

Summary Report

Procaine 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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REVIEW OF NOMINATIONS

Procaine hydrochloride (procaine HCl; UNII code: 95URV01IDQ) was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society (SSPS), McGuff Compounding Pharmacy Services, Inc. (McGuff CPS), the American Association of Naturopathic Physicians (AANP), the Alliance for Natural Health USA (ANH-USA), the Integrative Medicine Consortium (IMC), and the Outsourcing Facilities Association (OFA). Procaine HCl was nominated for use in the treatment of life-threatening arrhythmias as a 1-10% solution for intracardiac or infiltration administration. Procaine HCl was also nominated for use in local anesthesia/pain management as a 10-20mg/mL preservative-free and multi-dose vial for intramuscular, intra-articular, or injection at the tendon and ligament. Additionally, procaine HCl was nominated for use as a 2% injectable solution for use as an anesthetic.

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

- Prescriber and hospital preference for varying concentrations, dosage forms, volumes, or final product containers.
- It is relatively unsafe to expose the direct compounding area to hundreds of vials or ampules and hundreds of aseptic manipulations during the compounding of a typical batch size for an outsourcing facility; compounding from bulk is more safe and efficient.
- Commercially available finished products have an inherent variance in potency creating an uncertain final concentration for the new product.
- Use of state of the art equipment, like the SKAN isolator technology, requires the use of bulk starting materials.
- Procaine is the only utilized ester anesthetic, and the least toxic anesthetic in general and is necessary to avoid chondrotoxicity, myotoxicity, systemic toxicity, and to reduce anesthetic neurotoxicity.
- Due to its muscle-relaxing properties and vasodilatory effects, procaine is clinically necessary to optimize the effectiveness of tissue bed blocks; for the application of trigger point infiltration; for patients who are challenging for venipuncture or catheterization; and for prolotherapy, neural therapy, the biopuncture system of homeopathic injection, and the mesotherapy system of injections.
- There are unique uses of procaine IV that are not capable of being reproduced with other IV anesthetics.
- For use by Doctors of Oriental Medicine licensed for expanded practice in New Mexico whose practice depends on the use of procaine from compounding pharmacies as alternatives are not available due to limited statutory status and formularies.
- There are no commercially available drug products that contain procaine HCl.
- Patients respond differently and the compounded drug product may be the only formulation to effectively treat the indication for which it is intended to treat.
- Patient sensitivities to manufactured product dyes, fillers, preservatives, or other excipients.
- Manufacturer backorders.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of procaine 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, 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 procaine HCl; name variations of procaine 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(s); strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms and/or routes of administration similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing procaine 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

Procaine HCl is a component of an FDA-approved product that has been discontinued by the manufacturer, not for safety or efficacy reasons. The desired compounded products identified in the submitted nominations do not substantially differ from the commercially available product; therefore, a systematic literature review was not completed.

Outreach to medical specialists and specialty organizations

Using the indications from the nominations and the results of the literature review, five (5) medical specialties that would potentially use procaine HCl were identified: anesthesiology, cardiology, pain medicine, surgery, and wound care. Semi-structured interviews were conducted with subject matter experts within these specialties. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. Two (2) experts were contacted for interviews, of which two (2) accepted and zero (0) declined interviews. One (1) interview was conducted with two (2) interviewees but was not recorded. A specialty organization was contacted for assistance in identifying a specialist; they replied with a statement that there is a clinical need for compounding using bulk drug substances, they were unable to identify a practitioner who is currently using procaine. The University of Maryland, Baltimore IRB and the Food & Drug Administration RIHSC reviewed the study and found it to be exempt. Subject matter experts provided their oral informed consent to participate in interviews.

Survey

General professional medical associations and specialty associations for anesthesiology, cardiology, pain medicine, surgery, and wound care, identified from the nominations, were contacted to facilitate distribution of an online survey. A Google™ search was conducted to identify relevant professional associations within each specialty. Associations were included if their members are predominantly practitioners, national associations, and organizations focused on practice within the US. Organizations without practicing physicians and state or regional organizations were excluded. The association's website was searched in order to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used.

An online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to eight (8) associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

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

Table 1. Participating associations

Specialty	Association
Pain Medicine	American Academy of Pain Medicine (AAPM)
Primary Care	American Academy of Environmental Medicine (AAEM)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Anesthesiology	American Society of Anesthesiologists (ASA)	Declined, requires a PI who is an ASA member
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Surgery	American College of Surgeons (ACS)	Failed to respond
Wound Care	American Professional Wound Care Association (APWCA)	Failed to respond
	Wound Healing Society (WHS)	Failed to respond

CURRENT AND HISTORIC USE

Summary of background information

- Procaine HCl is not available as an FDA-approved product. Procaine HCl was previously available as an injectable product, Novocain, at concentrations ranging from 1-10%; however, this product has been discontinued by the manufacturer, not for safety or efficacy reasons.
- Procaine HCl is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for procaine HCl.
- Procaine HCl is available in Belgium (see Table 4).

Table 3. Currently approved products – US

No approved products in the US

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

Active Ingredient	Concentration	Dosage Form	ROA	Approved For Use		
				Country	Status	Approval Date
Procaine HCl	1%, 4%	Solution	Intravenous	Belgium	Medical Prescription	02/05/2015

Abbreviation: ROA, route of administration.

^aMedicine 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.

Summary of literature review

No literature review was conducted.

Table 5. Types of studies

No literature review was conducted

Table 6. Number of studies by country

No literature review was conducted

Table 7. Number of studies by combinations

No literature review was conducted

Table 8. Dosage by indication – US

No literature review was conducted

Table 9. Dosage by indication – non-US countries

No literature review was conducted

Table 10. Compounded products – US

No literature review was conducted

Table 11. Compounded products – non-US countries

No literature review was conducted

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

One (1) interview was conducted with two (2) interviewees.

Table 12. Overview of interviewees

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Procaine HCl	Interview Summary Response
ANE_01	MD	Anesthesiology	Trauma center	Not specified	<ul style="list-style-type: none">Interested in having access to compounded “caine” products.
ANE_02	NP	None	Trauma center	Not specified	<ul style="list-style-type: none">Interested in having access to compounded “caine” products.

Abbreviations: MD, Doctor of Medicine; NP, Nurse Practitioner.

Summary of survey results

Table 13. Characteristics of survey respondents [6 people responded to the survey^a]

Board Certification	MD	PhD	No Response
Anesthesiology	1	0	0
Neurology	1	0	0
Pain Medicine	3	0	0
No Board Certification	0	1	1
No Response	0	0	1

Abbreviation: MD, Doctor of Medicine; PhD, Doctor of Philosophy.

^aSome respondents reported more than one (1) board certification.

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

No survey respondents reported using procaine HCl

Table 15. Compounded use of procaine HCl in practice

No survey respondents reported using procaine HCl

Table 16. Indications for which procaine HCl is considered a standard therapy

No survey respondents reported using procaine HCl

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

No survey respondents reported using procaine HCl

Table 18. Change in frequency of compounded procaine HCl usage over the past 5 years

No survey respondents reported using procaine HCl

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

No survey respondents reported using procaine HCl

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

No survey respondents reported using procaine HCl

CONCLUSION

Procaine HCl (UNII code: 95URV01IDQ) was nominated on the 503B Bulks List for a variety of indications as an injectable solution in a range of strengths. Out of the foreign medical registries searched, procaine HCl is currently only available in Belgium. Procaine HCl was previously available in the US as an injectable product, Novocain; however, this product has been discontinued by the manufacturer, not for safety or efficacy reasons.

Procaine HCl is a component of an FDA-approved product that has been discontinued by the manufacturer, not for safety or efficacy reasons. The desired compounded products identified in the submitted nominations do not substantially differ from the commercially available product; therefore, a systematic literature review was not completed.

One (1) interviewee expressed interest in having increased access to compounded medications for all substances in the “caine” drug class.

From the survey, none of the six (6) respondents reported using procaine HCl.

APPENDICES

Appendix 1. References

No literature review was conducted.

Appendix 2. Survey instrument

Start of Block: Welcome Page

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

OMB Control No. 0910-0871

Expiration date: June 30, 2022

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

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

End of Block: Welcome Page

Start of Block: Procaine

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

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

Skip To: Q13. If What type(s) of product(s) do you use, prescribe, or recommend for procaine?... != Compounded drug product Is Not Selected

Skip To: Q2. If What type(s) of product(s) do you use, prescribe, or recommend for procaine?... = Compounded drug product Is Selected

Display This Question:

If What type(s) of product(s) do you use, prescribe, or recommend for procaine?... = Compounded drug product

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

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

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

- Single
- Combination

Skip To: Q5. If Do you use compounded procaine as a single agent active ingredient, or as on... != Combination Is Not Selected

Display This Question:

If Loop current: Do you use compounded procaine as a single agent active ingredient, or as on... = Combination Is Selected

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

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

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

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

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

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

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

- Yes
- No

Skip To: End of Block If Do you stock non-patient-specific compounded procaine in your practice locat... = No

Display This Question:

If Do you stock non-patient-specific compounded procaine in your practice locat... = Yes

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

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

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

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

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

- Convenience
- Emergencies
- Other (please describe) _____

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded procaine? Please... = Convenience

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded procaine? Please... = Emergencies

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

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

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

End of Block: Procaine

Start of Block: Background Information

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

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

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

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

End of Block: Background Information