

Summary Report

Budesonide

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
OME	Otitis media with effusion
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) in their evaluation of the use of budesonide (UNII code: Q3OKS62Q6X), 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 budesonide 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 budesonide 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 budesonide 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

Budesonide was nominated for inclusion on the 503B Bulks List by Fagron. Budesonide was nominated for treatment of otitis media with effusion (OME) via a 0.5 mg/mL injection.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of budesonide.⁶⁻¹⁴

The reason provided for nomination to the 503B Bulks List was that there are FDA-approved forms of budesonide, but it would not be feasible to prepare an injectable formulation from any of the existing FDA-approved medications.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of budesonide 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 budesonide; name variations of budesonide 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

budesonide. 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 two concepts: budesonide and otitis media (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 research articles or conference abstracts in English. Searches were conducted on March 23, 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 23, 2020 for clinical practice guidelines that recommended the use of budesonide and provided sufficient information on dosing and administration.

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 budesonide 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 budesonide 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 budesonide 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 budesonide; setting; total number of patients; number of patients who received budesonide; patient population; indication for use of budesonide; dosage form and strength; dose; ROA; frequency and duration of therapy; use of budesonide in a combination product; use and formulation of budesonide in a compounded product; use of budesonide 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 budesonide 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 budesonide: otolaryngology, pediatrics and neonatology, and primary care and internal 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 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 budesonide 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

- Budesonide is not available as an FDA-approved product in the nominated dosage form.
- Budesonide is not available as an OTC product in the nominated dosage form in the US.
- There is a current United States Pharmacopeia (USP) monograph for budesonide.
- Budesonide is not available in the nominated dosage form and ROA in any of the foreign 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 118 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 112 titles and abstracts were screened. After screening, the full text of 3 articles were reviewed. Finally, 0 studies were included. Three studies were excluded for the following reason: wrong study design (2 studies), used as brand/proprietary product (1).

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

Characteristics of included studies

No studies included.

Use of budesonide

No studies included.

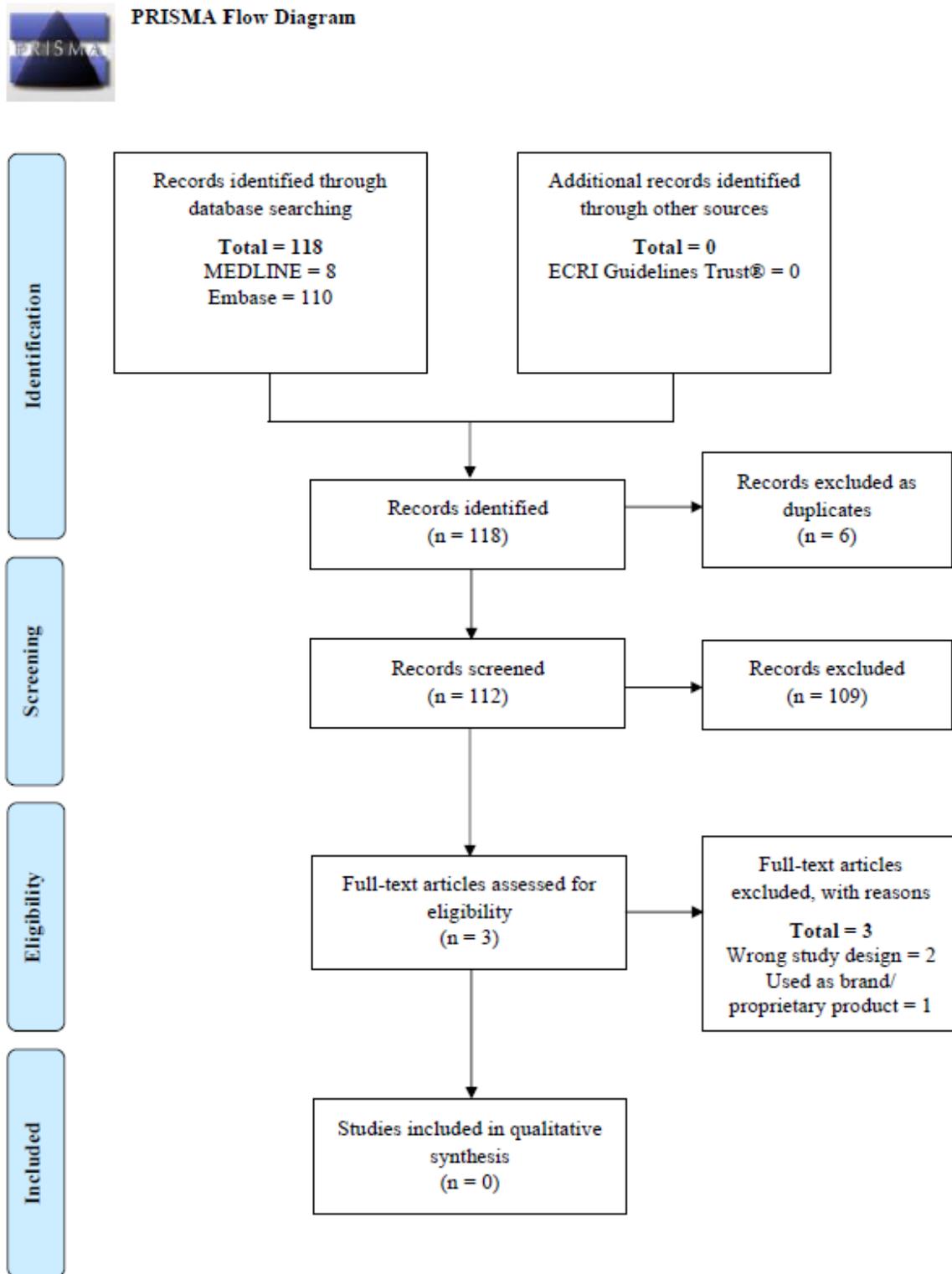
Pharmacology and historical use

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

OME is defined as “the presence of fluid in the middle ear without signs or symptoms of acute ear infection.”¹⁵ Watchful waiting, ear tube placement, or adenoidectomy are the recommended treatments; according to the OME guideline from the American Academy of Otolaryngology – Head and Neck Surgery Foundation, the American Academy of Pediatrics, and the American Academy of Family Physicians, published in 2004 and updated in 2016, the use of steroids is not recommended.^{15,16}

In a 2014 article, Yang et al stated that while watchful waiting is the established recommendation for OME, temporary medical treatment may be required in older children and adults; steroids can be used for OME due to their anti-inflammatory activity, in addition to being able to “remove fluid in [the] middle ear, decrease mucin production, and enhance the function of Eustachian tube.” The authors compared budesonide to dexamethasone and sodium chloride in their single-blind, randomized, three-arm, parallel-controlled prospective study. The patients had their eardrum punctured with a syringe that extracted the effusion, and then another syringe was used to inject the assigned solution (a proprietary budesonide suspension used for inhalation, dexamethasone, or sodium chloride). The authors concluded that when administered to children older than 12 years and adults with OME, tympanic injection of budesonide had the best therapeutic efficacy when compared to dexamethasone and sodium chloride. The authors indicated that tympanic budesonide injection was an effective way of treating OME in older children or adults.¹³

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

No studies included

Table 4. Number of studies by country

No studies included

Table 5. Summary of included studies

No studies included

Table 6. Dosage by indication – US

No studies included

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

No studies included

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 budesonide. Amongst these 5 SMEs, there were 5 medical doctors. The SMEs specialized and/or were board-certified in gastroenterology, primary care, and pediatrics, working in academic medical centers. The SMEs had been in practice for 2 to 34 years.

None of the SMEs had used budesonide for otitis media. Amoxicillin is typically the first-line medication for younger children with an ear infection and fever. Two SMEs said that budesonide can be used for older children with chronic ear infections but injection of budesonide into the ear is not something primary care doctors would do. One SME stated that there is a controversy about using steroids for effusion (where fluid persists behind the ear). According to the SME, what general practitioners would do for a bad ear infection before antibiotics were commonly used was to stick a needle through the eardrum and take the pus out “but I have never heard of going the other way, where you stick steroids in. I can’t think of how that would be a good idea to stick steroids next to somebody’s brain.”

The SMEs stated that budesonide is also used as a nebulizer for treatment of asthma, as an injection for use in allergies, urticaria, and hives, as a slurry for eosinophilic esophagitis, and as an inhalation for prevention of bronchopulmonary dysplasia neonates. One SME mentioned that budesonide is a drug that people are “currently getting very excited about,” to prevent bronchopulmonary dysplasia in neonates.

One SME stated that they did not see big market push for injectable budesonide because there are many injectable steroids commercially available. To be cost-effective, the clinic at which the SME worked only stocked 2-3 injectable steroids for use in allergic conditions.

Results of survey

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

A separate survey was distributed by the Ambulatory Surgery Center Association (ASCA); 230 people responded to this survey (refer to Appendix 2.2 for survey instrument).

Amongst respondents to the ASCA survey, 97 (42% of 230 total respondents) were very familiar with the term ‘503B outsourcing facility,’ 86 (37%) were somewhat familiar with this term, and 47 (20%) were not familiar with this term (refer to Table 15).

One hundred ten survey respondents (54% of 203 people who responded to this question) utilized a 503B outsourcing facility to acquire compounded drugs; 93 survey respondents (46%) did not utilize a 503B outsourcing facility. Two respondents (0.7% of 290 responses, where respondents were allowed to select multiple drug products) obtained budesonide from a 503B outsourcing facility (refer to Table 16).

The most common types of procedures performed at the facilities where the ASCA survey respondents worked were: ophthalmology (115, 17% of responses, where respondents were allowed to select multiple procedure types); orthopedics (89, 13%); pain (80, 12%); podiatry (74, 11%); and plastics (72, 10%) (refer to Table 17).

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which budesonide prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded budesonide

No respondents to survey distributed via professional medical associations

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

No respondents to survey distributed via professional medical associations

Table 15. Ambulatory Surgery Center Association respondents' familiarity with compounding terms

Compounded drugs (medications prepared to meet a patient-specific need)	Responses, n (N=230)
Very familiar	153
Somewhat familiar	70
Not familiar	7
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed to meet a patient-specific need)	Responses, n (N=230)
Very familiar	118
Somewhat familiar	91
Not familiar	21
503B Outsourcing facility (a facility that compounds larger quantities without a patient-specific prescription)	Responses, n (N=230)
Very familiar	97
Somewhat familiar	86
Not familiar	47

Table 16. Products obtained from a 503B outsourcing facility

Product	Responses, n (N=290)^a
Amitriptyline / Ketoprofen / Oxymetazoline	1
Budesonide	2
Calcium gluconate	2
Droperidol	2
Epinephrine	11
Epinephrine for ophthalmic administration	16
Epinephrine / Lidocaine for ophthalmic administration	31
Epinephrine / Bupivacaine / Fentanyl	3
Fentanyl	10
Flurbiprofen	3
Flurbiprofen for ophthalmic administration	6
Hydromorphone	5
Ipamorelin	1
Ketoprofen / Nifedipine	3
Lidocaine / Epinephrine / Tetracaine	13
Meperidine	3
Morphine	5
Naloxone	5
Neomycin	5
Phentolamine	1
Promethazine	5
Remifentanyl	4
Sufentanyl	2
Tramadol	2

None of the above	75
Do not obtain any compounded drugs from 503B outsourcing facility	74

^aSurvey respondents allowed to select multiple products.

Table 17. Type of specialty procedures performed at ambulatory surgery facility

Procedure Type	Responses, n (N=686)^{a,b}
Dental	23
Dermatology	9
Endoscopy	65
Neurosurgery	22
Obstetrics/gynecology	39
Ophthalmology	115
Otolaryngology	58
Orthopedics	89
Pain	80
Plastics	72
Podiatry	74
Other ^b	40

^aSurvey respondents were allowed to select multiple procedure types.

^bNo respondents provided description for 'Other' procedure type.

CONCLUSION

Budesonide was nominated for inclusion on the 503B Bulks List as a 0.5 mg/mL injection to treat OME. Budesonide is not available in the nominated dosage form and ROA in any of the foreign registries searched.

No articles were included from the literature review, but 1 study provided valuable information about the use of budesonide in otitis media. This study found that in children older than 12 years and adults with OME, tympanic injection of budesonide had the best therapeutic efficacy when compared to dexamethasone and sodium chloride.

From the interviews conducted, none of the SMEs had used budesonide for otitis media. They stated that budesonide can be used for chronic ear infection, but amoxicillin is a first-line therapy. One SME stated that the injection of steroid in the ear is not a common practice. Given the commercial availability of several injectable steroids, 1 SME did not see the need for injectable budesonide.

Zero people responded to the survey distributed via professional medical associations and available on the project website. Among respondents to the ASCA survey, 2 (0.7% of 290 responses, where respondents were allowed to select multiple drug products) obtained budesonide from a 503B outsourcing facility.

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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 20, 2020
- Date last searched: March 23, 2020
- Limits: Humans (search hedge); English language
- Number of results: 8

1	budesonide/	4383
2	bude#onid\$.tw.	5209
3	or/1-2	6139
4	exp otitis media/	24328
5	injections, intratympanic/	204
6	otitis.tw.	24689
7	tympanitis.tw	45
8	otic\$.tw.	3514
9	(ear adj2 (effus\$ or infect\$ or inflamm\$ or secret\$)).tw.	4750
10	intratympanic\$.tw.	1373
11	tympanic\$.tw.	11001
12	auricular\$.tw	10648
13	or/4-12	57957
14	and/3,13	14
15	exp animals/ not humans/	4680951
16	14 not 15	13
17	limit 16 to english language	8

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 23, 2020
- Limits: Humans (search hedge); English language
- Number of results: 110

1	budesonide'/de	20508
2	budesonid*':ti,ab,tn	8494
3	budezonid*':ti,ab,tn	6
4	#1 OR #2 OR #3	21667
5	otitis media'/exp	40322
6	intratympanic drug administration'/de	137
7	auricular drug administration'/de	11
8	otitis':ti,ab	34143
9	tympanitis':ti,ab	77
10	otic*':ti,ab	4926
11	(ear NEAR/2 (effus* OR infect* OR inflamm* OR secret*)):ti,ab	6160
12	intratympanic*':ti,ab	1640
13	tympanic*':ti,ab	14950
14	auricular*':ti,ab	16460
15	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	84011
16	#4 AND #15	126
17	[animals]/lim NOT [humans]/lim	6006575
18	#16 NOT #17	124
19	#16 NOT #17 AND [english]/lim	110

Appendix 2.1. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded budesonide. 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 budesonide to your patients?

- Yes
- No

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

- Injection
- None of the above

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

- Otitis media with effusion
- Other (please explain) _____

5. I use compounded budesonide 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 budesonide.
- Other (please explain) _____

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

- Yes
- No
- I'm not sure

7. I obtain compounded budesonide 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 2.2. Survey instrument for Ambulatory Surgery Center Association

Welcome. We want to understand your clinical use of compounded drugs. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in bulk 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 utilize a 503B outsourcing facility to acquire compounded drugs?

- Yes. If yes, why? _____
- No. If no, why not? _____

3. Do you obtain any of the following products from a 503B outsourcing facility? (check all that apply)

- I do not obtain any compounded drugs from 503B outsourcing facilities
- Amitriptyline / Ketoprofen / Oxymetazoline
- Budesonide
- Calcium gluconate
- Droperidol
- Epinephrine
- Epinephrine for ophthalmic administration
- Epinephrine / Lidocaine for ophthalmic administration
- Epinephrine / Bupivacaine / Fentanyl
- Fentanyl
- Flurbiprofen
- Flurbiprofen for ophthalmic administration
- Hydromorphone
- Ipamorelin
- Ketoprofen / Nifedipine
- Lidocaine / Epinephrine / Tetracaine HCl
- Meperidine
- Morphine
- Naloxone
- Neomycin
- Phentolamine
- Promethazine
- Remifentanyl

- Sufentanil
- Tramadol
- None of the above

4. What type of specialty procedures are performed in your facility? (check all that apply)

- Dental
- Dermatology
- Endoscopy
- Neurosurgery
- Obstetrics/gynecology
- Ophthalmology
- Otolaryngology
- Orthopedics
- Pain
- Plastics
- Podiatry
- 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.