Summary Report

Progesterone

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

Progesterone (UNII code: 4G7DS2Q64Y) was nominated for inclusion on the 503B Bulks List by Fagron, the Specialty Sterile Pharmaceutical Society (SSPS), McGuff Compounding Pharmacy Services, Inc, Alliance for Natural Health (ANH), Integrative Medicine Consortium (IMC), the American Association of Naturopathic Physicians (AANP), US Compounding, and the Outsourcing Facilities Association (OFA).

While the exact medical condition for which the compounded product is generally unknown, progesterone is generally used to treat alopecia. Progesterone will be compounded as topical solution with the strength based on the prescriber's request; the therapeutic dose is 0.1%. Additionally, progesterone was nominated for use as a 1-4mg/kg injection to treat traumatic brain injury and a 100mg/mL oil solution for intramuscular injection for treatment of abnormal uterine bleeding unrelated to menstrual cycle, assisted reproductive technology, female infertility, contraception, endometrial hyperplasia, and secondary amenorrhea. Lastly, progesterone was nominated for use as a 0.1-25% topical cream for various indications including an alternative to oral treatment as a component of hormone replacement therapy and treating menopausal vasomotor symptoms, treating or preventing hormone-mediated allergies, bloating, breast tenderness, decreased sex drive, depression, fatigue, fibrocystic breasts, headaches, hypoglycemia, increased blood clotting, infertility, irritability, memory loss, miscarriages, osteoporosis, premenopausal bone loss, symptoms of premenstrual syndrome, thyroid dysfunction, unclear thinking, uterine cancer, uterine fibroids, water retention, weight gain, and treating vulval lichen sclerosis.

Progesterone was nominated for use in combination with additional active pharmaceutical ingredients (API), refer to Table 7 for the nominated combination formulations.

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

- The commercially available injectable form is an intramuscular oil product that comes in only one strength (50mg/mL). The availability of a compounded progesterone product allows for better weight-based and/or individualized dosing strategies.
- Currently there is no FDA-approved progesterone cream in the proposed strengths. Progesterone transdermal cream provides another route of administration for patients who cannot tolerate oral or injectable progesterone.
- Manufacturer backorder.
- There may be a need for a different strength or dosage form than what is commercially available.
- 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.
- The commercially available product is formulated in peanut oil that cannot be tolerated in patients with a peanut allergy. Additionally, the commercially available product may contain dyes or parabens that patients cannot tolerate.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of progesterone 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 progesterone; name variations of progesterone 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 progesterone. 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 May 29, 2019. The search included a combination of (progesterone[TIAB] OR progesteron[TIAB] OR progesterona[TIAB]) AND (intramuscular OR injection OR topical OR cream OR oil OR solution) 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.

Upon receipt of new nominations for substances for which a literature review had already been conducted, additional search strategies were developed in both PubMed and Embase for dosage forms, ROA and/or indications that were not captured in the original searches. The additional search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: progesterone; alopecia; and topical therapy (see Appendix 1 for complete search strategies). Results were limited to original research articles or conference abstracts in English language. All searches were conducted on July 19, 2019. Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence for screening.

Study selection

Literature reviews and/or meta-analyses, cost-effectiveness, and epidemiological studies were excluded. Progesterone is a component of an FDA-approved product, as a result, articles were excluded if progesterone was utilized as the FDA-approved product or in the same concentration and formulation as the FDA-approved product. Additional exclusion criteria included any dosage form/ROA that differed from the nominated dosage form/ROA. Articles were considered relevant based on the identification of a clinical use of progesterone or the implementation of progesterone 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.

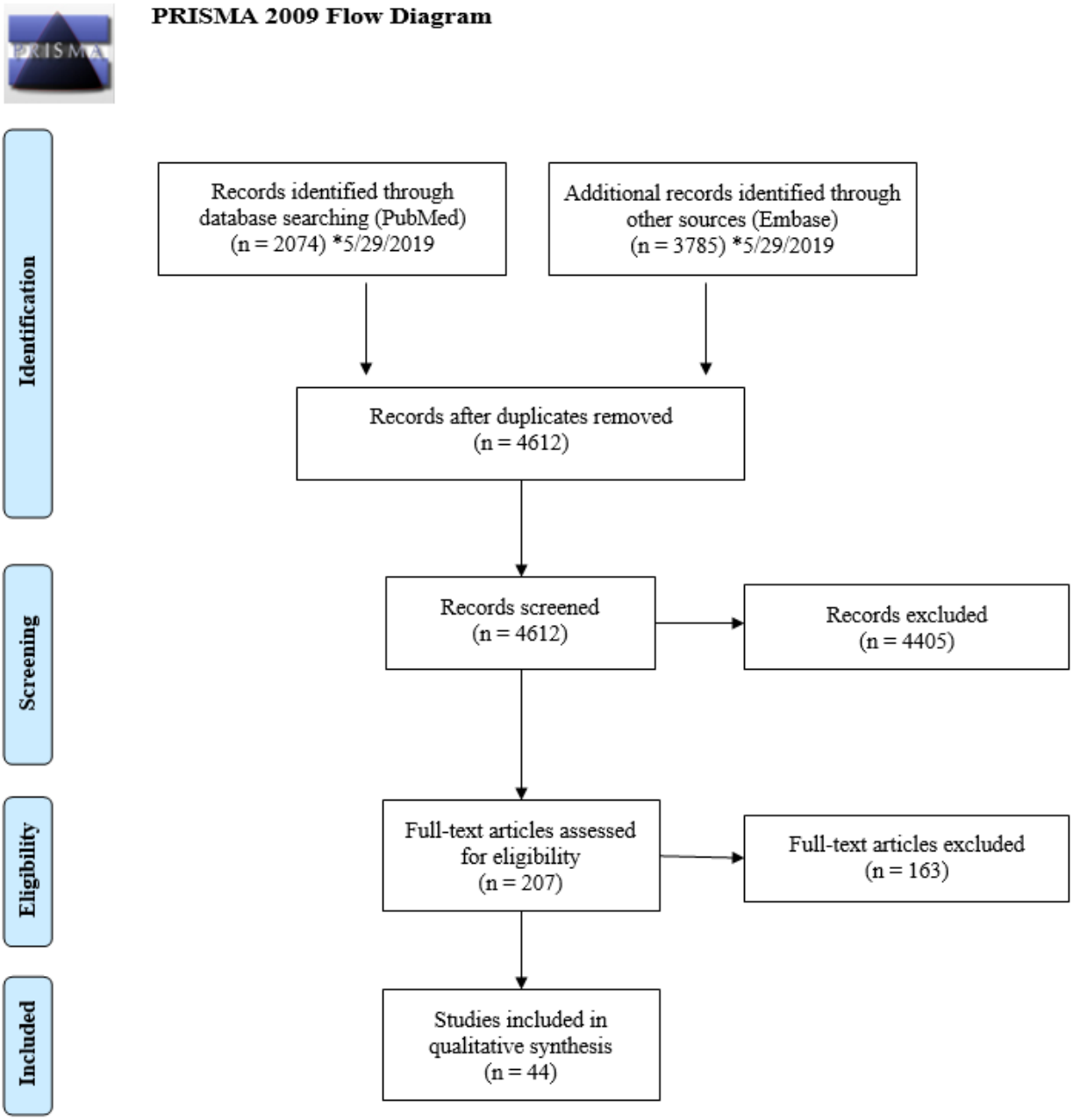
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for progesterone 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 progesterone compared to alternative therapies.

Results

Please refer to Figure 1 and Figure 2.

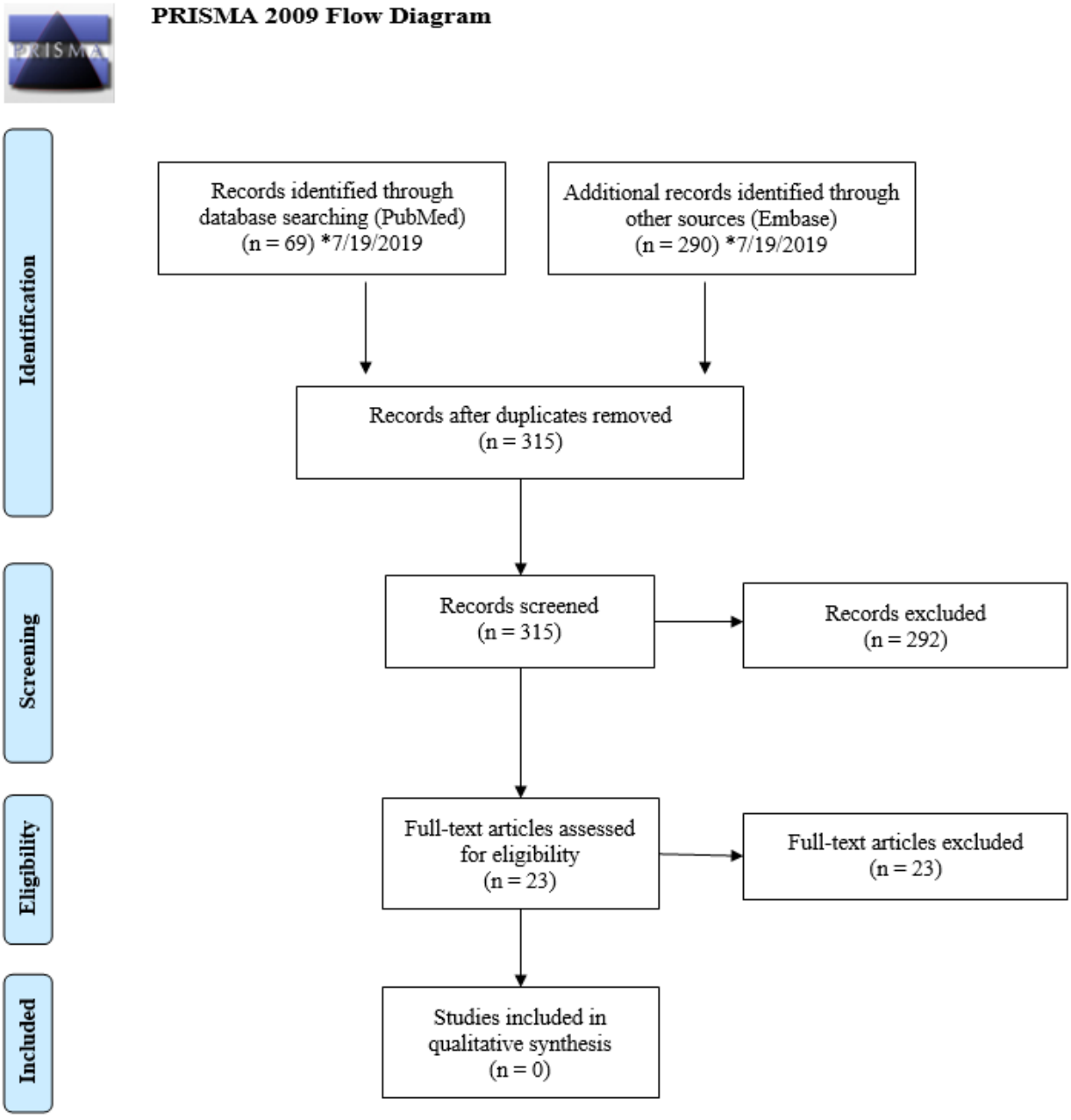
Figure 1. Summary of literature screening and selection (PRISMA 2009 Flow Diagram) - Initial Search



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.

Figure 2. Summary of literature screening and selection (PRISMA 2009 Flow Diagram) - Additional Search



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, eight (8) medical specialties that would potentially use progesterone were identified: critical care, dermatology, endocrinology, naturopathy, neurology, obstetrics and gynecology, primary care, and pulmonology. 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 four (4) accepted and zero (0) declined interviews. One (1) 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. 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 critical care, dermatology, endocrinology, naturopathy, neurology, obstetrics and gynecology, primary care, and pulmonology, identified from the nominations, 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 13 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)
Primary Care	American Academy of Environmental Medicine (AAEM)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Critical Care	Society of Critical Care Medicine (SCCM)	Declined, "this project is so unique that SCCM may not be the audience for the survey; I have impression that this project is so narrow that the link between improvement in ICU care is very remote and does not justify the study"
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
Pulmonology	American Thoracic Society (ATS)	Failed to respond

CURRENT AND HISTORIC USE

Summary of background information

- Progesterone is available as an FDA-approved product in the US and is available in Abu Dhabi, Belgium, Canada, and the EU.
- Progesterone is not available as an OTC product in the US. There is a current United States Pharmacopeia (USP) monograph.

Table 3. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	ROA	Status	Approval Date[b]
Progesterone	50mg/mL	Injectable	Injection	Prescription	Prior to 1/1/1982

Abbreviations: 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]
Progesterone	25, 50, 100mg/mL	Injection, solution	Intramuscular, subcutaneous	Abu Dhabi	–	–
				Belgium	Prescription	7/24/2013
				Canada	Prescription	4/13/2016
				EU	–	6/10/2011

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 ROA 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

- Total number of studies included: 44 studies (12 descriptive, 25 experimental, and 7 observational).
- Most of the studies were from the US (16).
- The most common indication for the use of progesterone in the US and non-US studies was luteal phase support.
- Compounded products were identified from both US (cream and gel products) and non-US (2% ointment product) studies.

Table 5. Types of studies

Types of Articles	**Number of Studies**
Descriptive[1-12]	12
Experimental[13-37]	25
Observational[38-44]	7

Table 6. Number of studies by country

Country	Number of Studies
Argentina[11]	1
Austria[20]	1
Canada[29]	1
Chile[36]	1
China[27,35,37,38]	4
Denmark[28]	1
Egypt[1]	1
Germany[24]	1
Iran[18,22,31]	3
Israel[17]	1
Italy[13-15,40]	4
Mexico[9]	1
South Korea[5,23]	2
The Netherlands[42]	1
Turkey[21,39]	2
UK[3,7,30]	3
US[2,4,6,8,10,12,16,19,25,26,32-34,41,43,44]	16
	Total US: 16 Total non-US Countries: 28

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Progesterone 0.1% / Minoxidil 7%	0
	Progesterone 0.1% / Fluocinolone acetonide 0.01% / Minoxidil 7%	0
	Progesterone 0.1% / Minoxidil 5-7% / Tretinoin 0.025%	0
Others found in literature	Progesterone 100 mg / estradiol 5 mg – Intramuscular suspension[9]	1
	Progesterone 80 mg / Human chorionic gonadotrophin 2000 IU – Intramuscular[37]	1
	Progesterone / Tocopherol - cream[26]	1
	Progesterone / Dehydroepiandrosterone / Pregnenolone – cream[10]	1
	Progesterone 3% / Estradiol 20% / Estriol 80% – cream[29]	1
	Progesterone 40 mg / Estradiol 1 mg / Testosterone 2 mg – gel[6]	1

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Luteal phase support[2,19,41,43,44]	100 mg/day or every other day	100mg	Oil	Intramuscular	–
Hormone replacement therapy[6,8,32]	100mg/day	100mg	–	Intramuscular	–
	1.25mL/day	–	Cream	Topical	–
	–	40mg	Gel		
Depression[10]	50 mg/mL/day	–	Cream	Topical	–
Early pregnancy[34]	100mg	100mg	Oil	Intramuscular	Once
Endometrial development/pregnancy support[33]	100mg/day	100mg	–	Intramuscular	–
In vitro fertilization[16]	50-100mg/day	–	–	Intramuscular	–
Lichen sclerosus[12]	10mg/day	2%	Cream	Topical	6 months
Pregnancy rate[25]	100mg	100mg	Oil	Intramuscular	Once
Pulmonary lymphangiomyomatosis[4]	800mg/1-2 times a month	800mg	Injection	Intramuscular	–
Vasomotor symptoms/prevention of menopausal bone loss[26]	20mg/day	–	Cream	Topical	12 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
Luteal phase support[17,21,24,27,37-40]	60-250mg/day or every other day	60-250mg	Injection, oil	Intramuscular	5 times-17 days
					Until 10th gestational week
Contraception[9]	100mg/day	100mg	Suspension	Intramuscular	3 days
Cyclic breast pain[30]	5g/day	1%	Cream	Topical	–
Desmoid tumors[11]	100mg/day-4 times/week	100mg	–	Intramuscular	3 months
Effect on function/texture of skin in peri-and postmenopausal women[20]	1g/day	2%	Ointment	Topical	16 weeks
Hormone replacement therapy[36]	100mg/day	100mg	Oil	Intramuscular	–
In vitro fertilization[5,31]	100mg/day	100mg	Oil	Intramuscular	2-20 weeks
					Until confirmed pregnancy
Postnatal depression[7]	100mg/day	100mg	–	Intramuscular	7 days
Pregnancy outcome[22,42]	250mg/week-100mg/day	100-250mg	Oil	Intramuscular	Until 12th gestational week
					18 weeks
Prevent bone loss[28] in menopause[29]	–	3%	Cream	–	At least 12 months
	25.7mg/day	–		Transdermal	2 years
Prevent preterm labor[23]	250mg/week	250mg	–	Intramuscular	–
Prevention of ovarian hyperstimulation syndrome[15]	200mg/day	–	–	Intramuscular	14 days
Prophylaxis for midtrimester amniocentesis[14]	200mg/day	200mg	–	Intramuscular	3 days

Premenstrual exacerbations of asthma[3]	100mg/day	100mg	–	Intramuscular	–
Traumatic brain injury[1,35]	1mg/kg	–	Injection	Intramuscular	5 days
Ventilatory performance during partial support mechanical ventilation[18]	1mg/kg	–	–	Intramuscular	Once
Vulval lichen sclerosus[13]	–	2%	–	Topical	3 months

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

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Hormone replacement therapy[6]	2012	• Compounded progesterone 40 mg, estradiol 1 mg, and testosterone 2 mg	Gel	40 mg
Lichen sclerosus[12]	1990	• Progesterone powder micronized in a water-miscible vehicle containing petrolatum, mineral oil, cetyl alcohol, steryl alcohol, sodium lauryl sulfate, cholesterol and parabens	Cream	2%
Vasomotor symptoms/ prevention of menopausal bone loss[26]	1999	• Compounded with mixed tocopherol cream to contain 20 mg of progesterone per quarter teaspoon	Cream	–

Abbreviation: "–", not mentioned.

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Effect on function/texture of skin in peri- and postmenopausal women[20]	• Progesterone 2% in a neutral standard cream vehicle (Ultrasicc®, an oil-in-water cream base, or Ultrabas®, a water-in-oil cream base)	Ointment	2%

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

Four (4) interviews were conducted.

Table 12. Overview of interviewees

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Progesterone	Interview Summary Response
END_01	MD	Internal Medicine Endocrinology and Metabolism	Academic medical institution	No	• Did not report using this substance.
OBG_01	MD	Obstetrics and Gynecology	Academic medical institution	Yes	• Concerned about compounded products and sees decreased need for them. • An exception for using compounded progesterone is for patients who have peanut allergies or need a lower dose. • Absorption concerns with progesterone.
END_03	MD	Endocrinology and Metabolism	Academic medical institution	Yes	• Mostly uses commercially available products. • Uses compounded products when flexibility with dosing is needed or patient preference.
DER_07	MD	Dermatology/ Immunology	Independent consultant	No	• Would not stock in office due to lack of supportive literature data for alopecia

Abbreviations: MD, Doctor of Medicine.

Compounding progesterone:

- Difficult to compound
    - One interviewee stated, "one of the biggest concerns that we have is that we think that oral and topical progesterone [and] oral and topical progesterone with estradiol…are difficult to compound."
- Decreased need due to more available FDA products

    - One interviewee stated, "… and then for Progesterone we have oral micronized Progesterone, we have Progesterone available in FDA forms in vaginal insert, and as a cream that are approved for reproductive endocrine reasons. And then we have a new oral Estradiol Progesterone combination that just came out."
- The interviewee stated compounded progesterone is used when there are "people who need micronized progesterone orally that have peanut allergies, or need a lower dose. The lowest dose of the progesterone available is 100mg, and sometimes we need a 50mg dose, although we're concerned about whether we're providing adequate uterine protection with that. And then the third is the preservative-free."
- Absorption concerns
    - "Big concern about Progesterone is how poorly absorbed it is. It's been rapidly inactivated in the liver. The micronization process does allow you to get plasma in tissue levels when it's given orally, but you'll also have to have appropriate formulation in dosing to get an effect on the endometrium"
    - With transdermal, lower doses, or poorly formulated progesterone product, there may be inadequate endometrial protection. "And there are now published case results that have shown this. There was an Australian case series using custom compounded therapy that had three patients who got endometrial cancer, and that was using troches that had different types of Estrogen and Progesterone, and over two to four years. And one of the things that happens with all of the Progesterone FDA-approved Progesterone products is that the FDA requires at least 12 months of endometrial safety using histological evaluation of the endometrium by biopsy. And when you're using compounded non-regulated and approved dose of the Progesterone you don't have that same safety data."

Supplemental Information

- One 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 that are demonstrably difficult to compound.[45-55]
    - The nominated hormones for inclusion on the demonstrably difficult to compound list includes bio-identical hormones in the pellet form, estradiol in the oral and topical dosage forms and estradiol with progesterone also in the oral and topical dosage forms.[49,55]
    - Progesterone has low aqueous solubility.[55]
    - There is concern progesterone will not be uniformly distributed within the mixture,[55] and have different potencies.[50]
    - There are FDA-approved bioidentical hormone therapies available including micronized oral or vaginal progesterone, and an oral estradiol/progesterone product in late stage development.[50,51,54]

Summary of survey results

Table 13. Characteristics of survey respondents [61 people responded to the survey[a]]

Board Certification	DO	MD	ND	No Response
Dermatology	0	3	0	0
Emergency Medicine	1	0	0	0
Endocrinology, Diabetes and Metabolism	0	0	1	0
Family Medicine	0	1	0	0
Fellow of the American Board of Naturopathic Oncology	0	0	1	0
General Surgery	0	1	0	0
Integrative Medicine	0	1	0	0
Naturopathic Doctor	0	0	6	0
Naturopathic Physician	0	0	9	0
Pediatric Dermatology	0	1	0	0
No Board Certification	0	1	4	0
No Response	0	0	0	40

Abbreviations: DO, Doctor of Osteopathic Medicine; 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=56[a])
Compounded	12[b]
FDA-approved	8
OTC	4
Dietary	3
Unsure	1
No response	38

[a]Out of 61 respondents, 56 reported using, prescribing, or recommending multiple types of progesterone product.
[b]Eight (8) respondents used in combination (see Figure 3 below for specifics).

Figure 3. Compounded combinations reported in the survey

Active ingredients in combination products:

- Progesterone, estradiol
- Progesterone, DHEA, estriol
- Progesterone, estradiol, estriol
- Progesterone, estradiol, testosterone
- Progesterone, estradiol, estriol, testosterone
- "4 balance, 4 balance+"

Table 15. Compounded use of progesterone in practice[a]

Indication[b]	Strength	Dosing Frequency	Dosage Form	ROA	Duration of Treatment	Patient Population
Menopause[c]	25-300mg	Daily-twice daily	Capsule, SR capsule, tablet	Oral	As needed Varies Long-term 6 months-20 years	Females 45+ Aging females
	25-200mg		Cream	Transdermal		
	50-100mg	Daily	Cream	Vaginal		
	100-300mg	Daily	Troche	–		
	10-300mg	Daily	Capsules, suppository, tablets, troches	Oral, sublingual, vaginal		
	25-225 mg	Daily	Gel	Oral, transdermal, vaginal		
Menstrual disorders[d]	25-200mg	Daily	Capsule, tablet	Oral	As needed Long-term Until resolution 6 months-5 years Cyclic until menopause	Female 18+ Cyclic females
	100-300mg	Daily	Troche	Sublingual		
	20-50mg	Daily	Cream, gel	Topical		
	30 mg	Twice daily	Cream	Transdermal		
	25-200mg	1-2 weeks/month	Capsule, cream	Oral, transdermal		
	10-300mg	Daily	Capsules, suppository, tablets, troches	Oral, sublingual, vaginal		
	25-225 mg	Daily	Gel	Oral, transdermal, vaginal		
Progesterone deficiency	5-20mg	Daily	Capsule, tablet	Oral	As needed	Males 40+

	25-225 mg	Daily	Gel	Oral, transdermal, vaginal	Long-term	Male, female
	10-300mg	Daily	Capsules, suppository, tablets, troches	Oral, sublingual, vaginal		
Infertility	10-100mg	Daily	Cream, tincture	Oral, vaginal	6 months-2 years	Female 20-40
Pre-mature ovarian insufficiency	100-200mg	Daily-twice daily	Capsules, cream	Oral, transdermal	Long-term	Females
Transgenderism			Capsules, cream	Oral, transdermal	Short-term or ongoing	–
Dysglycemia, dysautonomia, vasovagal disorders, peripheral edema, degenerative disorders, and irritable bowel syndrome	30 mg	Twice daily	Cream	Transdermal	Long-term	Adults
"Hormone balance, cancer prevention!"	–	–	–	–	–	–

Abbreviations: "–", not mentioned; ROA, route of administration.
[a]Eleven (11) respondents.
[b]Quotations are direct words from respondents.
[c]Includes progesterone deficiency in menopausal women; perimenopause; menopausal symptoms and conditions such as hot flashes, osteoporosis, insomnia, night sweats.
[d]Includes premenopausal women, menorrhagia, menstrual migraines, premenstrual dysphoric disorder (PMDD), premenstrual syndrome (PMS) and PMS related symptoms such as anxiety, hot flashes, breast tenderness.

Table 16. Indications for which progesterone is considered a standard therapy

Indication	Standard Therapy			
	Compounded, n (N=12)	Non-compounded, n (N=5)	Unsure, n (N=1)	No Response, n (N=38)
Menopause[b]	5	1	0	0
Menstrual disorders[c]	4	3	0	0
"Infertility, pregnancy when deficient"	1	2	0	0
Premature ovarian insufficiency	1	0	0	0
"Many hormonal imbalances"	1	0	0	0
Progesterone deficiency	1	0	0	0
Joint pain	0	1	0	0
Bioidentical hormone replacement therapy	1	0	0	0
Other[d,e]	1[d]	1[e]	0	0
No response	1	0	1	38

[a]Some respondents reported more than one indication.
[b]Includes progesterone deficiency in menopausal women; perimenopause; menopausal symptoms and conditions such as hot flashes, osteoporosis, insomnia, night sweats.
[c]Includes premenopausal women, menorrhagia, irregular menses, insomnia, menstrual migraines, premenstrual dysphoric disorder (PMDD), premenstrual syndrome (PMS) and PMS related symptoms such as anxiety, hot flashes, breast tenderness
[d]One (1) respondent replied, "many conditions!!"
[e]One (1) respondent replied, "there is no effective standard therapy"

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

Theme	Reasons
Cost	• "It is less expensive and very reliable."
Flexibility	• "Better flexibility of dosing and more efficacious products" • "Only one dose available commercially" • "I use an oral dosage form that comes in drops with a precise dose that I use to go up and down to imitate and stimulate a natural menstrual cycle" • "Control of dosing - use low doses someones - sometimes mix with vaginal estriol" • "Non availability of different dosages, cost, dyes and additives in approved drugs" • "I use both, but the compounded is more effective and flexible, fewer SE's" • "Prometrium has peanut oil, only available in 2 strengths, and most importantly, is IR and not SR which gives better levels not only through the night (for sleep) but the rest of the following day (for cardiac, brain, and bone benefits)"
Sensitivity/allergies	• "I use both. FDA-approved when using estradiol patches; Compounded if patient cannot tolerate the limited dosing options or if allergic to peanut (carrier oil)." • "allergies, better patient outcomes, more dosing options"
Other	• "Better !!"

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

	Respondents, n (N=12)
No–use has remained consistent	6
Yes–I use it LESS often now	0
Yes–I use it MORE often now • "Seeing more infertility patients" • "Needed" • "Patient awareness about their conditions and treatment options has increased	5
No response	1

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

	Respondents, n (N=12)
No	8
Yes	3
No response	1

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

	Respondents, n (N=3)
In what practice location(s) do you stock non-patient-specific compounded progesterone?	
Physician office	3
Outpatient clinic	0
Emergency room	0
Operating room	0
Inpatient ward	0
Other	0
How do you obtain your stock of non-patient-specific compounded progesterone?	
Purchase from a compounding pharmacy	0
Purchase from an outsourcing facility	3
Compound the product yourself	0
Other	0
Why do you keep a stock of non-patient-specific compounded progesterone?	
Convenience	3
Emergencies	0
Other	0

CONCLUSION

Progesterone (UNII code: 4G7DS2Q64Y) was nominated for inclusion on the 503B Bulks List for various indications via a 1-4 mg/kg injection, 100mg/mL intramuscular oil solution, a topical 0.1-25% cream, and a topical 0.1% solution. Progesterone is available as an FDA-approved product and has a current USP monograph. Progesterone is available in Abu Dhabi, Belgium, Canada, and the EU.

From the literature review conducted, the most common indication for the use of progesterone in the US and non-US studies was luteal phase support. Compounded products were identified from both US (cream and gel products) and non-US (2% ointment product) studies.

From the interviews, two (2) interviewees did not use progesterone while the other two (2) interviewees reported use of progesterone. One (1) interviewee was concerned about the difficulty of compounding progesterone, and the absorption of compounded progesterone. This interviewee reported exceptions for using compounded progesterone for patients who have peanut allergies or need a lower dose. One (1) interviewee who reported use of progesterone predominately uses commercially available products and will only use compounded products when flexibility with dosing is needed or patient preference. One (1) of the interviewees who does not use progesterone stated they would not stock in office due to a lack of supportive literature data for alopecia.

From the survey responses, 56 out of 61 respondents used progesterone. The most common indication respondents used compounded progesterone for was menopause and/or menstrual disorders. Cost, flexibility, and sensitivity/allergies were some of the reasons for using compounded progesterone over an FDA-approved product. Three (3) respondents reported stocking compounded progesterone in the physician office and obtaining progesterone from an outsourcing facility for convenience.

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APPENDICES

Appendix 1. Search strategies for new nominations

PubMed search strategy

- Platform: PubMed
- Years searched: 1946 to Present
- Date searched: July 19, 2019
- Number of results: 69

1	Search ("progesterone"[MeSH] OR progesteron*[tiab])	109243
2	Search ("alopecia"[MeSH] OR alopeci*[tiab] OR "hair loss"[tiab] OR effluvi*[tiab] OR "hair regrowth"[tiab] OR bald*[tiab])	26019
3	Search ("administration, topical"[MeSH] OR "drug combinations"[MeSH] OR "drug compounding"[MeSH] OR "therapeutic use"[subheading] OR "drug therapy"[subheading] OR "administration and dosage"[subheading] OR topical[tiab] OR cream[tiab] OR ointment[tiab] OR treat*[tiab] OR therap*[tiab] OR compound*[tiab])	9364029
4	Search ("animals"[MeSH] NOT "humans"[MeSH])	4599558
5	Search (#1 AND #2 AND #3)	112
6	Search (#5 NOT #4)	95

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date searched: July 19, 2019
- Limits: English language
- Number of results: 290

1	'progesterone'/de	100368
2	'progesteron*':ti,ab,tn	105337
3	#1 OR #2	140419
4	'alopecia'/exp	50681
5	'alopeci*':ti,ab	24500
6	'hair loss':ti,ab	7679
7	'effluvi*':ti,ab	589
8	'hair regrowth':ti,ab	922
9	'bald*':ti,ab	4983
10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	61397

11	'topical drug administration'/de OR 'cutaneous drug administration'/de	79379
12	'drug combination'/de	120101
13	'drug formulation'/de	115479
14	'drug therapy':lnk	3730827
15	'drug combination':lnk	804980
16	'drug comparison':lnk	582238
17	'drug administration':lnk	1667508
18	'topical':ti,ab	128826
19	'cream':ti,ab	23655
20	'ointment':ti,ab	17344
21	treat*':ti,ab	7431367
22	'therap*':ti,ab	3880054
23	'compound*':ti,ab	975153
24	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	8220367
25	[animals]/lim NOT [humans]/lim	5866332
26	#3 AND #10 AND #24	360
27	#26 NOT #25	339
28	#27 AND [english]/lim	290

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 **progesterone**. 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: Progesterone

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

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

---

Display This Question:

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

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

Display This Question:

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

Q4. In which combination(s) do you use compounded **progesterone**? Please check all that apply.

- ☐ Progesterone 0.1% / Fluocinolone acetonide 0.01% / Minoxidil 7%
- ☐ Progesterone 0.1% / Minoxidil 7%
- ☐ Progesterone 0.1% / Minoxidil 5-7% / Tretinoin 0.025%
- ☐ Other (please describe) _____

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

_____

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

_____

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

_____

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

- o Yes
- o No

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

Display This Question:

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

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

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

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

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

_____

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

_____

End of Block: Progesterone

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