Summary Report

Ciprofloxacin hydrochloride

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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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 ciprofloxacin hydrochloride (ciprofloxacin HCl; UNII code: 4BA73M5E37), 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 ciprofloxacin HCl 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 ciprofloxacin HCl 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 ciprofloxacin HCl 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

Ciprofloxacin HCl was nominated for inclusion on the 503B Bulks List by Triangle Compounding Pharmacy, Inc. Ciprofloxacin HCl was nominated for treatment of bacterial infections via an oral or topical powder, gel, or suspension. The strength various from 0.01% to 50% depending on the dosage form and route of administration (ROA).

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of ciprofloxacin HCl.[6,7]

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

- Allergies and sensitivities to inactive ingredients or excipients
- Oral suspensions and tablets are available but are not appropriate for use in the ears or topical gels

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of ciprofloxacin HCl 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, 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 ciprofloxacin HCl; name variations of ciprofloxacin HCl 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 ciprofloxacin HCl. 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: ciprofloxacin HCl, topical or otic administration, and therapeutic use for bacterial infection (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 human studies in English language. Searches were conducted on April 6, 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 April 6, 2020 for clinical practice guidelines that recommended the use of ciprofloxacin HCl and provided sufficient information on dosing and administration. A systematic literature review was not conducted for oral suspension due to the availability of FDA-approved ciprofloxacin HCl products in this dosage form and ROA.

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 ciprofloxacin HCl was used in the nominated dosage form, ROA and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if ciprofloxacin HCl 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 ciprofloxacin HCl 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 ciprofloxacin HCl; setting; total number of patients; number of patients who received ciprofloxacin HCl; patient population;

indication for use of ciprofloxacin HCl; dosage form and strength; dose; ROA; frequency and duration of therapy; use of ciprofloxacin HCl in a combination product; use and formulation of ciprofloxacin HCl in a compounded product; use of ciprofloxacin HCl 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 ciprofloxacin HCl was used in a clinical setting. The systematic literature review and indication from the nomination were reviewed to identify the following medical specialties that would potentially use ciprofloxacin HCl: dermatology, infectious disease, and primary care/family medicine. 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 interview 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 ciprofloxacin HCl 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

- Ciprofloxacin HCl is available as an FDA-approved product.
- Ciprofloxacin HCl is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for ciprofloxacin HCl.
- Ciprofloxacin HCl is available in the nominated dosage form and ROA in Canada, Namibia, and UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Ciprofloxacin	50-100 mg/ml	Suspension	Oral	Prescription	9/26/1997
	60 mg/ml	Suspension	Otic		12/10/2015

[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

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

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Ciprofloxacin	5%	Suspension	–	Namibia	–	8/18/2004
	500 mg/5ml		Oral	Canada	Prescription	9/15/1998
	250 mg/5ml			UK	Prescription	4/19/1996

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

Results of literature review

Study selection

Database searches yielded 1940 references; 1 additional reference was identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 1348 titles and abstracts were screened. After screening, the full text of 237 articles were reviewed. Finally, 3 studies were included. Two hundred thirty-four studies were excluded for the following reasons: wrong study design (158 studies); used in FDA-approved dosage form or ROA (27); ciprofloxacin HCl only mentioned briefly (26); ciprofloxacin HCl used as brand or proprietary product (11); wrong dosage form or ROA (9); ciprofloxacin HCl not used clinically (1); not used in humans (1); wrong substance (1).

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

Characteristics of included studies

The 3 included studies were published between 2002 and 2018. There was 1 experimental study, 1 observational study, 1 descriptive study, and 0 clinical practice guidelines. The 3 studies were conducted in the US.

A total of 657 patients participated in the 3 included studies. The number of patients in each study ranged from 1 to 532.

Outcome measures differed among the studies and included: resolution of infection and safety profiles.

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

Use of ciprofloxacin HCl

One patient received ciprofloxacin HCl as an experimental treatment for *Mycobacterium celatum* infection, but the ROA, dose, and duration of treatment were not mentioned. Three hundred fifty-five patients received ciprofloxacin HCl as experimental prophylaxis for otorrhea following tympanostomy tube placement surgery, administered topically once. Thirty-two patients received ciprofloxacin HCl as a treatment for pouchitis, administered in a 1000 mg/day dose for 14 days.

Refer to Table 6 for summaries of dosage by indication.

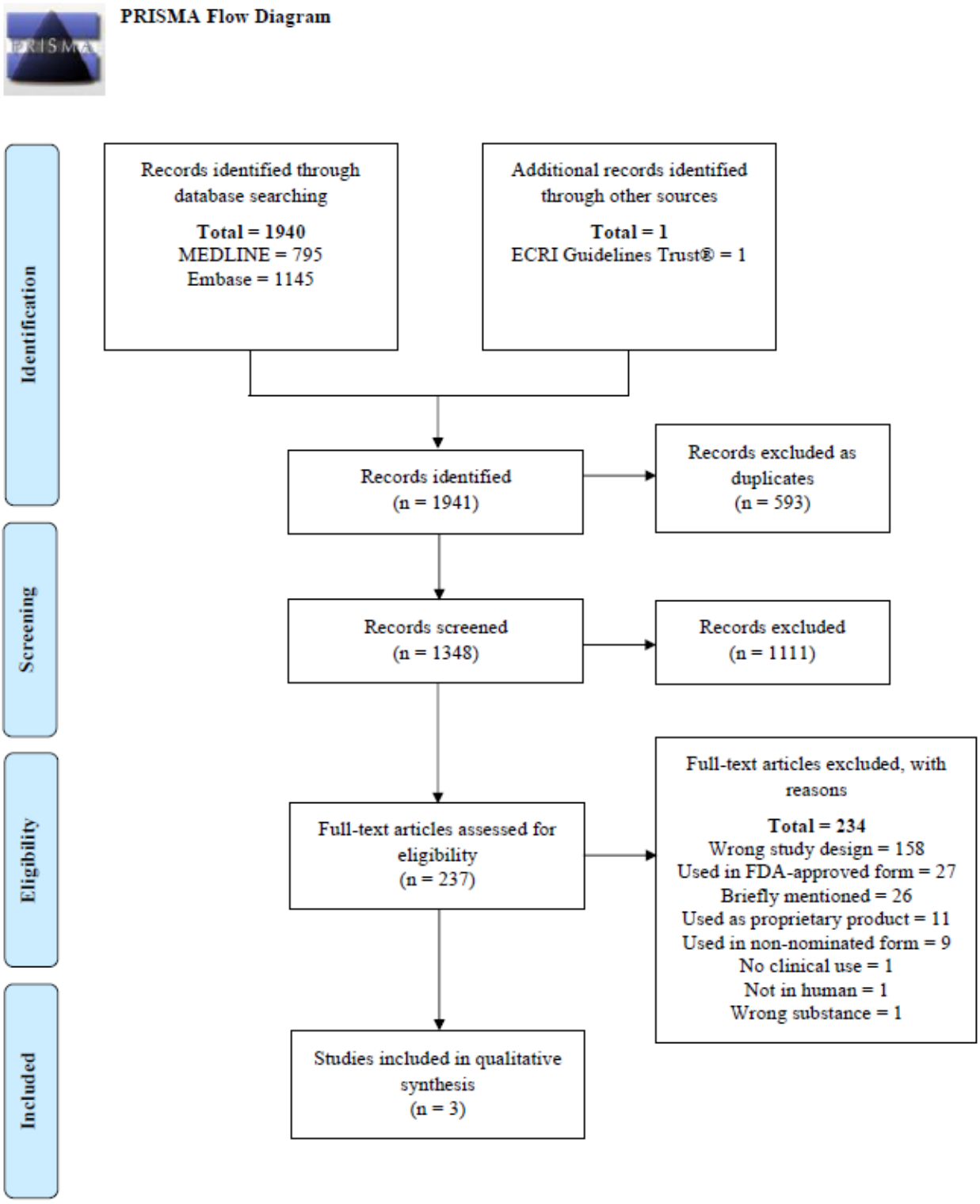
Ciprofloxacin HCl was not used as a compounded product, nor was it used in a combination product.

In 1 study, the authors' conclusion stated that the use of ciprofloxacin HCl for the prophylaxis of otorrhea following tympanostomy tube placement surgery "reduces postoperative complications" and may be a good alternative to ear drops that need to be administered postoperatively by caregivers. In 2 studies, the authors' conclusions were not related to the use of ciprofloxacin. Refer to Table 5 for a summary of the authors' conclusions.

Pharmacology and historical use

No additional references were found that provided information about the pharmacological or historical use of ciprofloxacin HCl in topical (or otic) dosage forms.

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[8]	1
Experimental[9]	1
Observational[10]	1

Table 4. Number of studies by country

Country	**Number of Studies**
United States (US)[8-10]	3
	Total US: 3 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: *M. celatum* infection					
Chavarria *et al.*, 2018, US[8]	Case report	68-year-old male patient with *Mycobacterium celatum* infection	• Clarithromycin, ciprofloxacin, and ethambutol	Resolution of infection	"*M. celatum* should be suspected when acid-fast bacilli that are biochemically similar to and behave like *M. avium*-intracellulare or *M. xenopi* are identified in patients that do not respond to an appropriate treatment regimen."
Indication 2: Prophylaxis of otorrhea following tympanostomy tube placement (TTP) surgery					
Park *et al.*, 2015, US[9]	Prospective, randomized, double-blind, sham controlled phase 3 clinical trials	532 children with bilateral middle ear effusion	1:2 randomization to • Tympanostomy tube placement • Tympanostomy tube placement with ciprofloxacin (OTO-201)	Efficacy (treatment failure defined by presence of otorrhea or use of rescue antibiotics) and safety (audiometry, otoscopy, tympanometry)	"The integrated analysis of 2 phase 3 clinical trials demonstrated that a single intratympanic administration of OTO-201 reduces the risk of postoperative complications following TTP and may provide an attractive alternative to antibiotic ear drops by eliminating the need for caregiver administration postoperatively"
Indication 3: Pouchitis					
Shen *et al.*, 2002, US[10]	–	61 patients with ulcerative colitis after ileal pouch-anal anastomosis Pouchitis: 31 patients (64.5 %, 41.4 y ± 12.0) Cuffitis: 4 patients (75%, 39.5 y ± 14.8) Irritable pouch syndrome (IPS): 26 patients (65.4%, 43.3 y ± 15.9)	Pouchitis (31) • Ciprofloxacin • Metronidazole Cuffitis (4) • Hydrocortisone • Mesalamine IPS (26) • Antidiarrheal • Anticholinergic • Antidepressant	Etiology of bowel symptoms using the Pouchitis Disease Activity Index (PDAI)	"There is an overlap of symptoms among patients with pouchitis, cuffitis, and IPS, and endoscopic evaluation can differentiate among these groups. Distinction between these three groups has therapeutic implications"

Abbreviations: "–", not mentioned
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
M. celatum infection[8]	–	–	–	–	–
Prophylaxis of otorrhea following tympanostomy tube placement surgery[9]	–	6 %	Gel	Topical	Once
Pouchitis[10]	1000 mg/day	–	–	–	14 days

Abbreviations: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

No studies included

Table 8. Number of studies by combination

No combination product(s) were nominated

Table 9. Compounded products – US

No compounded products from reported studies

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. Five SMEs discussed ciprofloxacin HCl. Amongst the 5 SMEs, there were 4 medical doctors and 1 pharmacist. The SMEs specialized and/or were board-certified in dermatology, infectious disease, and primary care and family practice, working in academic medical centers and consulting. The SMEs had been in practice for 9 to 40 years.

The SMEs reported using ciprofloxacin for infections in the eye, external ear (swimmer's ear), and skin (impetigo, acrocephalics, wound).

According to one SME, first line agents for ear infections would be amoxicillin and Augmentin® (amoxicillin/clavulanate). For swimmer's ear, ciprofloxacin can be very useful as a topical formulation; it is currently available as ear drops and suspensions. There is no powder or gel formulation available so it could potentially be useful to have those dosage forms. For example, if the patient has a very wet infection in the ear, a powder form could be used since it can act as a desiccant. Ciprofloxacin for ear infections can be used in combination with other drugs such as steroids or antifungals. Liquid steroids can be added if the eardrum or ear canal is swollen and it is hard for ciprofloxacin drops to penetrate as steroids will reduce inflammation. If a fungus is suspected or it is not clear what is growing, ciprofloxacin can be combined with an antifungal. One SME stated that they do not use compounded products but can see it being useful to make an ear wick, where the antibiotic is soaked on the gauze and placed into the ear for a day or two to help expand the ear canal.

For skin infections, the SMEs had differing opinions on the use of topical ciprofloxacin. One SME stated that the powder form can be used for skin infections due to yeast in weepy and wet areas (e.g. under the breast for overweight female patients). However, another SME stated that wounds are notorious for having a tremendous number of bacteria present, due to the presence of bacteria on the skin, but the bacteria does not necessarily impede the ability of the wound to heal. There can be wounds that do become infected and have to be treated in order to start healing. However, the preference would be to use a systemic formulation. The SME was skeptical of the data to support topical use and was concerned that due to an increase in antimicrobial resistance it may cause more harm than good. The SME did refer to a 2019 study where a ciprofloxacin-loaded povidone foil was being investigated for use in a wound infection model[11], but the SME did not discuss the results or implications from the study.

Some SMEs had experience using compounded products, but none had used compounded ciprofloxacin.

Results of survey

One person responded to the survey distributed via professional medical associations and available on the project website, refer to Table 11 for respondent characteristics.

Among respondents, 1 (100%) used ciprofloxacin HCl. The respondent used ciprofloxacin HCl as a topical suspension for treatment of bacterial infections.

The 1 respondent who reported using ciprofloxacin HCl utilized the substance as a compounded drug product due to a lack of commercial products in an appropriate dosage form, strength or combination and no commercially available products with ciprofloxacin HCl.

The respondent did not stock non-patient-specific compounded ciprofloxacin HCl at their practice.

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	**Responses, n (N=1)**
Doctor of Medicine (MD)	1
Practice Setting	**Responses, n (N=1)**
Physician office or private practice	1

Table 12. Conditions for which ciprofloxacin HCl prescribed or administered

Condition	**Responses, n (N=1)**
Bacterial infections	1

Table 13. Reasons for using compounded ciprofloxacin HCl

Reason	**Responses, n (N=1)[a]**
Commercial products are not available in the dosage form, strength, or combination	1
Patient allergies prevent use of commercial products	0
Patient conditions prevent use of commercial products	0
No commercial products	1
Other	0

[a]Survey respondents allowed to select multiple reasons.

Table 14. Use of non-patient-specific compounded ciprofloxacin HCl

Do you stock non-patient-specific compounded ciprofloxacin HCl at your practice?	**Responses, n (N=1)**
Yes	0
No	1

CONCLUSION

Ciprofloxacin HCl was nominated for inclusion on the 503B Bulks List as an oral and topical powder, gel, and suspension to treat bacterial infections. Ciprofloxacin HCl is available in the nominated dosage form and ROA in Canada, Namibia, and UK.

From the literature review and interviews conducted, ciprofloxacin HCl was used for injections in the eye, ear, and skin, *M. celatum* infection, pouchitis, and prophylaxis of otorrhea following tympanostomy tube placement surgery. The interviewed SMEs had differing opinions on the use of ciprofloxacin in the nominated dosage forms. One SME stated that since ciprofloxacin is not available as a powder or gel, it is not currently used but that it might be useful to have these dosage forms. One SME stated that a topical powder could be useful for wet infections or wounds due to powder serving as a desiccant. However, another SME said there is not enough evidence to support its use as a topical powder and was skeptical about the topical use in general, due to the risk of antimicrobial resistance. Some SMEs had experience using compounded products, but none had used compounded ciprofloxacin.

One person responded to the survey. The respondent used compounded ciprofloxacin HCl as a topical suspension to treat bacterial infections due to a lack of availability of commercial products. The respondent did not stock non-patient-specific compounding ciprofloxacin HCl at their practice setting.

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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 April 3, 2020
- Date last searched: April 6, 2020
- Limits: Humans (search hedge); English language
- Number of results: 795

1	ciprofloxacin/	13108
2	ciprofloxacin$.tw.	25728
3	or/1-2	28221
4	administration, topical/	38106
5	administration, cutaneous/	21834
6	administration, inhalation/	30312
7	topical$.tw.	103235
8	transcutaneous$.tw.	14179
9	inhal$.tw.	107319
10	aural$.tw.	3874
11	auricular$.tw.	10674
12	intraaural$.tw.	13
13	intraauricular$.tw.	19
14	otic$.tw.	3518
15	exp gels/	50857
16	powders/	13687
17	dry powder inhalers/	982
18	(ear? adj2 drop?).tw.	387
19	powder?.tw.	65983
20	or/4-19	387350

21	exp skin diseases, bacterial/	24245
22	exp otitis/	28398
23	anti-infective agents, local/	16800
24	anti-bacterial agents/	329869
25	ad.fs.	1397902
26	dt.fs.	2192080
27	tu.fs.	2197664
28	pc.fs.	1268253
29	otitis$.tw.	24735
30	(ear? adj2 (effus$ or inflamm$ or secret$)).tw.	2892
31	infect$.tw.	1699478
32	treat$.tw.	5383019
33	or/21-32	9122847
34	and/3,20,33	1031
35	exp animals/ not humans/	4686014
36	34 not 35	850
37	limit 36 to english language	795

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: April 6, 2020
- Limits: Humans (search hedge); English language
- Number of results: 1145

1	ciprofloxacin'/mj	15359
2	ciprofloxacin plus dexamethasone'/de	173
3	ciprofloxacin plus fluocinolone acetonide'/de	8
4	ciprofloxacin*':ti,ab,tn	35622
5	#1 OR #2 OR #3 OR #4	39657
6	topical drug administration'/de	81608
7	cutaneous drug administration'/de	620
8	auricular drug administration'/de	11
9	inhalational drug administration'/de	49965
10	topical*':ti,ab	146566
11	transcutaneous*':ti,ab	18988
12	inhal*':ti,ab	160785
13	aural*':ti,ab	5263
14	auricular*':ti,ab	16488
15	intraaural*':ti,ab	27
16	intraauricular*':ti,ab	49
17	otic*':ti,ab	4940
18	gel'/exp	73810
19	powder'/exp	35661
20	powder inhaler'/exp	4728
21	ear drops'/de	749
22	powder$':ti,ab	84499

23	(ear$ NEAR/2 drop$):ti,ab	538
24	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	578533
25	topical treatment'/de	12462
26	bacterial skin disease'/exp	91232
27	topical antiinfective agent'/de	8119
28	otitis'/exp	52865
29	drug dose':lnk	622468
30	drug administration':lnk	1724874
31	drug therapy':lnk	3857619
32	prevention':lnk	1162533
33	otitis*':ti,ab	34206
34	(ear$ NEAR/2 (effus* OR inflamm* OR secret*)):ti,ab	3536
35	infect*':ti,ab	2284208
36	treat*':ti,ab	7806678
37	#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36	12060730
38	#5 AND #24 AND #37	1501
39	[animals]/lim NOT [humans]/lim	6013410
40	#38 NOT #39	1255
41	#38 NOT #39 AND [english]/lim	1145

Appendix 2. Survey instrument

Welcome. We want to understand your clinical use of compounded ciprofloxacin HCl. 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)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer ciprofloxacin HCl to your patients?

   - o Yes
   - o No

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

   - o Oral powder
   - o Oral gel
   - o Oral suspension
   - o Topical powder
   - o Topical gel
   - o Topical suspension
   - o None of the above

4. I prescribe or administer ciprofloxacin HCl for the following conditions or diseases: (check all that apply)

   - o Bacterial infections
   - o Other (please explain) _____

5. I use compounded ciprofloxacin HCl because: (check all that apply)

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

6. Do you stock non-patient-specific compounded ciprofloxacin HCl at your practice?

   - o Yes
   - o No
   - o I'm not sure

7. I obtain compounded ciprofloxacin HCl from the following: (check all that apply)

   - o Compound myself at my practice
   - o Have the product compounded by an in-house pharmacy
   - o Purchase, or have a patient purchase, from a compounding pharmacy
   - o Purchase, or have a patient purchase, from an outsourcing facility
   - o Other (please explain) _____

8. What is your practice setting? (check all that apply)

   - o Physician office/private practice
   - o Outpatient clinic
   - o Hospital/health system
   - o Academic medical center
   - o Emergency room
   - o Operating room
   - o Other (please describe) _____

9. What degree do you hold? (check all that apply)

   - o Doctor of Medicine (MD)
   - o Doctor of Osteopathic Medicine (DO)
   - o Doctor of Medicine in Dentistry (DMD/DDS)
   - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
   - o Naturopathic Doctor (ND)
   - o Nurse Practitioner (NP)
   - o Physician Assistant (PA)
   - o 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 (AAAI)	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

[a]Associations that declined in Year 1 were not contacted in Year 2.