Summary Report

Pregnenolone

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 2U01FD005946

Prepared by:

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REVIEW OF NOMINATION

Pregnenolone (UNII code: 73R90F7MQ8) was nominated for inclusion on the 503B Bulks List by the International Academy of Compounding Pharmacists (IACP) to treat an unspecified medical indication via a dosage form, route of administration (ROA), and strength that varies based upon the compounding requirement or prescription.

No reasons were provided for why pregnenolone was nominated to the 503B Bulks List.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of pregnenolone products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, ROA, and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for pregnenolone; name variations of pregnenolone 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 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing pregnenolone. 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 Februrary 4, 2019. The search included a combination of pregnenolone[TIAB] AND ("spinal cord"[TIAB] OR memory[TIAB] OR cogniti*[TIAB] OR "rheumatoid arthritis"[TIAB] OR postmenopause[TIAB] OR hypercholesterolemia[TIAB] OR bipolar[TIAB] OR schizophrenia[TIAB] OR obesity[TIAB] OR pain[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 pregnenolone or the implementation of pregnenolone 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.

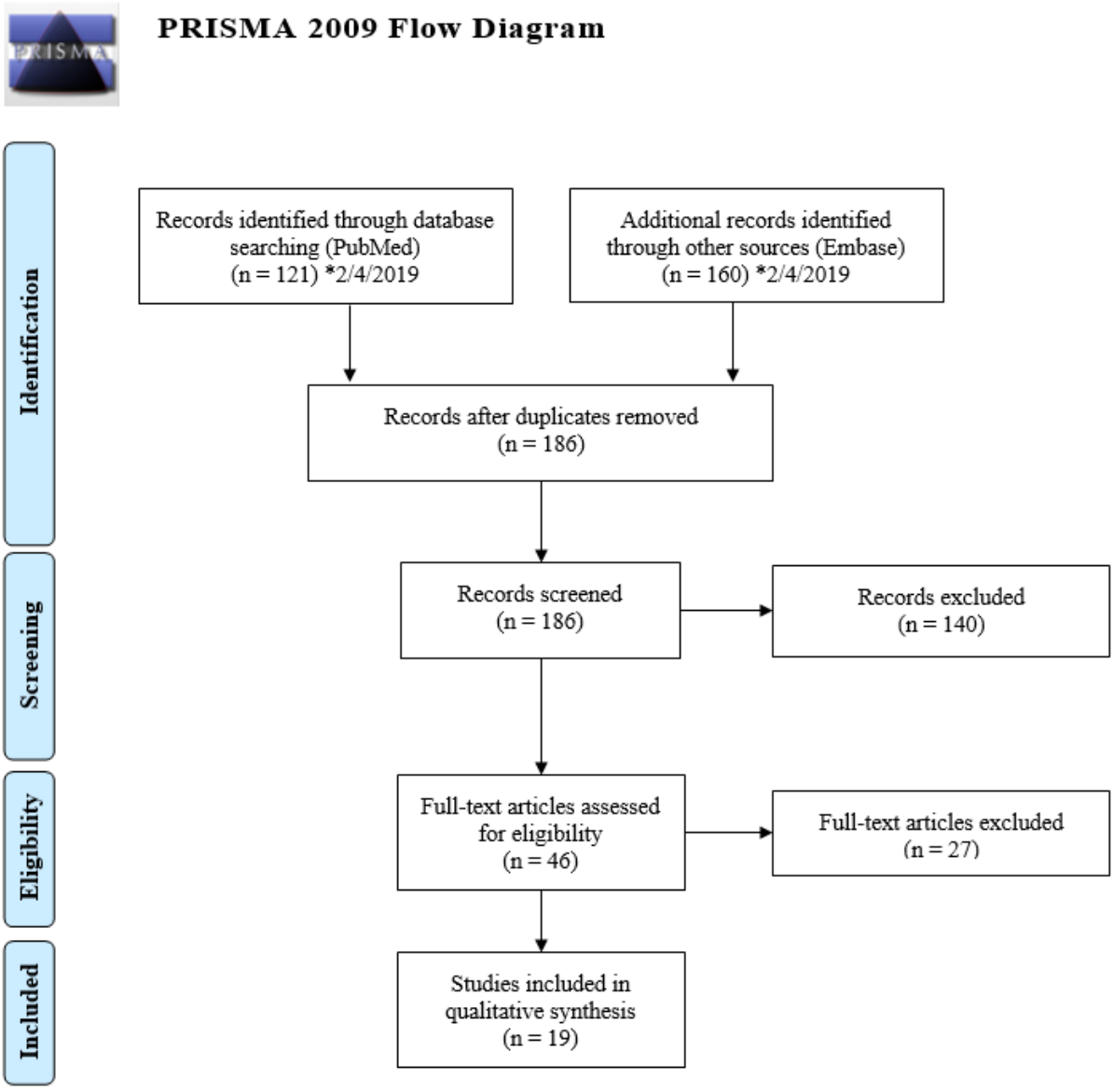
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for pregnenolone 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 pregnenolone 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 results of the literature review, eight (8) medical specialties that would potentially use pregnenolone were identified: endocrinology, naturopathy, neurology, obstetrics and gynecology, pain medicine, primary care, psychiatry, and rheumatology. 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. Five (5) experts were contacted for interviews, of which three (3) accepted. One (1) expert specializing in psychiatry, replied with a statement that they do not utilize the substance. One (1) medical expert specializing in neurology failed to respond to the interview request. Most interviews were recorded and transcribed via ©Rev.com, while one (1) interview was not recorded due to equipment failure. Another interview occurred by email. 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 endocrinology, naturopathy, neurology, obstetrics and gynecology, pain medicine, primary care, psychiatry, and rheumatology, identified from the nomination, literature review, and interviews, 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 twelve (12) 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
Naturopathy	American Association of Naturopathic Physicians (AANP)
Pain Medicine	American Academy of Pain Medicine (AAPM)
Primary Care	American Academy of Environmental Medicine (AAEM)
Rheumatology	American College of Rheumatology (ACR)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Endocrinology	American Association of Clinical Endocrinologists (AACE)	Declined, "endocrinologists are not generally in the compounding space."
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Neurology	American Academy of Neurology (AAN)	Failed to respond
Obstetrics and Gynecology	American College of Obstetricians and Gynecologists (ACOG)	Declined, survey not approved for distribution
Primary Care	American Academy of Family Physicians (AAFP)	Failed to respond
	American College of Physicians (ACP)	Failed to respond
Psychiatry	American Psychiatric Association (APA)	Declined, "we have put this ask to our members and unfortunately, we have not received any information on psychiatrists using compounded products"

CURRENT AND HISTORIC USE

Summary of background information

- Pregnenolone is not available as an FDA-approved product.
- Pregnenolone is available as an oral and sublingual OTC supplement in the US.
- There is no current United States Pharmacopeia (USP) monograph for pregnenolone.
- Pregnenolone is not available in any of the national medical 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 selected non-US countries and regions

Summary of literature review

- Total number of studies included: 19 (1 descriptive, 17 experimental, 1 observational).
- Most of the studies were from the US (11).
- The most common indication for pregnenolone in the US and non-US studies was schizophrenia.
- Compounded products were identified from both the US and non-US studies.

Table 5. Types of studies

Types of Articles	Number of Studies
Descriptive[1]	1
Experimental[2-18]	17
Observational[19]	1

Table 6. Number of studies by country

Country	Number of Studies
Germany[5]	1
Iran[4]	1
Israel[3,7,15-17]	5
Singapore[10]	1
US[1,2,6,8,9,11-14,18,19]	11
	Total US: 11 Total non-US Countries: 8

Table 7. Number of studies by combinations

No combination products were nominated

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Schizophrenia[8,9,18]	100-500mg/day	50mg	Tablets	Oral	8-14 weeks
Bipolar depression[2,11]	100-500mg/day	–	Capsule	Oral	12 weeks
Mood, cognition, and/or memory[12,14]	15-100mg/day	15-50mg	Capsule	Oral	4-8 weeks
Hypercholesterolemia[19]	15-300mg	–	Capsule, tablet	Oral	3-9 months
Pain[13]	–	–	–	–	4 weeks
Rheumatoid arthritis[1,6]	100-300mg/day	–	Suspension	Intramuscular	7 days-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
Schizophrenia[3,4,7,10,15-17]	30-500mg/day	50-100mg	Capsule, tablet	Oral	8 weeks
Obsessive compulsive disorder[5]	400mg/day	400mg	Capsule	Oral	3 doses

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

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Mood, cognition, and/or memory[12,14]	2004, 2010	• "Obtained from pharmacy"	Capsule	15mg-50mg
		• Pregnenolone powder formulated into capsules		
Bipolar depression[2]	2014	• Pregnenolone powder formulated into capsules	Capsule	–

Abbreviation: "–", not mentioned.

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Schizophrenia[10]	• "Obtained from pharmacy"	Tablet	100mg

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

Three (3) interviews were conducted. One (1) interview was not recorded due to equipment failure.

Table 12. Overview of interviewees

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Pregnenolone	Interview Summary Response
END_01	MD	Endocrinology and Metabolism Internal Medicine	Academic medical institution	Not specified	• Not specified.
END_02	MD	Endocrinology, Diabetes, and Metabolism	Academic medical institution	No	• Does not see need for pregnenolone.
OBG_01	MD	Obstetrics and Gynecology	Academic medical institution	No	• Does not use pregnenolone.

Abbreviation: MD, Doctor of Medicine.

Use of pregnenolone in practice

- One (1) interviewee stated that they do not think there is any known benefit, and so has not used pregnenolone personally.
    - In addition, they stated that the person in their practice who specializes in reproductive endocrinology does not use it either.
- One (1) interviewee commented that pregnenolone "gets combined when people put things together but not for any good reason."

Pregnenolone as office stock

- One (1) interviewee stated that they see no reason to keep hormonal substances in the office; if they really wanted to use it, they would write a prescription to a compounding pharmacy.
    - "The other thing is people get all these levels check because they will go to some doctor who checks everything and then can't do anything about it, and then sends them to us and then they come with these sheets of like labs…pregnenolone is on here…yeah. I don't know. Yeah. I don't think that needs to be ready for widespread use."

Supplemental information

- One (1) interviewee provided references regarding the serious health and safety risks associated with the use of compounded "bioidentical" hormone products in menopausal women, as well as scientific, positional statements, and other publicly available documents nominating hormones to the demonstrably difficult to compound list.[20-30]
    - Information included a patient-oriented summary regarding what to expect with taking pregnenolone supplements.[23]

Summary of survey results

Table 13. Characteristics of survey respondents [60 people responded to the survey[a]]

Board Certification	DO	MD	ND	No Response
Anesthesiology	0	1	0	0
Endocrinology, Diabetes and Metabolism	0	0	1	0
Fellow of the American Board of Naturopathic Oncology	0	0	1	0
Naturopathic Doctor	0	0	6	0
Naturopathic Physician	0	0	9	0
Neurology	0	1	0	0
Pain Medicine	0	3	0	0
Rheumatology	1	0	0	0
No Board Certification	0	1	3	0
No Response	0	0	0	41

Abbreviations: DO, Doctor of Osteopathic Medicine; MD, Doctor of Medicine; ND, Naturopathic Doctor.
[a]Some respondents reported more than one (1) terminal clinical degree or board certification.

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

Types of Products	Respondents, n (N=31[a])
Compounded	0
FDA-approved	0
Over-the-counter	2
Dietary	4
Unsure	0
No Response	26

[a]Out of 60 respondents, 31 reported using, prescribing, or recommending multiple types of pregnenolone product.

Table 15. Compounded use of pregnenolone in practice

No survey respondents provided this information

Table 16. Indications for which pregnenolone is considered a standard therapy[a]

Indication	Standard Therapy		
	Compounded, n (N=0)	**Non-compounded, n (N=5)**	**No Response, n (N=26)**
Adrenal fatigue, dysregulation	0	2	0
Cognitive decline, brain fog	0	2	0
Depression	0	1	0
Fatigue	0	2	0
Hypothyroid	0	1	0
Infertility	0	1	0
Other[b]	0	1	0
Progesterone deficiency	0	1	0
No Response	0	0	26

[a]Some respondents reported more than one indication.
[b]"Varies depending on individual patient circumstances."

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 pregnenolone usage over the past 5 years

No survey respondents provided this information

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

No survey respondents provided this information

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

No survey respondents provided this information

CONCLUSION

Pregnenolone (UNII code: 73R90F7MQ8) was nominated for inclusion on the 503B Bulks List for an unspecified medical condition. The desired ROA and dosage form were not provided. Pregnenolone is not approved in any of the national medical registries searched. It is available as an oral and sublingual OTC supplement in the US.

From the literature review conducted, most of the studies were from the US. The most common indication for the use of pregnenolone in the US was schizophrenia, followed by bipolar depression and for mood, cognition, and/or memory. The most common indication from the non-US studies was schizophrenia. Compounded products were identified from both the US and non-US studies.

None of the three (3) experts interviewed said that they use, prescribe, or recommend pregnenolone. One (1) interviewee stated that they see no reason to keep hormonal substances as office stock. One (1) interviewee provided a patient-oriented summary regarding what to expect with taking pregnenolone supplements.

From the survey responses, 31 out of 60 respondents used pregnenolone, none of which reported using compounded products. Respondents used non-compounded pregnenolone for a variety of indications, including adrenal fatigue and dysregulation, cognitive decline and brain fog, depression, fatigue, hypothyroid, infertility, and progesterone deficiency.

APPENDICES

Appendix 1. References

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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 **pregnenolone**. 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: Pregnenolone

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

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

Display This Question:

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

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

Display This Question:

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

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

_____

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

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

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

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

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

_____

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

- Yes
- No

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

Display This Question:

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

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

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

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

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

_____

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

_____

End of Block: Pregnenolone

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