Summary Report

Hydroquinone

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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REVIEW OF NOMINATIONS

Hydroquinone (UNII code: XV74C1N1AE) was nominated for inclusion on the 503B Bulks List by Sincerus Florida, LLC, Fagron, the Outsourcing Facilities Association (OFA), and Triangle Compounding Pharmacy. While the exact medical condition for which the compounded product is being requested is generally unknown, hydroquinone is generally indicated for hyperpigmentation. Hydroquinone was also nominated for use in wrinkles, acne, skin discoloration, and melasma. Hydroquinone was nominated for use in various topical dosage forms and strengths ranging from 3-8% as requested by the prescriber, including gels, creams, ointments, solutions, suspensions, and other formulations. Hydroquinone was nominated for use in combination with other active pharmaceutical ingredients (API), refer to table 7 for the combination formulations.

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

- The FDA-approved product may be inappropriate due to the dosage form, strength, or flavor of the commercially available product.
- Compounding from a bulk drug substance means that only the ingredients necessary to achieve the desired clinical outcome are utilized eliminating any fillers, excipients, binders, dyes, preservatives, or other materials that may be irritating, hazardous, or allergenic.
- Variance in the API of finished products may introduce unacceptable inaccuracies into the compounded product; compounding from the bulk substance is more accurate.
- There is no FDA-approved drug product currently available on the market.
- Patients respond differently and the compounded drug product may be the only formulation to effectively treat the indication for which it is intended to treat.
- The need for a different combination or a different base than what is commercially available.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of hydroquinone 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 hydroquinone; name variations of hydroquinone 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 hydroquinone. 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 June 11, 2019. The search included a combination of (hydroquinone[TIAB] OR "benzene-1,4-diol"[TIAB] OR "1,4-dihydroxybenzene"[TIAB]) AND (tretinoin[TIAB] OR "kojic acid"[TIAB] OR triamcinolone[TIAB] OR "glycolic acid"[TIAB] OR hydrocortisone[TIAB] OR "ascorbyl palmitate"[TIAB] OR "hyaluronic acid"[TIAB] OR desoximetasone[TIAB] OR "green tea extract"[TIAB] OR sinecatechins[TIAB] OR "soya protein"[TIAB] OR "soybean protein"[TIAB] OR niacinamide[TIAB] OR "betamethasone dipropionate"[TIAB] OR "potassium azeloyl diglycinate"[TIAB] OR topical* OR cream OR gel OR ointment OR solution OR suspension OR emulsion) AND (melasma[TIAB] OR wrinkles[TIAB] OR acne[TIAB] OR hyperpigmentation[TIAB] OR pigmentation[TIAB] OR dermat*[TIAB] OR treat*[TIAB] OR therap*[TIAB] OR clinic*[TIAB]) AND (humans[MeSH Terms] AND English[lang]) NOT autism. 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

Literature reviews and/or meta-analyses, cost-effectiveness, and epidemiological studies were excluded. Hydroquinone is a component of an FDA-approved product, as a result, articles were excluded if hydroquinone was utilized as the FDA-approved product or in the same concentration and formulation as the FDA-approved product. Articles were considered relevant based on the identification of a clinical use of hydroquinone or the implementation of hydroquinone 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.

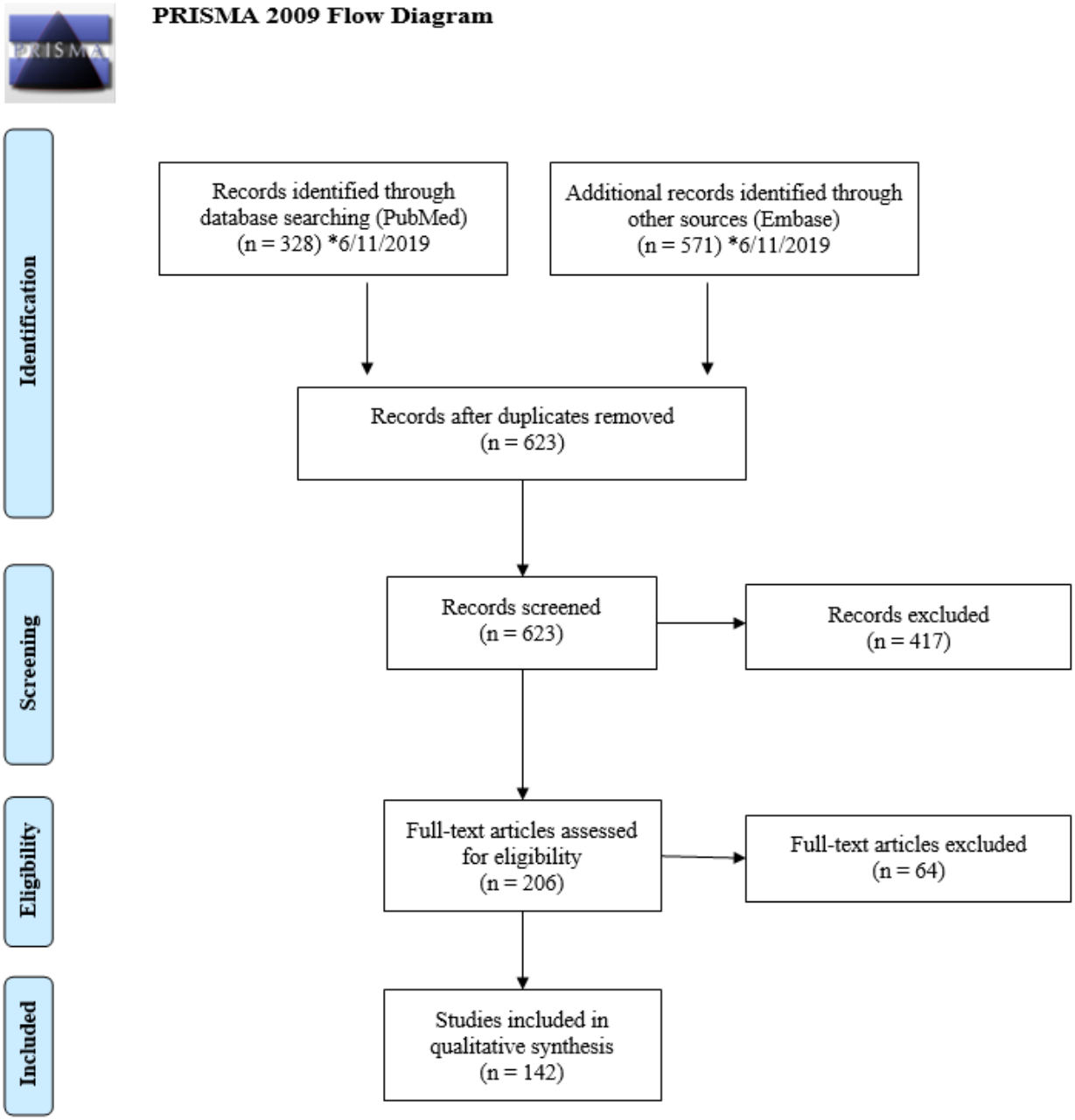
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for hydroquinone 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 hydroquinone 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

For more information, visit www.prisma-statement.org.

Outreach to medical specialists and specialty organizations

Using the indications from the nominations and the results of the literature review, one (1) medical specialty that would potentially use hydroquinone was identified: dermatology. Semi-structured interviews were conducted with subject matter experts within this specialty. 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. One (1) experts were contacted for interviews, of which one (1) accepted and zero (0) declined interviews. Interview was 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, identified from the nominations and literature review, 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 four (4) 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

CURRENT AND HISTORIC USE

Summary of background information

- Hydroquinone is available as an FDA-approved product, but not in any of the nominated combinations.
- Hydroquinone is available in various topical dosage forms as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for hydroquinone.
- Hydroquinone is available in Abu Dhabi, New Zealand, and Saudi Arabia.

Table 3. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	ROA	Status	Approval Date
Hydroquinone / Fluocinolone acetonide / Tretinoin	4% / 0.01% / 0.05%	Cream	Topical	Prescription	01/18/2002

Abbreviation: ROA, route of administration.
[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

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

Active Ingredient	Concentration	Dosage Form	ROA	Approved For Use		
				Country	Status	Approval Date[b]
Hydroquinone	2-4%	Cream	–	Abu Dhabi	Active	–
	2%	Cream	Topical	New Zealand	Pharmacy[c]	11/25/1964
	0.05-4%	Cream	Topical	Saudi Arabia	Prescription	–

Abbreviations: "–", not mentioned; ROA, route of administration.
[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA and approval status) provided in a useable format. Information was recorded only for products with strengths, forms and/or routes of administration similar to those requested in the nominations. See Methodology for full explanation.
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.
[c]Pharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Summary of literature review

- Total number of studies included: 142 studies (8 descriptive, 133 experimental, and 1 observational).
- Most of the studies were from the US (45 studies).
- The most common indications for the use of hydroquinone in both the US and non-US studies were melasma and hyperpigmentation.
- Compounded products were identified from both US and non-US studies, but not in any of the nominated formulations.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive[1-8]	8
Experimental[9-141]	133
Observational[142]	1

Table 6. Number of studies by country

Country	Number of Studies
Argentina[16]	1
Brazil[22,40,60,64,90,98]	6
China[44,52,138,140]	4
Egypt[11,14,15,67,99]	5
France[2]	1
Hong Kong[86]	1
India[18,19,25,27,31,32,46,48-50,66,70,79,91,102,112-116,119,120]	22
Iran[12,13,17,38,39,41,43,47,85,96,100,111,121-123,137,139]	17
Iraq[130]	1
Israel[61,62]	2
Italy[125]	1
Japan[68,74,97,101,117,132-136]	10

Mexico[42,124]	2
The Netherlands[82,128]	2
Pakistan[9,59,92,106,141]	5
Philippines[95]	1
Puerto Rico[110,126]	2
Singapore[88]	1
South Korea[6,26,75,84]	4
Sweden[10]	1
Switzerland[69]	1
Taiwan[24,127]	2
Thailand[23,105]	2
Turkey[104]	1
UK[4]	1
US[1,3,5,7,8,20,21,28-30,33-37,45,51,53-58,63,65,71-73,76,77,80,81,83,87,89,94,103,107-109,129,131,142]	43
Multiple Countries • France, UK[78] • US, Japan[93] • US, Thailand[118]	3
	Total US[a]: 45 Total non-US Countries[a]: 99

[a]Studies 93 and 118 counted in both US and non-US total.

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Hydroquinone 8% / Ascorbyl palmitate 2% / Betamethasone dipropionate 0.05% / Hyaluronic acid sodium salt 0.2% / Kojic acid 6% / Niacinamide 2% / Potassium azeloyl diglycinate 8% / Lidocaine 1% / Prilocaine 7%	0
	Hydroquinone 6% / Ascorbyl palmitate 2% / Green tea extract 2% / Hydrocortisone 0.5% / Kojic acid 6%	0
	Hydroquinone 8% / Ascorbyl palmitate 2% / Green tea extract 2% / Kojic acid 4%	0
	Hydroquinone 8% / Ascorbyl palmitate 2% / Green tea extract 2% / Kojic acid 4% / Tretinoin 0.025%	0
	Hydroquinone 4% / Ascorbyl palmitate 2% / Hyaluronic acid sodium salt 0.5% / Hydrocortisone 0.5% / Kojic acid	0
	Hydroquinone 4% / Ascorbyl palmitate 2% / Hyaluronic acid sodium salt 0.5% / Kojic acid 4% / Tretinoin 0.05%	0
	Hydroquinone 4% / Ascorbyl palmitate 2% / Hydrocortisone 0.5% / Kojic acid 6% / Tretinoin 0.025%	0
	Hydroquinone 6% / Desoximetasone 0.05% / Tretinoin 0.05%	0
	Hydroquinone 6% / Glycolic acid 10% / Tretinoin 0.1%	0
	Hydroquinone 3-6% / Glycolic acid / Tretinoin / Triamcinolone	0
	Hydroquinone 6% / Hyaluronic acid sodium salt 1%	0
	Hydroquinone 4% / Hydrocortisone 0.5%	0
	Hydroquinone 4-8% / Hydrocortisone 0.5% / Kojic acid 4-6% / Tretinoin 0.025-0.05%	0
	Hydroquinone 4-8% / Hydrocortisone 1-4% / Tretinoin 0.025-0.05%[84]	1
	Hydroquinone 4-8% / Kojic acid 4%	0
	Hydroquinone 4-8% / Kojic acid 4% / Tretinoin 0.025-0.1%	0

	Hydroquinone 4% / Kojic acid 6% / Niacinamide 2% / Soya protein 1% / Tretinoin 0.025%	0
	Hydroquinone 4-6% / Tretinoin 0.025-0.05% / Triamcinolone acetonide 0.025%	0
Others found in literature	Hydroquinone 3-5% / Ascorbic acid 0.2-10%[110,117,132,134-136]	6
	Hydroquinone 6% / Ascorbyl acid 0.1% / Tretinoin 0.05% / Triamcinolone acetonide 0.05%[58]	1
	Hydroquinone 5% / Azelaic acid 20%[123]	1
	Hydroquinone 1.6% / Azelaic acid 4% / Methylprednisolone aceponate 0.04% / Salicylic acid 2%[104]	1
	Hydroquinone 2% / Betamethasone valerate 0.1% / Kojic acid 1%[32]	1
	Hydroquinone 3% / Dexamethasone 0.01%[38]	1
	Hydroquinone 4-5% / Dexamethasone 0.03-0.1% / Tretinoin 0.03-1.1%[2,12,41,69,80]	5
	Hydroquinone 2-4% / Fluocinolone acetonide 0.01% / Tretinoin 0.025-0.05%[7,8,19,20,24,48,49,52,53,56,57,59,64,91,102,108]	16
	Hydroquinone 2-4% / Glycolic acid 5-10%[46,67,88,90]	4
	Hydroquinone 4% / Glycolic acid 10% / Hyaluronic acid 0.01%[67]	1
	Hydroquinone 2% / Glycolic acid 2-10% / Kojic acid 1-2%[27,88]	2
	Hydroquinone 4% / Hyaluronic acid 0.01%[67]	1
	Hydroquinone 4% / Hydrocortisone butyrate 0.1% / Retinoic acid 0.03%[125]	1
	Hydroquinone 2-5% / Hydrocortisone 1% / Tretinoin 0.05-0.1%[4,75,114,115]	4
	Hydroquinone 2% / Kojic acid 1%[32]	1
	Hydroquinone 5% / Lactic acid 7%[117,132-136]	6
	Hydroquinone 2-4% / Mometasone furoate 0.1-1% / Tretinoin 0.025-0.05%[31,48,50,66]	4

	Hydroquinone 4% / Retinol 0.15-0.3%[28,55,56]	3
	Hydroquinone 2-4% / Tretinoin 0.025-0.1%[86,113,129]	3
	Hydroquinone 5% / Tretinoin 0.05% / Triamcinolone acetonide 0.1%[82,128]	2
	Hydroquinone 0.05% / Undecylenic acid 0.1%[107]	1

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Melasma/hyperpigmentation[1,3,5,7,8,20,21,28-30,33-37,45,51,53-58,65,71-73,76,77,80,81,93,103,108,109,118,142]	–	2-6%	Cream	Topical	4 weeks - 8 months
		2-10%	Ointment, solution		–
		2-5%	Lotion		3 months
		2-4%	–		2-6 months
		–			–
Photodamage[63,87,89,129]	–	4%	Cream	Topical	24 weeks
			–		90 days – 24 weeks
Skin lightening[83,94,131]	–	2-4%	Cream	Topical	2-12 weeks
Onychomycosis[107]	–	0.05%	Solution	Topical	At most 1 year

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

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Melasma/hyperpigmentation[4,6,9-19,22-27,31,32,38-44,46-50,52,59-62,64,66-68,70,74,75,82,85,86,88,90-93,95-102,104-106,110-128,130,132-134,136,137,139-141]	0.3g/week	1.6-5%	Cream	Topical	2 weeks -18 months
	–	2%	Gel		12 weeks
	–	4-5%	Ointment		2 -16 weeks
	–	5%	Sheet		2 months
	–	3-5%	Solution		2-4 months
	–	2-5%	–		3 weeks – 6 months
Solar lentigines[69,78]	–	4-5%	Cream	Topical	4-5 months
Riehl's melanosis[138]	–	2%	Cream	Topical	–
Cosmetic color improvement of nipple-areola complex[135]	–	5%	Ointment	Topical	8-12 weeks
Facial (acne[79]) scars[84]	–	4%	Cream	Topical	2-4 weeks
			–		3-6 months
Graft-versus-host disease[2]	–	5%	Ointment	Topical	3 months

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

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Melasma[45]	1996	• 4% padimate O, 5% glycolic acid, 10% propylene glycol, 0.1% sodium bisulfate, q.s. alcohol gel. Stored in opaque bottles.	–	2%

Abbreviation: "–", not mentioned.

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Melasma/hyperpigmentation [47,67,68,88,97,104,105,117,121,123,132-134,136,137]	• GMP-approved facility. Vehicles: water, cetostearyl alcohol, petrolatum, paraffin, sodium lauryl sulfate, antioxidants, and antimicrobial preservatives. Hydroquinone was dissolved in water to make the aqueous phase of the cream. "Creams were packed in similar epoxy resin–coated aluminum tubes with a 5-mm nozzle and stored at room temperature until use."[47] • "Powdered and levigated with propylene glycol to form a smooth paste. This paste was incorporated into the prepared cream base with triturating until homogeneity. The prepared formulations were packed in opaque air tight containers and stored out of sun and at 4 temperature degree."[67] • "Mixing official drug products and adding salicylic acid; components of mixture were azelaic acid (20%) 30 g cream, hydroquinone (4%) 60 g cream, methylprednisolone aceponate (0.1%) 60 g cream, salicylic acid 3 g) so approximate percentages of active materials after the dilution effect in 150 g cream mixture obtained were azelaic acid 4%, hydroquinone 1.6%, methylprednisolone 0.04%, salicylic acid 2%"[104] • "Separate airless tube by P&O Healthy Care, Thailand"[105]	Cream	1.6-4%
	• "Prepared by Dermatologic Cosmetic Lab and stored in glass bottles"[88]	Gel	2%
	• "Prepared with a hydrophilic base ointment at least once a month and stored in a dark, cool (4 C) place"[97] • HQ-LA: petrolatum polyethylene ointment base (Plastibase, Taisho Pharmacology, Osaka, Japan); HQ-AA: hydrophilic ointment (Taisho Pharmacology)[117] • "Prepared at the department of pharmacy at university of Tokyo. Plastibase (petrolatum polyethylene ointment base, Taisho Pharmacology, Osaka, Japan) and hydrophilic ointment were used as the ointment bases of the HQ-LA and HQ-AA ointments repectively. prepared at least once a month and stored in a dark, cool (4 C) place"[132-134,136]	Ointment	5%
	• "Silicone sheets are made from a silicone gel in which various chemicals can be dissolved. Because HQ is composed of needle crystals, it cannot be dissolved in silicone gel, so ethanol is added. Silicone gel containing HQ with and without RAs then poured into a flat container and hardened at a temperature of 130°C for 2 minutes.[68]	Sheet	5%
	• With or without azelaic acid, in base of etanol 70, propyleneglycol 15% to enhance penetration, ascorbic acid 5% as an antioxidant[123]	Solution	4-5%

	• "Liposomes containing 4% hydroquinone prepared by fusion method. Malvern unit particle size analyzer determined the diameter (particle diameter) and potential of these liposomes. The percentage of liposomal confinement was also determined by direct dialysis after the unencapsulated hydroquinone was isolated. The amount of hydroquinone was also determined by spectrophotometry. Lipid components include soybean phosphatidylcholine and cholesterol (American Avanti polar lipid), methylparaben, propylparaben, propylene glycol and vitamin E (German MERK), 4% hydroquinone powder (German MERK)"[121]	–	4%
Cosmetic color improvement of nipple-areola complex[135]	• "Plastibase (petrolatum polyethylene ointment base, Taisho Pharmacology, Osaka, Japan) was used as the ointment base of the HQ-LA ointment, while hydrophilic ointment was used as the ointment base for HQ-AA ointments. fresh ointments prepared at least once a month and stored in a dark, cool (4C) place"	Ointment	5%

Abbreviation: "–", not mentioned.

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

One (1) interviews were conducted.

Table 12. Overview of interviewee

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Hydroquinone	Interview Summary Response
DER_07	MD	Dermatology, Immunology	Consulting	Yes	• Used before but rarely, because the interviewee mostly took care of medical dermatology patients (auto-immune blistering diseases, collagen vascular diseases) and rarely had patients who had acne or pigment disorders. But familiar with varying reasons for using it. • There may be need for office stock, not to administer it in the office but to dispense to the patients the prescriber's favorite mixture.

Abbreviation: MD, Doctor of Medicine.

History

- It was available as OTC up to 4%. Back in the 80s, hydroquinone (under 5%) was recognized as safe and effective but in the 90s, the FDA removed it from the list.
- Before TriLuma came into market, hydroquinone has been used in other combinations, which could be why people are advocating for making it available.

Reasons for using hydroquinone

- Some patients do not tolerate retinoids and the commercially available product (TriLuma) has retinoid in it.

Concern

- The interviewee expressed concern about the use of concentrations greater than 5% because with long-term use, patient may experience exogenous ochronosis, especially if it's unsupervised use.

Combination use

- Hydroquinone can be used with other active ingredients to promote hydroquinone effect.
    - Kojic acid – used as bleaching cream
    - Vitamin C – used as anti-inflammatory, to help rejuvenate skin
    - Green tea extract – no great science behind it but thought to help wrinkles and protect from sun damage
    - Steroid – to calm inflammation, especially if tretinoin is included
- But interviewee worries that when all the active ingredients are mixed, stability and efficacy may be an issue.

Indications

- Melasma, pigmentation disorders – Used as long as it takes, typically 4-6 months
    - Works better with pigments that are superficial compared to deep dermal pigments
    - Patients with darker skin tones are more challenging to treat because they are at higher risk for both post-inflammatory hyperpigmentation and from melasma
- Wrinkles

Choice of formulation

- Based on patient preference and solubility
    - Cream is more elegant on face compared to ointment, and solutions tend to run off.
- Generally, prescribers allow pharmacist to determine which formulation would be most appropriate.

Summary of survey results

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

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 1 respondent, 1 reported using, prescribing, or recommending multiple types of hydroquinone products.

Table 15. Compounded use of hydroquinone in practice

No survey respondents provided this information

Table 16. Indications for which hydroquinone is considered a standard therapy

Indication	Standard Therapy	
	Compounded, n (N=0)	Non-compounded, n (N=1)
Melasma and pre/post laser therapy	0	1

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 hydroquinone usage over the past 5 years

No survey respondents provided this information

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

No survey respondents provided this information

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

No survey respondents provided this information

CONCLUSION

Hydroquinone (UNII code: XV74C1N1AE) was nominated for inclusion on the 503B Bulks List by Sincerus Florida, LLC, Fagron, OFA, and Triangle Compounding Pharmacy. While the exact medical condition for which the compounded product is being requested is generally unknown, hydroquinone is generally indicated for hyperpigmentation. Hydroquinone was also nominated for use in wrinkles, acne, skin discoloration, and melasma. Hydroquinone was nominated for use in various topical dosage forms and strengths ranging from 2-8% as requested by the prescriber, including gels, creams, ointments, solutions, suspensions, and other formulations. Hydroquinone is available in the US, Abu Dhabi, New Zealand, and Saudi Arabia.

From the literature review conducted, the most common indication for the use of hydroquinone in both the US and non-US studies were melasma and hyperpigmentation. Compounded products were identified from both the US and non-US studies, but not in any of the nominated formulations.

From the interview, one (1) interviewee has used it before for pigmentation disorders. One of the reasons for using compounded product over a commercially available product may be due to patient intolerance to retinoids. The interviewee stated that it is used long-term for pigmentation treatments so if there is a reason for office stock, it would be to dispense, not to administer in the office. However, the interviewee expressed concern for higher concentration products (greater than 5%) as it may cause exogenous ochronosis with long-term use.

From the survey responses, one (1) out of one (1) respondent used hydroquinone but not as a compounded product.

APPENDICES

Appendix 1. References

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Appendix 2. 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 **hydroquinone**. 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: Hydroquinone

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **hydroquinone**? 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 hydroquinone? Please check all th... != Compounded drug product

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

Q2. 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).

	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 **hydroquinone** 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 hydroquinone as a single agent active ingredient, or as one active ingredient... != Combination

Display This Question:

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

Q4. In which combination(s) do you use compounded **hydroquinone**? Please check all that apply.

- ☐ Hydroquinone 4% / Hydrocortisone 0.5%
- ☐ Hydroquinone 4% / Ascorbyl palmitate 2% / Hyaluronic acid sodium salt 0.5% / Hydrocortisone 0.5% / Kojic acid
- ☐ Hydroquinone 4% / Ascorbyl palmitate 2% / Hyaluronic acid sodium salt 0.5% / Kojic acid 4% / Tretinoin 0.05%
- ☐ Hydroquinone 4% / Ascorbyl palmitate 2% / Hydrocortisone 0.5% / Kojic acid 6% / Tretinoin 0.025%
- ☐ Hydroquinone 4% / Kojic acid 6% / Niacinamide 2% / Soya protein 1% / Tretinoin 0.025%
- ☐ Hydroquinone 6% / Hyaluronic acid sodium salt 1%
- ☐ Hydroquinone 6% / Desoximetasone 0.05% / Tretinoin 0.05%
- ☐ Hydroquinone 6% / Glycolic acid 10% / Tretinoin 0.1%
- ☐ Hydroquinone 6% / Ascorbyl palmitate 2% / Green tea extract 2% / Hydrocortisone 0.5% / Kojic acid 6%
- ☐ Hydroquinone 8% / Ascorbyl palmitate 2% / Green tea extract 2% / Kojic acid 4%
- ☐ Hydroquinone 8% / Ascorbyl palmitate 2% / Green tea extract 2% / Kojic acid 4% / Tretinoin 0.025%
- ☐ Hydroquinone 8% / Ascorbyl palmitate 2% / Betamethasone dipropionate 0.05% / Hyaluronic acid sodium salt 0.2% / Kojic acid 6% / Niacinamide 2% / Potassium azeloyl diglycinate 8%

- ☐ Hydroquinone 3-6% / Glycolic acid / Tretinoin / Triamcinolone
- ☐ Hydroquinone 4-8% / Hydrocortisone 1-4% / Tretinoin 0.025-0.05%
- ☐ Hydroquinone 4-8% / Hydrocortisone 0.5% / Kojic acid 4-6% / Tretinoin 0.025-0.05%
- ☐ Hydroquinone 4-8% / Kojic acid 4%
- ☐ Hydroquinone 4-8% / Kojic acid 4% / Tretinoin 0.025-0.1%
- ☐ Hydroquinone 4-6% / Tretinoin 0.025-0.05% / Triamcinolone acetonide 0.025%
- ☐ Other (please describe) _____

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

_____

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

_____

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

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

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

_____

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

- ○ Yes
- ○ No

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

Display This Question:

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

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

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

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

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

_____

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

_____

End of Block: Hydroquinone

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