Summary Report

Deoxy-D-Glucose

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

Deoxy-d-glucose (UNII code: 9G2MP84A8W) was nominated for inclusion on the 503B Bulks List by Outsourcing Facilities Association (OFA) and Sincerus Florida, LLC. While the exact medical condition for which the compounded product is being requested is generally unknown, deoxy-d-glucose is generally indicated to treat warts and the Herpes virus (HSV). Deoxy-d-glucose was nominated for use in various topical dosage forms, including gels, creams, and other formulations, and strengths, the therapeutic dose is 0.2%, as requested by the prescriber. Deoxy-d-glucose has been used in combination with other active pharmaceutical ingredients (API); refer to Table 7 for the combination formulations.

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

- 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.
- There are no FDA-approved products that contain this substance.
- Compounding from a bulk drug substance means that only the ingredients necessary to achieve the desired clinical outcome are utilized eliminating any fillers, excipients, binders, dyes, preservatives, or other materials that may be irritating, hazardous, or allergenic.
- Variance in the active pharmaceutical ingredients (API) of finished products may introduce unacceptable inaccuracies into the compounded product; compounding from the bulk substance is more accurate.
- Compounding in combination with other APIs may shorten the duration of symptoms of an HSV infection.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of deoxy-d-glucose 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 deoxy-d-glucose; name variations of deoxy-d-glucose 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 deoxy-d-glucose. 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

Two databases (PubMed and Embase) were searched including any date through March 1, 2019. The search included a combination of ("deoxy-d-glucose"[TIAB] OR "2-deoxyglucose"[TIAB] OR "2-deoxy-d-arabinohexose"[TIAB] OR "2-desoxy-d-glucose"[TIAB] OR "2-deoxy-d-arabino-hexose"[TIAB] OR deoxyglucose[TIAB] OR "2-DG"[TIAB] OR "2-DDG"[TIAB]) AND (treat*[TIAB] OR therap*[TIAB] OR clinic*[TIAB] OR topical[TIAB] OR derm*[TIAB] OR skin[TIAB] OR herpes[TIAB] OR virus[TIAB] OR vir*[TIAB] OR genital[TIAB] OR peni*[TIAB] OR vag*[TIAB]) AND (humans[MeSH Terms] AND English[lang]) NOT autism. Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to Covidence®, merged, and sorted for removal of duplicate citations.

Study selection

Articles were not excluded on the basis of study design. Articles were considered relevant based on the identification of a clinical use of deoxy-d-glucose or the implementation of deoxy-d-glucose in clinical practice. Articles were excluded if not in English, a clinical use was not identified, incorrect salt form, or if the study was not conducted in humans. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

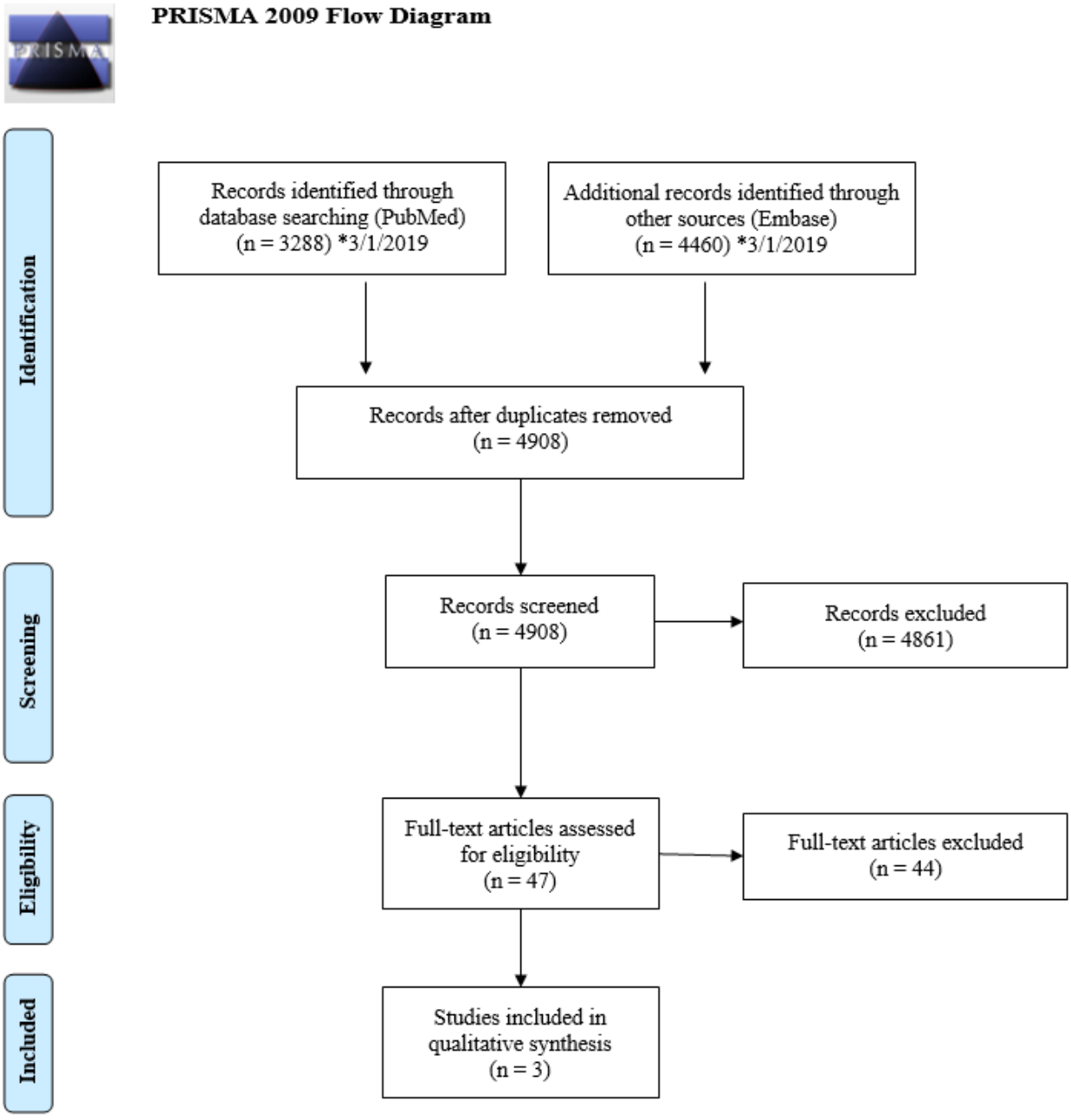
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for deoxy-d-glucose use; dose; strength; dosage form; ROA; frequency and duration of therapy; any combination therapy utilized; if applicable, formulation of compounded products; study design; and any discussion surrounding the use of deoxy-d-glucose compared to alternative therapies.

Results

Please refer to Figure 1.

Figure 1. Summary of literature screening and selection (PRISMA 2009 Flow Diagram)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

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 deoxy-d-glucose were identified: dermatology, infectious disease, naturopathy, obstetrics and gynecology, and oncology. 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 one (1) accepted. One (1) medical expert specializing in oncology was contacted for an interview however the expert failed to respond to the interview request. The interview was recorded and transcribed via ©Rev.com. QSR International's Nvivo 12 software was utilized for qualitative data analysis. 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 dermatology, infectious disease, naturopathy, obstetrics and gynecology, and oncology, identified from the nominations, literature review, and interview, 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 six (6) 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
Dermatology	American Academy of Dermatology (AAD)
	American Society for Dermatologic Surgery (ASDS)
Naturopathy	American Association of Naturopathic Physicians (AANP)

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
Obstetrics and Gynecology	American College of Obstetricians and Gynecologists (ACOG)	Declined, survey not approved for distribution
Oncology	American Society of Clinical Oncology (ASCO)	Declined

CURRENT AND HISTORIC USE

Summary of background information

- Deoxy-d-glucose is not available as an FDA-approved product.
- Deoxy-d-glucose is not available as an OTC product in the US.
- There is no current United States Pharmacopeia (USP) monograph for deoxy-d-glucose.
- Deoxy-d-glucose is not approved in any of the foreign medicine registries searched.

Table 3. Currently approved products – US

No approved products in the US

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

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

Summary of literature review

- Total number of studies included: 3 studies, all experimental.
- Most of the studies were from the US (2).
- The most common indications for the use of deoxy-d-glucose in the US were genital herpes infection and cutaneous herpes simplex. The most common indication from the non-US studies was supratentorial glioma.
- Compounded products were identified from the US studies, but not in any of the nominated formulations.

Table 5. Types of studies

Types of Studies	**Number of Studies**
Descriptive	0
Experimental[1–3]	3
Observational	0

Table 6. Number of studies by country

Country	**Number of Studies**
India[3]	1
US[1,2]	2
	Total US: 2 Total non-US Countries: 1

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Deoxy-d-glucose 0.2% / Not mentioned – topical cream, gel	0
	Deoxy-d-glucose 0.2% / Acyclovir 3% / Lidocaine HCl monohydrate 1% – topical cream, gel	0
	Deoxy-d-glucose 0.2% / Cimetidine 10% / Ibuprofen 2% / Lidocaine 5% / Salicylic acid 15% – topical cream, gel	0

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Genital herpes infection[1]	–	0.19%	Gel	Topical/intravaginal	3 weeks
Cutaneous herpes simplex[2]	–	0.19%	–	Topical	6 months

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

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Supratentorial glioma (grade 3/4)[3]	200mg/kg	–	Aqueous solution	Oral	4 weeks

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

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Genital herpes infection[1]	1979	• In miconazole nitrate 2% crème. If hypersensitivity present, used buffered-acid jelly as vehicle instead.	Gel	0.19%
Cutaneous herpes simplex[2]	1982	• First series: In lanolin base • Second series: In hydroalcoholic vehicle	–	0.19%

Abbreviation: "–", not mentioned.

Table 11. Compounded products – non-US countries

No compounded products from reported studies

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

One (1) interview was conducted. One (1) medical expert specializing in oncology was contacted for an interview however the expert failed to respond to the interview request.

Table 12. Overview of interviewee

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with deoxy-d-glucose	Interview Summary Response
DER_06	MD	Dermatology/ Immunology	Consulting	Not specified	• It was considered to be helpful for HSV. • Interviewee stated the studies[1,2] about intravaginal use "was published in 1979 which was before any of the 'vir' drugs (acyclovir, the first, was approved in 1982). The studies in both papers are inadequately designed." • "When we have drugs that we know are effective, I find it morally offensive that there are shysters who have products for which there is no data to support their use. I think it keeps people from using things that are effective."

Abbreviation: MD, Doctor of Medicine.

Summary of survey results

Table 13. Characteristics of survey respondents [11 people responded to the survey[a]]

Board Certification	MD	ND	No Response
Dermatology	2	0	0
Fellow of the American Board of Naturopathic Oncology	0	1	0
Naturopathic Doctor	0	3	0
Naturopathic Physician	0	3	0
No Board Certification	0	0	0
No Response	0	0	5

Abbreviations: MD, Doctor of Medicine; ND, Naturopathic Doctor.
[a]Some respondents reported more than one terminal clinical degree or board certification.

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

Types of Products	Respondents, n (N=1[a])
Compounded	1[b]
FDA-approved	0
Over-the-counter	0
Dietary	0
Unsure	0
No response	0

[a]Out of 11 respondents, 1 reported using, prescribing, or recommending deoxy-d-glucose product.
[b]One respondent used in combination but left no response.

Table 15. Compounded use of deoxy-d-glucose in practice

No survey respondents provided this information

Table 16. Indications for which deoxy-d-glucose is considered a standard therapy

Indication	Standard Therapy	
	Compounded, n (N=1)	Non-Compounded, n (N=0)
No response	1	0

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

No survey respondents provided this information

Table 18. Change in frequency of compounded deoxy-d-glucose usage over the past 5 years

	Respondents, n (N=1)
No–use has remained consistent	1
Yes–I use it LESS often now	0
Yes–I use it MORE often now	0

Table 19. Do you stock non-patient specific compounded deoxy-d-glucose in your practice?

	Respondents, n (N=1)
No	0
Yes[a]	1

[a]Respondent reports stocking non-patient-specific compounded deoxy-d-glucose for emergencies.

Table 20. Questions related to stocking non-patient specific compounded deoxy-d-glucose

No additional survey respondents provided this information

CONCLUSION

Deoxy-d-glucose (UNII code: 9G2MP84A8W) was nominated for inclusion on the 503B Bulks List by OFA and Sincerus. Deoxy-d-glucose has been used in combination with other active pharmaceutical ingredients (API), refer to table 7 for the combination formulas. While the exact medical condition for which the compounded product is being requested is generally unknown, deoxy-d-glucose is generally indicated to treat warts and the Herpes virus (HSV). Deoxy-d-glucose was nominated for use in various topical dosage forms and strengths (the therapeutic dose is 0.2%) as requested by the prescriber, including gels, creams, and other formulations. Deoxy-d-glucose is not approved in any of the foreign medicine registries searched.

From the literature review conducted, the most common indication in the US were genital herpes infection and cutaneous herpes simplex. The most common indications from the non-US studies was supratentorial glioma. Compounded products were identified from US studies, but not used in nominated formulations.

From the interviews, the interviewee stated that it was considered to be helpful for HSV but now there are more effective drugs.

From the survey responses, one (1) out of 11 respondents used compounded deoxy-d-glucose. One (1) respondent reported stocking compounded deoxy-d-glucose in the physician office for emergencies.

APPENDICES

Appendix 1. References

1. Blough HA, Giuntoli RL. Successful treatment of human genital herpes infections with 2-deoxy-D-glucose. *JAMA J Am Med Assoc*. 1979;241(26):2798-2801.
2. McCray MK, Zugerman C. 2-Deoxy-D-glucose for herpes simplex? *J Am Acad Dermatol*. 1982;6(4):550-551.
3. Mohanti B, Rath G, Anantha N, et al. Improving cancer radiotherapy with 2-deoxy-D-glucose: phase I/II clinical trials on human cerebral gliomas. *Int J Radiat Oncol Biol Phys*. 1996;35(1):103-111.

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 **deoxy-d-glucose**. 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: Deoxy-d-glucose

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **deoxy-d-glucose**? 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 deoxy-d-glucose? Please check all th... != Compounded drug product

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

Display This Question:

If What type(s) of product(s) do you use, prescribe, or recommend for deoxy-d-glucose? Please check all th... = Compounded drug product

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

Display This Question:

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

Q4. In which combination(s) do you use compounded **deoxy-d-glucose**? Please check all that apply.

- ☐ Deoxy-d-glucose 0.2% / Acyclovir 3% / Lidocaine HCl monohydrate 1%
- ☐ Deoxy-d-glucose 0.2% / Cimetidine 10% / Ibuprofen 2% / Lidocaine 5% / Salicylic acid 15%
- ☐ Other (please describe) _____

Q5. For which, if any, diseases or conditions do you consider compounded **deoxy-d-glucose** standard therapy?

_____

Q6. Does your specialty describe the use of compounded **deoxy-d-glucose** in medical practice guidelines or other resources?

_____

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

_____

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

- Yes
- No

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

Display This Question:

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

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

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

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

Q13. For which, if any, diseases or conditions do you consider **deoxy-d-glucose** standard therapy?

_____

Q14. Does your specialty describe the use of **deoxy-d-glucose** in medical practice guidelines or other resources?

_____

End of Block: Deoxy-d-glucose

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