

Summary Report

Hydrogen peroxide

Prepared for:

Food and Drug Administration

Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List

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Table of Contents

INTRODUCTION	5
REVIEW OF NOMINATION	5
METHODOLOGY	5
Background information	5
Systematic literature review	6
Interviews.....	7
Survey	7
CURRENT AND HISTORIC USE	8
Results of background information.....	8
Results of literature review	8
Results of interviews.....	16
Results of survey.....	17
CONCLUSION.....	17
REFERENCES	18
APPENDICES	20
Appendix 1. Search strategies for bibliographic databases.....	20
Appendix 2. Survey instrument	24
Appendix 3. Survey distribution to professional associations	27

Table of Tables

Table 1. Currently approved products – US	8
Table 2. Currently approved products – select non-US countries and regions	8
Table 3. Types of studies	12
Table 4. Number of studies by country	12
Table 5. Summary of included studies	13
Table 6. Dosage by indication – US	15
Table 7. Dosage by indication – non-US countries	15
Table 8. Number of studies by combination	15
Table 9. Compounded products – US	15
Table 10. Compounded products – non-US countries	16
Table 11. Characteristics of survey respondents	17
Table 12. Conditions for which hydrogen peroxide prescribed or administered	17
Table 13. Reasons for using compounded hydrogen peroxide	17
Table 14. Use of non-patient-specific compounded hydrogen peroxide	17

Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) to evaluate the use of hydrogen peroxide (UNII code: BBX060AN9V), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

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

REVIEW OF NOMINATION

Hydrogen peroxide was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA).

Hydrogen peroxide was nominated for a variety of unspecified medical conditions via an injectable 3% intravenous infusion.

Nominators provided references from published peer-reviewed literature to describe the pharmacology, and support the clinical use, of hydrogen peroxide.⁶

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

- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Intravenous hydrogen peroxide is not available commercially.
- Intravenous hydrogen peroxide from an outsourcing facility will improve patient safety by providing a sterile, standardized preparation of intravenous hydrogen peroxide.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of hydrogen peroxide 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 hydrogen peroxide; name variations of hydrogen peroxide 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 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing hydrogen peroxide. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: hydrogen peroxide, intravascular administration, and therapeutic or preventative use (refer to Appendix 1 for full search strategies). Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to original human studies in English language. Searches were conducted on March 8, 2020. The reference lists of relevant systematic reviews and meta-analyses were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust[®] repository was searched on March 8, 2020 for clinical practice guidelines that recommended the use of hydrogen peroxide and provided sufficient dosing and administration instructions.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

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

Data extraction

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

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances hydrogen peroxide was used in a clinical setting. The systematic literature review and indications from the nomination were reviewed to identify the following medical specialties that would potentially use hydrogen peroxide: naturopathy and pain management. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

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

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

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

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

CURRENT AND HISTORIC USE

Results of background information

- Hydrogen peroxide is not available as an FDA-approved product in the nominated dosage form and ROA.
- Hydrogen peroxide is not available as an OTC product in the nominated dosage form and ROA in the US.
- There is a current United States Pharmacopeia (USP) monograph for hydrogen peroxide.
- Hydrogen peroxide is not available in the nominated dosage form and ROA in any of the national medical registries searched.

Table 1. Currently approved products – US

No approved products in the US

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

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

Results of literature review

Study selection

Database searches yielded 566 references; 5 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 446 titles and abstracts were screened. After screening, the full text of 24 articles was reviewed. Seven studies were included; after multiple reports of the same study were merged, there were 5 included studies. Seventeen studies were excluded for the following reasons: wrong study design (10 studies); non-nominated dosage form, ROA, or combination (4); unable to obtain full text (3).

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

Characteristics of included studies

The 5 included studies were published between 1963 and 2006. There were 2 experimental studies, 0 observational studies, 3 descriptive studies, and 0 clinical practice guidelines. The 5 studies were conducted in the US.

A total of 106 patients participated in the 5 included studies. The number of patients in each study ranged from 1 to 84.

Outcome measures differed among the included studies and included: tumor control, clinical improvement, arteriograms, and wound healing.

Refer to Table 7 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of hydrogen peroxide

Forty-one patients received hydrogen peroxide as a treatment for head and neck tumors, administered intra-arterially in strengths ranging from 0.06-0.18% over 1-4 weeks. One patient received hydrogen peroxide as a treatment for reduction in arteriosclerotic plaques, administered intra-arterially in 100 infusions over 28-29 days. One patient received hydrogen peroxide as a treatment for vascular collapse of unknown etiology, administered intra-arterially 6 times. Fifteen patients received hydrogen peroxide as a treatment for delayed wound healing, administered intra-arterially and intravenously for 1 week to 3 months.

Refer to Table 6 for summaries of dosage by indication.

Hydrogen peroxide was used as a compounded product but was not used in a combination product (refer to Table 9).

In 2 studies, the authors' conclusion stated that the use of hydrogen peroxide showed effectiveness for the reduction of arteriosclerotic plaques, wound healing and vascular collapse of unknown etiology.^{7,8} In 1 study, the authors concluded that further studies were necessary for the use of hydrogen peroxide as treatment for head and neck tumors.⁹ In 1 study, the authors concluded that the results were too inconsistent to properly assess the value of intra-arterial hydrogen peroxide, though it would be logical to attempt combining it with a methotrexate infusion.¹⁰ In 1 study, the authors commented that as patients gain access to treatments such as intravenous hydrogen peroxide, healthcare providers need to be watchful for potentially fatal complications, as seen with 1 patient who received treatment for a misdiagnosed spider bite.¹¹ Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 5 included studies, 6 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of hydrogen peroxide.

According to a 2007 review by Atwood, the rationale for the intravenous use of hydrogen peroxide can be traced to Dr. Charles H. Farr, the self-named "father of oxidative medicine."¹² According to Farr, hydrogen peroxide has a regulatory effect on the immune system by stimulating cells to produce cytokines. However, Atwood noted that the references Farr cited to prove his point did not provide support and were not relevant to clinical use. Those studies stemmed from a flurry of interest that hydrogen peroxide gained in the 1960s, but they were uncontrolled, had inconsistent outcomes, and while the positive studies were all reported by the same group, another group was unable to replicate the findings and so enthusiasm diminished.¹² Overall, the author described Farr's use of hydrogen peroxide as reckless, and commented that he never published his findings in a peer-reviewed journal.¹² In addition, hydrogen peroxide is known to be caustic to living tissues, and acts in direct contrast to Farr's claims of being "available for numerous intracellular and extracellular functions."¹² The author noted that extracellular hydrogen peroxide is broken down to oxygen and water, forming dangerous oxygen bubbles in the blood stream which can cause emboli, and if intact hydrogen peroxide were to come into contact with a cell, it would not enter the cell in an "orderly fashion;" rather, it would damage the cell membrane and destroy the cell.¹² The author concluded that "the information that 'oxidative medicine' practitioners rely upon as the basis for their prescribing intravenous hydrogen peroxide is wholly inadequate to justify such treatment."¹²

Other indications for intravenous hydrogen peroxide found in excluded studies were influenzal pneumonia, contrast echocardiography, and management of patients with the Chikungunya virus.¹³⁻¹⁶ In the 1920 study looking at influenzal pneumonia, the intent of the use of hydrogen peroxide was to

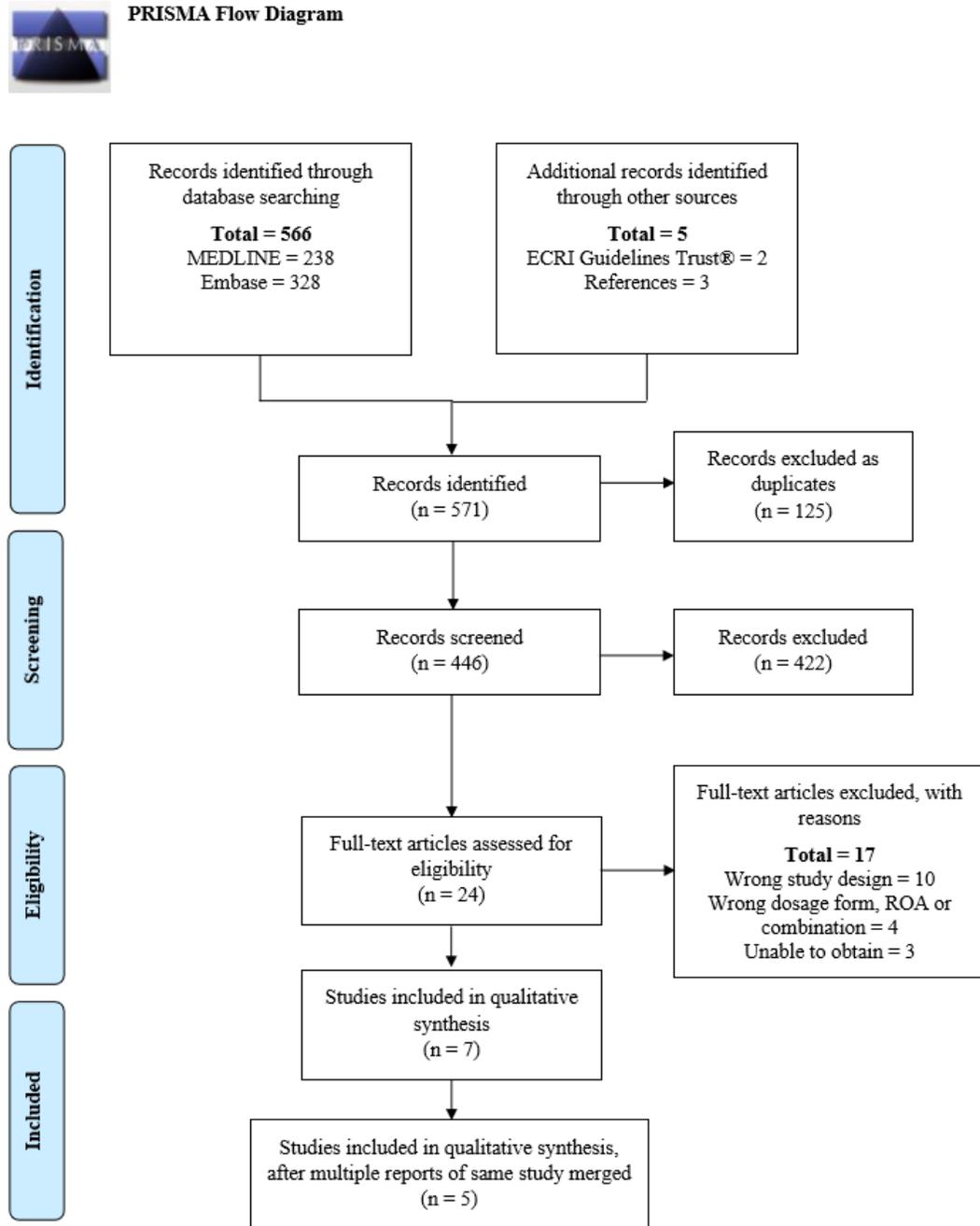
battle extreme toxemia and anoxæmia.¹³ The authors reported that with slow administration, they did not see the production of gas emboli, and they did see benefit with decreased mortality.¹³ In the 1979 and 1988 studies using hydrogen peroxide for contrast echocardiography, they describe satisfactory results, though they emphasized being careful with administration to prevent gas emboli.^{14,15} In the 2015 study examining the use of intravenous ascorbic acid and hydrogen peroxide in the management of patients with Chikungunya, the interventions were administered to address the moderate to severe persistent pain associated with the Chikungunya virus.¹⁶ The infusion of hydrogen peroxide was a 3% solution administered with magnesium chloride and methylcobalamin.¹⁶ The authors concluded that their protocol showed the use of intravenous hydrogen peroxide and ascorbic acid was effective with a post-infusion reduction of pain of more than 61%, though randomized controlled studies needed to be done to explore treatment options.¹⁶

Another study had patients receive oxidative therapy in the form of intravenous hydrogen peroxide for intractable pain.⁶ In this study, patients received weekly infusions of 0.03% hydrogen peroxide, and then completed a survey to evaluate changes in pain, function, and medication use.⁶ The authors concluded that intravenous hydrogen peroxide “can significantly improve patients in a majority of chronic painful conditions” and that chronic infection was associated with (or the cause of) chronic pain in the patients who were part of the study.⁶

One of the included studies suggested combining methotrexate infusion with hydrogen peroxide infusion for the treatment of head and neck tumors.¹⁰ The authors’ argument was that “hydrogen peroxide will provide the oxygen which stimulates metabolic activity so that more tumor cells will be exposed to methotrexate during the metaphase at which time they are more vulnerable to adverse biological effects of the drug.”¹⁰

It should also be noted that several of the included studies mentioned the addition of antispasmodic tolazoline (Priscoline) to the hydrogen peroxide infusion.^{8,17}

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



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

Table 3. Types of studies

Types of Studies	Number of Studies
Descriptive ^{7,8,11}	3
Observational	0
Experimental ^{10,17}	2

Table 4. Number of studies by country

Country	Number of Studies
US ^{7,8,10,11,17}	5
Total US: 5	
Total Non-US Countries: 0	

Table 5. Summary of included studies

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Head and neck tumors					
Balla <i>et al.</i> , 1964, US ^{b7}	Case reports	5 In-patients with different cancers involving the head (80%, range 29-86 y)	<ul style="list-style-type: none"> Intra-arterial hydrogen peroxide plus radiation therapy (5) 	Resolution of tumor	The authors noted increased wound healing in patients who had cancer treated by hydrogen peroxide and radiation therapy.
Mailams and Balla, 1963, US ⁹	Investigational program	22 Patients (gender and age not specified)	<ul style="list-style-type: none"> Intra-arterial hydrogen peroxide with dextrose 5% in conjunction with irradiation therapy (22) 	Tumor control	The results shown in this study justify further investigation; this treatment must be carefully supervised.
Yollick and Corgill, 1963, US ¹⁰	Experimental treatment	5 In-patients (100%, range 43-65 y)	<ul style="list-style-type: none"> Intra-arterial hydrogen peroxide combined with radiotherapy (5) 	Tumor control	The results are too inconsistent to be able to assess the value of intra-arterial hydrogen peroxide, but it would be logical to combine with methotrexate infusion.
Indication 2: Reduction in arteriosclerotic plaques and vascular collapse of unknown etiology					
<p>Urschel <i>et al.</i>, 1967, US¹⁸</p> <p>Urschel, 1968, US⁸</p> <p>Urschel, 1967, US¹⁹</p>	Clinical trial, case report	<ul style="list-style-type: none"> 1 In-patient with symptoms suggesting basilar artery insufficiency (0%, 57 y) 1 In-patient with vascular collapse of unknown etiology, unresponsive to the conventional methods of resuscitation (0%, 60 y) Patients with arteriosclerosis receiving irradiation therapy (gender and age not specified) 	<ul style="list-style-type: none"> Intra-arterial hydrogen peroxide with Priscoline, 5% dextrose in water (1) Intra-arterial hydrogen peroxide (1) Intra-arterial hydrogen peroxide adjunct to irradiation therapy (number of patients not specified) 	Neurologic and arteriographic results; electrocardiogram (ECG) and blood pressure	<ul style="list-style-type: none"> The arteriographic and clinical improvement of the patient were maintained after treatment with hydrogen peroxide after 6-months. With each infusion of hydrogen peroxide, the authors observed reversal of ECG abnormalities and hypotension; patient expired after cessation of hydrogen peroxide therapy. Post-mortem analysis showed a decrease in number and severity of atheromatous plaques and an increase in vessel flexibility and elasticity for the segment of the aorta being infused.

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 3: Wound healing					
Balla <i>et al.</i> , 1964, US ^{b7}	Case reports	9 In-patients receiving treatment to promote wound healing in refractory wounds (56%, range 19-68 y)	<ul style="list-style-type: none"> Intra-arterial hydrogen peroxide with or without antibiotics (9) 	Wound healing	Regional superoxygenation with intra-arterial hydrogen peroxide improves wound healing due to correction of tissue anoxia.
Wetter and Davis, 2006, US ¹¹	Observation of 1 patient with misdiagnosis	1 In-patient receiving treatment for an ulcerated plaque attributed to a spider bite (100%, 37 y)	<ul style="list-style-type: none"> Intravenous hydrogen peroxide (1) 	–	“This case is a cautionary tale for health care providers. To avoid misdiagnosis, we should investigate ulcerations appropriately. Moreover, as patients gain increased access to treatments such as intravenous hydrogen peroxide, we must be vigilant for potentially fatal complications.”

Abbreviations: “–”, not mentioned.

^aAs defined by authors.

^bMore than one indication in the same study.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Head and neck tumors ^{7,10,17}	–	0.06-0.18%	Solution	Intra-arterial	1-4 weeks
	250 mL	0.12%	–		
Reduction in arteriosclerotic plaques and vascular collapse of unknown etiology ⁸	18 mL/minute	0.12-0.48%	–	Intra-arterial	100 treatments over 29 days
	250 mL/day		–		4-16 weeks
	–		–		6 times
Wound healing ^{7,11}	–	–	–	Intra-arterial	1-6 weeks
	–		–	Intravenous	3 months

Abbreviations: “–”, not mentioned.

Table 7. Dosage by indication – non-US countries

No studies included

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Reduction in arteriosclerotic plaques ⁸	1968	250 mL of 0.12% hydrogen peroxide with 12.5 mg Priscoline in 5% dextrose in water	–	–

Table 10. Compounded products – non-US countries

No studies included

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Six SMEs discussed hydrogen peroxide. Amongst these 6 SMEs, there was 1 medical doctor, 1 pharmacist, 1 nurse practitioner, 2 naturopathic doctors, and 1 doctor of dental surgery. The SMEs specialized and/or were board-certified in anesthesiology, naturopathic medicine, oncology, oral and maxillofacial surgery, pain medicine, and palliative care, working in academic medical centers and private practices/clinics. The SMEs had been in practice for 6 to 39 years.

Hydrogen peroxide acts as a cytokine stimulant in the plasma where it undergoes a manganese catalase enzyme reaction and is essentially reduced to water. At this point, the peroxide is no longer in circulation, but the manganese catalase activity has been triggered; the faster this reaction is triggered, the more stimulating immune cytokines, such as tumor necrosis factor (TNF) and interleukins 1 and 6 (IL-1, IL-6), occur.

One SME stated that dilute hydrogen peroxide is used for patients with acute infections, but also in patients “with chronic resistant or drug resistant infections.” The pharmacy typically compounds hydrogen peroxide into a 3% sterile product, and “you’re diluting a max dose of 3 mL of 3% hydrogen peroxide into 250-500 mL of normal saline and then it’s infused over 60-90 minutes.” After an infusion, patients typically have a transient temperature increase, in addition to an increase in immune activity. For a nonchronic or an acute patient, the SME stated that they would probably administer hydrogen peroxide twice weekly for 2-3 weeks during the acute phase. For chronic recurring infections, they may continue to receive hydrogen peroxide depending on how long they are symptomatic.

One SME stated that hydrogen peroxide is also “popular in terms of the so-called alternative cancer therapy practitioners,” however, the SME has never used it themselves. The SME stated that there is not good data on its use and is more comfortable administering high dose intravenous vitamin C to generate peroxide.

One SME said that while they knew of some people who use it, they have not used it and stated “it scares me because everyone uses it wrong. I have had people soak their feet in it and try to drink it. They think it is magic. I tell people to stay away from it.”

Hydrogen peroxide 1-1.5% was described to have an antiviral effect by another SME in reference to COVID-19 protocols. However, it was commented that the effect is not clear, and that they would not think it would be used intravenously. Other SMEs had not seen hydrogen peroxide used as an injectable product and were not sure where the use was coming from, thinking of it only as a topical product for incisions or wounds.

Results of survey

Zero people responded to the survey distributed via professional medical associations and available on the project website.

Table 11. Characteristics of survey respondents

No survey respondents provided this information

Table 12. Conditions for which hydrogen peroxide prescribed or administered

No survey respondents provided this information

Table 13. Reasons for using compounded hydrogen peroxide

No survey respondents provided this information

Table 14. Use of non-patient-specific compounded hydrogen peroxide

No survey respondents provided this information

CONCLUSION

Hydrogen peroxide was nominated for inclusion on the 503B Bulks List as an injectable 3% intravenous infusion to treat a variety of unspecified medical conditions. Hydrogen peroxide is not available in the nominated dosage form and ROA in any of the national medical registries searched.

From the literature review and interviews, indications for intravenous and intra-arterial hydrogen peroxide included influenzal pneumonia, contrast echocardiography, cancer, reduction of arteriosclerotic plaques, infection, wound healing, and pain management. The original concept behind the use of hydrogen peroxide, as detailed by Dr. Charles Farr, was to have a regulatory effect on the immune system by stimulating cells to produce cytokines. However, there was disparity amongst SMEs regarding the evidence supporting the use of hydrogen peroxide. The concept behind utilizing hydrogen peroxide is to produce a catalase reaction in the plasma, which then triggers the stimulation of immune cytokines. However, besides concerns about efficacy, there also exist safety concerns. In 1 study, a previously healthy young man received weekly intravenous hydrogen peroxide for 3 months for an ulceration mistakenly attributed to a spider bite, a mistake that eventually proved to be fatal.¹¹ In their conclusion, the authors specifically called on practitioners to be vigilant for potentially fatal complications from patient access to treatments like hydrogen peroxide.¹¹ In addition, it has been noted that there is a potential for hydrogen peroxide to be used incorrectly; patients have been described to soak their feet in it, as well as attempt to drink it.

No survey responses were received.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to March 6, 2020
- Date last searched: March 8, 2020
- Limits: Humans (search hedge); English language
- Number of results: 238
- Notes: Tested additional keywords for hydrogen peroxide, such as ‘hydroperoxide’ and ‘h2o2’. Additional results not relevant.

1	hydrogen peroxide/	57256
2	hydrogen peroxide.tw.	52295
3	hydrogenperoxide.tw.	50
4	or/1-3	82116
5	exp administration, intravenous/	141866
6	infusions, parenteral/	26196
7	infusions, intra-arterial/	9655
8	injections/	42200
9	injections, intra-arterial/	9160
10	injections, intralesional/	6514
11	instillation, drug/	1439
12	((parenteral\$ or regional\$) adj2 (administ\$ or therap\$ or treat\$ or deliver\$ or infus\$ or perfus\$)).tw.	25012
13	intravenous\$.tw.	335064
14	intra venous\$.tw.	568
15	intravascular\$.tw.	46962
16	intra vascular\$.tw.	296
17	intraarterial\$.tw.	6140
18	intra arterial\$.tw.	16054

19	intralesion\$.tw.	7051
20	intra lesion\$.tw.	331
21	intratumo?r\$.tw.	18707
22	intra tumo?r\$.tw.	2303
23	or/5-22	574259
24	drug therapy/	30357
25	dt.fs.	2184738
26	ad.fs.	1393722
27	tu.fs.	2191668
28	pc.fs.	1264415
29	therap\$.tw.	2704689
30	treat\$.tw.	5356136
31	prevent\$.tw.	1379508
32	prophyla\$.tw.	161148
33	or/24-32	9409210
34	and/4,23,33	503
35	exp animals/ not humans/	4675662
36	34 not 35	258
37	limit 36 to english language	238

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 8, 2020
- Limits: Humans (search hedge); English language
- Number of results: 328
- Tested keyword 'hydrogenperoxide'; yielded no additional relevant results.

1	hydrogen peroxide'/mj	22733
2	hydrogen peroxide':ti,ab,tn	62380
3	#1 OR #2	69311
4	intratumoral drug administration'/de	7046
5	intravascular drug administration'/exp	417229
6	peritumoral drug administration'/de	233
7	regional perfusion'/exp	13122
8	injection'/exp	247453
9	drug instillation'/de	1783
10	intravenous*':ti,ab	482508
11	intra venous*':ti,ab	1434
12	intravascular*':ti,ab	67454
13	intra vascular*':ti,ab	675
14	intraarterial*':ti,ab	29968
15	intra arterial*':ti,ab	22697
16	intratumoral*':ti,ab	24797
17	intra tumoral*':ti,ab	2386
18	intratumoural*':ti,ab	1795
19	intra tumoural*':ti,ab	381
20	intralesion*':ti,ab	10077
21	intra lesion*':ti,ab	595

22	((parenteral* OR regional*) NEAR/2 (administ* OR therap* OR treat* OR deliver* OR infus* OR perfus*)):ti,ab	30660
23	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	1138823
24	drug therapy'/de	711199
25	drug dose':lnk	621819
26	drug administration':lnk	1718631
27	drug therapy':lnk	3843836
28	prevention':lnk	1159849
29	therap*':ti,ab	4074510
30	treat*':ti,ab	7768530
31	prevent*':ti,ab	1877329
32	prophyla*':ti,ab	257449
33	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32	13021316
34	#3 AND #23 AND #33	716
35	[animals]/lim NOT [humans]/lim	6001338
36	#34 NOT #35	360
37	#34 NOT #35 AND [english]/lim	328

Appendix 2. Survey instrument

Welcome. We want to understand your clinical use of compounded hydrogen peroxide. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this 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.

Thank you,

Dr. Ashlee Mattingly,
Principal Investigator
The University of Maryland School of Pharmacy

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.

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

1. How familiar are you with the following terms?

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

2. Do you prescribe or administer hydrogen peroxide to your patients?

- Yes
- No

3. Do you prescribe or administer hydrogen peroxide by any of the following dosage forms and/or routes of administration? (check all that apply)

- Intravenous infusion
- None of the above

4. I prescribe or administer hydrogen peroxide for the following conditions or diseases: (please list):

5. I use compounded hydrogen peroxide because: (check all that apply)

- Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
- Patient allergies prevent me from using commercially available products. (please explain) _____
- Patient conditions prevent me from using commercially available products. (please explain) _____
- There are no commercially available products containing hydrogen peroxide.
- Other (please explain) _____

6. Do you stock non-patient-specific compounded hydrogen peroxide at your practice?
- Yes
 - No
 - I'm not sure
7. I obtain compounded hydrogen peroxide from the following: (check all that apply)
- Compound myself at my practice
 - Have the product compounded by an in-house pharmacy
 - Purchase, or have a patient purchase, from a compounding pharmacy
 - Purchase, or have a patient purchase, from an outsourcing facility
 - Other (please explain) _____
8. What is your practice setting? (check all that apply)
- Physician office/private practice
 - Outpatient clinic
 - Hospital/health system
 - Academic medical center
 - Emergency room
 - Operating room
 - Other (please describe) _____
9. What degree do you hold? (check all that apply)
- Doctor of Medicine (MD)
 - Doctor of Osteopathic Medicine (DO)
 - Doctor of Medicine in Dentistry (DMD/DDS)
 - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
 - Naturopathic Doctor (ND)
 - Nurse Practitioner (NP)
 - Physician Assistant (PA)
 - Other (please describe)

Appendix 3. Survey distribution to professional associations

Specialty	Association^a	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women’s Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

^aAssociations that declined in Year 1 were not contacted in Year 2.