about varying indications and what it's being used for. If you want, I'll reach out to NeoStrata to ask them more about what availability they have.

Interviewer 1: Yeah, that would be great. Because I think the other piece would be kind of figuring out why would an outsourcing facility need to make it? If there is a company that makes it and whatever its safety profile is, why would these outsourcing facilities need to compound this particular product?

DER_03: Yeah, and I'm always sensitive about disclosing why I'm asking these questions. So, if there's a reason not to I would like to tell them that I am engaged with a project that has to do with helping to categorize for the FDA about products like glycolic acid. You know, I won't go into a lot of detail ...

Interviewer 1: No, I think that would be fine.

DER_03: ... but that I feel like I'm being transparent with them. I'm going to ask them the same sorts of questions like, why wouldn't we just get it from you guys as opposed to [inaudible 00:35:39].

Interviewer 1: Well, they would probably say, "that's what we wonder".

DER_03: Actually, somebody told me and gave me the name of somebody to call to talk to them. But, that's fine. I'll find out what I can. And then, if you want, I can also ask [redacted] what the program is that she's gonna do. I think it's like [redacted] in [redacted] about peels, so if I can find out anything about that, I'll let you know.

Interviewer 1: That would be great.

DER_03: I looked for it on the internet, the source of everything, I didn't find it. But I'll reach out to her one-on-one and maybe she can tell me.

Interviewer 1: Well, that would be great. Thank you.

DER_03: What's your timeline for when you're going to be rolling some of this stuff out?

Interviewer 1: So, we are finishing up our interviews with experts. So, we have 10 substances right now that we're looking into. So, we've done the literature review, we're doing our interviews to kind of make sure that we're going down the right pathway in terms of indications of these various substances, and then we're going to be putting together a survey to get an idea of across the country what's being done in terms of these products. So, we are hoping to wrap up these 10 substances around the May timeframe.

DER_03: Okay, okay good. Are any of those going to come back in derm?

Interviewer 1: So, we actually just got our list of 75 substances a couple weeks ago and we're still kind of sifting through those. I believe probably a few of them will have dermatology indications, so ... 25 of them have indications in dermatology so far.

DER_03: Oh my ... of course they do! It's derm. Okay.

Interviewer 1: Yeah, you all have a lot of them. So, we'll probably be in touch as we're ramping up our progress on those.

DER_03: Well, I'm not planning any extended travel. So, I'm available and it's always fun to talk to you guys.

Interviewer 1: Oh, well thank you.

DER_03: Best wishes for a lovely holiday and I'll end the call, Ashlee.

Interviewer 1: Oh, I think we had one more question for you, sorry.

DER_03: Oh sure. Go ahead.

Interviewer 2: Sorry, this is Melissa. Would you mind if I e-mail you later on when I have compiled the final list of all the indications that I've seen for glycolic acid just to see if we can narrow it down because it's kind of long and might be easier to see in the e-mail format, if you don't mind.

DER_03: Oh, that'd be fine. No problem.

Interviewer 2: Thank you so much.

DER_03: So, that's part of the challenge is, I don't know if I've even fully covered all of them. When [redacted] told me about atopic dermatitis I was scratching my head for about 30 seconds and I was like, oh I get it, I know why she's doing it.

Interviewer 1: Yeah.

DER_03: So, I suspect we'll find more. But, as I said before, dermatology has 2,000 diseases in the CPT code and only 10 of them are big enough to warrant anybody developing drugs for them. So, there's a lot of stuff that gets used quote-unquote off label.

Interviewer 1: Yeah.

Interviewer 1: Okay. Well, thank you so much for your time and I hope you enjoy your holiday!

DER_03: You too, thank you!

Interviewer 1: Alright, bye.

DER_03: Take care, bye.

Appendix 3. Survey instrument

Start of Block: Welcome Page

The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice. This survey is for **glycolic acid**. As a medical expert, we appreciate your input regarding the use of this substance in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

End of Block: Welcome Page

Start of Block: Glycolic acid

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **glycolic acid**? Please check all that apply.

- ☐ Compounded drug product
- ☐ FDA-approved drug product
- ☐ Over the counter drug product
- ☐ Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- ☐ Unsure

Skip To: Q13 If What type(s) of product(s) do you use, prescribe, or recommend for glycolic acid? Please check all th... != Compounded drug product

Skip To: Q2 If What type(s) of product(s) do you use, prescribe, or recommend for glycolic acid? Please check all th... = Compounded drug product

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Display This Question:

If What type(s) of product(s) do you use, prescribe, or recommend for glycolic acid? Please check all th... = Compounded drug product

Q2. Please list any conditions or diseases for which you use compounded **glycolic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q3. Do you use compounded **glycolic acid** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- ☐ Single
- ☐ Combination

Skip To: Q5 If Do you use compounded glycolic acid as a single agent active ingredient, or as one active ingredient... != Combination

Display This Question:

If Loop current: Do you use compounded glycolic acid as a single agent active ingredient, or as one active ingredient... = Combination

Q4. Please list all combination products in which you use compounded **glycolic acid**.

_____

Q5. For which, if any, diseases or conditions do you consider compounded **glycolic acid** standard therapy?

_____

Q6. Does your specialty describe the use of compounded **glycolic acid** in medical practice guidelines or other resources?

_____

Q7. Over the past 5 years, has the frequency in which you have used compounded **glycolic acid** changed?

- o Yes - I use it **MORE** often now (briefly describe why) _____
- o Yes - I use it **LESS** often now (briefly describe why) _____
- o No - use has remained consistent

Q8. Why do you use compounded **glycolic acid** instead of any FDA-approved drug product?

_____

Q9. Do you stock non-patient-specific compounded **glycolic acid** in your practice location?

- Yes
- No

Skip To: End of Block If Do you stock non-patient-specific compounded glycolic acid in your practice location? = No

Display This Question:

If Do you stock non-patient-specific compounded glycolic acid in your practice location? = Yes

Q10. In what practice location(s) do you stock non-patient-specific compounded **glycolic acid**? Please check all that apply.

- ☐ Physician office
- ☐ Outpatient clinic
- ☐ Emergency room
- ☐ Operating room
- ☐ Inpatient ward
- ☐ Other (please describe) _____

Q11. How do you obtain your stock of non-patient-specific compounded **glycolic acid**? Please check all that apply.

- ☐ Purchase from a compounding pharmacy
- ☐ Purchase from an outsourcing facility
- ☐ Compound the product yourself
- ☐ Other (please describe) _____

Q12. Why do you keep a stock of non-patient-specific compounded **glycolic acid**? Please check all that apply.

- ☐ Convenience
- ☐ Emergencies
- ☐ Other (please describe) _____

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded glycolic acid? Please check all that apply. = Convenience

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded glycolic acid? Please check all that apply. = Emergencies

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded glycolic acid? Please check all that apply. = Other (please describe)

Q13. For which, if any, diseases or conditions do you consider **glycolic acid** standard therapy?

_____

Q14. Does your specialty describe the use of **glycolic acid** in medical practice guidelines or other resources?

_____

End of Block: Glycolic acid

Start of Block: Background Information

Q15. What is your terminal clinical degree? Please check all that apply.

- ▢ Doctor of Medicine (MD)
- ▢ Doctor of Osteopathic Medicine (DO)
- ▢ Doctor of Medicine in Dentistry (DMD/DDS)
- ▢ Naturopathic Doctor (ND)
- ▢ Nurse Practitioner (NP)
- ▢ Physician Assistant (PA)
- ▢ Other (please describe) _____

Q16. Which of the following Board certification(s) do you hold? Please check all that apply.

- ▢ No Board certification
- ▢ Allergy and Immunology
- ▢ Anesthesiology
- ▢ Cardiovascular Disease
- ▢ Critical Care Medicine
- ▢ Dermatology
- ▢ Emergency Medicine
- ▢ Endocrinology, Diabetes and Metabolism
- ▢ Family Medicine
- ▢ Gastroenterology
- ▢ Hematology
- ▢ Infectious Disease
- ▢ Internal Medicine
- ▢ Medical Toxicology
- ▢ Naturopathic Doctor
- ▢ Naturopathic Physician
- ▢ Nephrology
- ▢ Neurology
- ▢ Obstetrics and Gynecology
- ▢ Oncology
- ▢ Ophthalmology
- ▢ Otolaryngology
- ▢ Pain Medicine
- ▢ Pediatrics
- ▢ Psychiatry
- ▢ Rheumatology
- ▢ Sleep Medicine
- ▢ Surgery (please describe) _____
- ▢ Urology
- ▢ Other (please describe) _____

End of Block: Background Information

Appendix 4. Raw survey data

See attached PDF for raw survey data.

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [x] Alpha lipoic acid (ALA)
- [x] Ascorbyl palmitate
- [x] Coenzyme Q10
- [x] Estriol
- [x] Glycolic acid
- [x] Hydroquinone
- [ ] Malic acid
- [ ] Methylcobalamin
- [x] Trichloroacetic acid
- [x] Vitamin A acetate
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **alpha lipoic acid (ALA)**? Please check all that apply.

- [x] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q3. Please list any conditions or diseases for which you use compounded **alpha lipoic acid (ALA)** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe): Atopic dermatitis	2-5%	Bid	Topical	Topical	2-4 months	Both sexes children and adults
Condition 2 (please describe): Psoriasis	2-5%	Bid	Topical	Topical	Indefinite	Children adults both sexes
Condition 3 (please describe):						
Condition 4 (please describe):						
Condition 5 (please describe):						

Q4.
Do you use compounded **alpha lipoic acid (ALA)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [ ] Single
- [x] Combination

Q5. Please list all combination products in which you use compounded **alpha lipoic acid (ALA).**

Versabase cream, vitamin d, multiple vitamin Bs, protopic, capric triglycerides,

Q6. For which, if any, diseases or conditions do you consider compounded **alpha lipoic acid (ALA)** standard therapy?

Psoriasis atopic dermatitis

Q7. Does your specialty describe the use of compounded **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

Q8. Over the past 5 years, has the frequency in which you have used compounded **alpha lipoic acid (ALA)** changed?

- ○ Yes - I use it **MORE** often now (briefly describe why)
- ◉ Yes - I use it **LESS** often now (briefly describe why) Better biological drugs for psoriasis so lead need for steroid soaring topicals
- ○ No - use has remained consistent

Q9. Why do you use compounded **alpha lipoic acid (ALA)** instead of any FDA-approved drug product?

Because it makes compliance better with different j gradients and the bases used allow for better penetration and one can customize for an indicidual

Q10. Do you stock non-patient-specific compounded **alpha lipoic acid (ALA)** in your practice location?

- ○ Yes
- ◉ No

Q11. In what practice location(s) do you stock non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **ascorbyl palmitate**? Please check all that apply.

- [ ] Compounded drug product
- [x] FDA-approved drug product
- [x] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q389. Please list any conditions or diseases for which you use compounded **ascorbyl palmitate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **ascorbyl palmitate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. Please list all combination products in which you use compounded **ascorbyl palmitate**.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **ascorbyl palmitate** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **ascorbyl palmitate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **ascorbyl palmitate** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **ascorbyl palmitate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **ascorbyl palmitate** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **ascorbyl palmitate**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **ascorbyl palmitate**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **ascorbyl palmitate**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **ascorbyl palmitate** standard therapy?

Sun damage

Q401. Does your specialty describe the use of **ascorbyl palmitate** in medical practice guidelines or other resources?

Yes

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **coenzyme Q10**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [x] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q403. Please list any conditions or diseases for which you use compounded **coenzyme Q10** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **coenzyme Q10** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **coenzyme Q10.**

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **coenzyme Q10** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **coenzyme Q10** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **coenzyme Q10** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **coenzyme Q10** standard therapy?

Fibromyalgia and when patient is on statin and other medicarions

Q415. Does your specialty describe the use of **coenzyme Q10** in medical practice guidelines or other resources?

Yes

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **estriol**? Please check all that apply.

- [x] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q417. Please list any conditions or diseases for which you use compounded **estriol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe): Lichen sclerosus et atrophicus	1-2 mg	Bid	Mg	Topical	Indefinitely	Peri to post menopausal women
Condition 2 (please describe): Atrophic vaginitis	5 mg	Biweekly	Mg	Intravaginal suppository	Indefinitely	Peri to post menopausal women
Condition 3 (please describe): Erosive desquamative vaginitis	1-2 mg	Bi weekly	Mg	Intravaginal suppositories	3-6months	Older adult women
Condition 4 (please describe):						
Condition 5 (please describe):						

Q418.
Do you use compounded **estriol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [x] Single
- [x] Combination

Q419. Please list all combination products in which you use compounded **estriol.**

Mucolox amd sometimes testosterone

Q420. For which, if any, diseases or conditions do you consider compounded **estriol** standard therapy?

Atrophic vaginitis and lichen sclerosis et ateophicus

Q421. Does your specialty describe the use of compounded **estriol** in medical practice guidelines or other resources?

Yea

Q422. Over the past 5 years, has the frequency in which you have used compounded **estriol** changed?

- (●) Yes - I use it **MORE** often now (briefly describe why) [More comfortable with experience of ise]
- ( ) Yes - I use it **LESS** often now (briefly describe why) [ ]
- ( ) No - use has remained consistent

Q423. Why do you use compounded **estriol** instead of any FDA-approved drug product?

It is less inflammatory and also a less potent estrogen

Q424. Do you stock non-patient-specific compounded **estriol** in your practice location?

- ( ) Yes
- (●) No

Q425. In what practice location(s) do you stock non-patient-specific compounded **estriol**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **estriol**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **estriol**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **estriol** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **estriol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **glycolic acid**? Please check all that apply.

- [ ] Compounded drug product
- [x] FDA-approved drug product
- [x] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q431. Please list any conditions or diseases for which you use compounded **glycolic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **glycolic acid** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. Please list all combination products in which you use compounded **glycolic acid.**

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **glycolic acid** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **glycolic acid** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **glycolic acid** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **glycolic acid** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **glycolic acid** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **glycolic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **glycolic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **glycolic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **glycolic acid** standard therapy?

Acne anti-aging sun damage

Q443. Does your specialty describe the use of **glycolic acid** in medical practice guidelines or other resources?

Yes

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **hydroquinone**? Please check all that apply.

- [ ] Compounded drug product
- [x] FDA-approved drug product
- [x] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q445. Please list any conditions or diseases for which you use compounded **hydroquinone** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **hydroquinone** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. In which combination(s) do you use compounded **hydroquinone**? Please check all that apply.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **hydroquinone** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **hydroquinone** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **hydroquinone** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **hydroquinone** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **hydroquinone** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **hydroquinone**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **hydroquinone**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **hydroquinone**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **hydroquinone** standard therapy?

Melisma and pre and post laser therapy

Q457. Does your specialty describe the use of **hydroquinone** in medical practice guidelines or other resources?

Yes

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **malic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **malic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **malic acid** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **malic acid.**

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **malic acid** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **malic acid** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **malic acid** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **malic acid** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **malic acid** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **malic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **malic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **malic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **malic acid** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **malic acid** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **methylcobalamin**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **methylcobalamin** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.

Do you use compounded **methylcobalamin** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. In which combination(s) do you use compounded **methylcobalamin**? Please check all that apply.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **methylcobalamin** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **methylcobalamin** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **methylcobalamin** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **methylcobalamin** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **methylcobalamin** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **methylcobalamin**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **methylcobalamin**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **methylcobalamin**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **methylcobalamin** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **methylcobalamin** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **trichloroacetic acid**? Please check all that apply.

- [ ] Compounded drug product
- [x] FDA-approved drug product
- [x] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q487. Please list any conditions or diseases for which you use compounded **trichloroacetic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **trichloroacetic acid** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **trichloroacetic acid.**

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **trichloroacetic acid** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **trichloroacetic acid** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **trichloroacetic acid** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **trichloroacetic acid** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **trichloroacetic acid** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **trichloroacetic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **trichloroacetic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **trichloroacetic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **trichloroacetic acid** standard therapy?

Cosmetic peels, actinic keratosis, sebaceous hyperplasia, acne scarring

Q499. Does your specialty describe the use of **trichloroacetic acid** in medical practice guidelines or other resources?

Yes

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **vitamin A acetate**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **vitamin A acetate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **vitamin A acetate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **vitamin A acetate.**

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **vitamin A acetate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **vitamin A acetate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **vitamin A acetate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **vitamin A acetate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **vitamin A acetate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **vitamin A acetate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **vitamin A acetate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **vitamin A acetate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **vitamin A acetate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **vitamin A acetate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

This question was not displayed to the respondent.

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

This question was not displayed to the respondent.

Q145. How has access to compounded medications affected patient care?

This question was not displayed to the respondent.