Summary Report

Vancomycin 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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Prepared by:

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REVIEW OF NOMINATIONS

Vancomycin hydrochloride (vancomycin HCl; UNII code: 71WO621TJD) was nominated for inclusion on the 503B Bulks List by Rebecca Mitchell, Special Sterile Pharmaceutical Society, Outsourcing Facilities Association, and Pentec Health. It was nominated to treat *Clostridium difficile* diarrhea, skin/subcutaneous tissue infections, staphylococcal/diphtheroid/early-onset prosthetic valve endocarditis, lower respiratory tract infections, staphylococcal enterocolitis, endophthalmitis, septicemia, bone infections, cellulitis, and pneumonia via various administration methods:

- Intravenous injection solution and preservative-free oral solution 0.125-2.5g – Rebecca Mitchell and Special Sterile Pharmaceutical Society
- Oral 250mg/5mL, injectable 5mg/0.5mL, or 5mg preservative-free, sulfite-free, isotonic intravitreal injection – Outsourcing Facilities Association
- Intravenous infusion injectable "equivalent to 100mg/mL" – Outsourcing Facilities Association and Pentec Health

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

- To ensure access to the bulk material in the event of a manufacturer backorder.
- 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 safer and more 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.
- Prescriber preference for varying concentrations, volumes, or final product containers.
- Patients respond differently, so the compounded drug product may be the only product to effectively treat the indication for which it is intended to treat.
- To compound a product with a concentration/dosage form that is not commercially available.
- Possible patient sensitivities to manufactured product dyes, fillers, preservatives, or other excipients.
- To prevent antibiotic resistance.
- Time limitation regarding utilization of commercially available FDA-approved products.
- Need for concentration-stable, ready-to-use products due to diluent bag evaporation implications.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of vancomycin 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 (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 vancomycin HCl; name variations of vancomycin 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 ROA similar to those requested in the nominations.

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

Vancomycin HCl is a component of an FDA-approved product. 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, two (2) medical specialties that would potentially use vancomycin HCl were identified: infectious disease and primary care. No interviews were conducted as vancomycin HCl is a component of an FDA-approved product, and the nominated products can be compounded from the commercially available products.

Survey

General professional medical associations and specialty associations for infectious disease and primary 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 five (5) 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.

Vancomycin HCl was included on two (2) surveys distributed to the associations in Table 1. Due to the identification of additional substances relevant to these associations, vancomycin HCl was included on a primary care survey with aluminum chloride hexahydrate, benzocaine, dexamethasone acetate, lidocaine,

menthol, phenylephrine HCl, quinacrine, scopolamine hydrobromide, tetracaine, triamcinolone, and triamcinolone diacetate.

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
Primary Care	American Academy of Environmental Medicine (AAEM)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Primary Care	American Academy of Family Physicians (AAFP)	Failed to respond
	American College of Physicians (ACP)	Failed to respond

CURRENT AND HISTORIC USE

Summary of background information

- Vancomycin HCl is available as an FDA-approved product.
- Vancomycin HCl is not available as an OTC product in the US.
- There is a current USP monograph for vancomycin HCl.
- Vancomycin HCl is available in eleven (11) countries (Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, and the UK) as various brand and generic products in oral and intravenous dosage forms.

Table 3. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	ROA	Status	Approval Date[b]
Vancomycin HCl	EQ 500mg base/mL, EQ 750mg base/mL, EQ 1g base/mL EQ 500mg base/vial, EQ 750mg base/vial, EQ 1g base/vial, EQ 5g base/vial, EQ 10g base/vial	Injectable	Injection	Prescription	03/17/1987
	EQ 100g base, EQ 250-1500mg base/vial	Powder	Intravenous		01/06/2016
	EQ 500mg base/100mL, EQ 1g base/200mL, EQ 1.5g base/300mL, EQ 2g base/400mL	Solution			02/15/2019
	EQ 25-250mg base/mL	For solution	Oral		Prior to 01/01/1982

Abbreviation: ROA, route of administration

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

Active Ingredient	Concentration	Dosage Form	ROA	Approved For Use		
				Country	Status	Approval Date[b]
Vancomycin	500mg, 1g	Powder	Intravenous	Australia	Schedule 4 – Prescription only	09/05/1991
				Ireland	Prescription only, non-renewal	05/08/1981
				Saudi Arabia	Prescription	–
	500mg/vial, 1g/vial			UK	Prescription-only	2/10/2004
	500mg, 1g		Oral	Australia	Schedule 4 – Prescription only	09/05/1991
Vancomycin HCl	500mg	–	–	Hong Kong	Prescription only	11/29/2010
	500mg	Infusion		Abu Dhabi	Active	–
	500mg/10mL, 1g/20mL EQ 500mg or 1g base/vial	Injection		Namibia	–	08/18/2004
	500mg, 1g	Powder		Abu Dhabi	Active	–
	500mg			Hong Kong	Prescription only	05/13/2015
	500mg/vial, 1g/vial			Namibia	–	2/22/1971
	500mg, 1g	-	Intravenous	Hong Kong	Prescription only	10/18/1983
	513mg, 1026mg	Powder		Australia	Schedule 4 – Prescription only	05/06/2005
	500mg, 1000mg, 512.76mg, 1025mg			Belgium	Medical prescription	01/31/2010
	500mg/vial, 1g/vial, 5g/vial, 10g/vial			Canada	Prescription	12/31/1992

	500mg, 1g			Ireland	Prescription-only, non-renewal	06/03/2011
	500mg, 513mg, 1000mg			New Zealand	Prescription	05/21/1988
	500mg/vial, 1g/vial (50mg/mL)			UK	Prescription-only	04/18/1990
	513mg, 1026mg		Oral	Australia	Schedule 4 – Prescription only	07/23/2010
	512.76mg, 1025mg			Belgium	Medical prescription	07/05/2011
	500mg/vial, 1g/vial (50mg/mL)			UK	Prescription-only	04/18/1990
Vancomycinum	500mg, 1000 mg		–	Latvia	Prescription	05/03/2011

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

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROAs 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.

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

Zero (0) interviews were conducted.

Table 12. Overview of interviewees

No interview was conducted

Summary of survey results

No survey data was received.

Table 13. Characteristics of survey respondents

No survey data was received

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

No survey data was received

Table 15. Compounded use of vancomycin HCl in practice

No survey data was received

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

No survey data was received

Table 17. Reasons for using a compounded product instead of an FDA-approved product

No survey data was received

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

No survey data was received

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

No survey data was received

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

No survey data was received

CONCLUSION

Vancomycin HCl (UNII code: 71WO621TJD) was nominated for inclusion on the 503B Bulks List for *Clostridium difficile* diarrhea, skin/subcutaneous tissue infections, staphylococcal/diphtheroid/early-onset prosthetic valve endocarditis, lower respiratory tract infections, staphylococcal enterocolitis, endophthalmitis, septicemia, bone infections, cellulitis, and pneumonia. The nominated ROA and dosage forms are intravenous injection solution and a preservative-free oral formulation. Vancomycin HCl is available in 11 out of the 12 foreign regulatory databases searched. No literature review or interviews were conducted, and no survey responses were received.

APPENDICES

Appendix 1. References

No literature review was conducted.

Appendix 2. Survey instrument

Vancomycin HCl

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 **vancomycin**. 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: Vancomycin HCl

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

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

Display This Question:

If What type(s) of product(s) do you use, prescribe, or recommend for vancomycin? Please check all t... = Compounded drug product

Q2 Please list any conditions or diseases for which you use compounded **vancomycin** 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 **vancomycin** 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 vancomycin as a single agent active ingredient, or as one active ingredient... != Combination

Display This Question:

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

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

_____

Page Break

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

_____

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

_____

Q7 Over the past 5 years, has the frequency in which you have used compounded **vancomycin** 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 **vancomycin** instead of any FDA-approved drug product?

_____

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

- ○ Yes
- ○ No

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

Page Break

Display This Question:

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

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

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

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

Page Break

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

_____

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

_____

End of Block: Vancomycin HCl

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