Summary Report

Testosterone

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Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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REVIEW OF NOMINATIONS

Testosterone (UNII code: 3XMK78S470) was nominated for inclusion on the 503B Bulks List by Fagron, Specialty Sterile Pharmaceutical Society (SSPS), McGuff Compounding Pharmacy Services, Inc. (McGuff CPS), the American Association of Naturopathic Physicians (AANP), Alliance for Natural Health (ANH-USA), Integrative Medicine Consortium (IMC), David Smith, and Rebecca Mitchell.

Testosterone was nominated for use in combination with anastrozole and other unspecified substances, refer to Table 7 for the nominated combination formulations.

Testosterone was nominated for use in hormone replacement therapy, often in treatment of male hypogonadism via sublingual formulations with strengths based on the patient and 12.5-200mg subcutaneous implantable pellets. Testosterone will also be compounded as a 0.01-30% topical cream as a single agent and in combination with additional active pharmaceutical ingredients (API). Additionally, testosterone will be compounded as a subdermal pellet in combination with anastrozole to treat testosterone deficiency in females with a history of breast cancer.

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

- Patients may have an allergy to an inactive ingredient found in the commercially available product.
- There are no sublingual formulations commercially available.
- There are no commercially available products that combine testosterone and anastrozole into a pellet; there is no FDA-approved anastrozole pellet.
- Patient may require a lower dose than what is commercially available, or otherwise individualized dosing not possible with the commercially available products.
- Manufacturer backorder.
- It is relatively unsafe to expose the direct compounding area to hundreds of vials or ampules and hundreds of aseptic manipulations during the compounding of a typical batch size for an outsourcing facility; compounding from bulk is safer and more efficient.
- Commercially available finished products have an inherent variance in potency creating an uncertain final concentration for the new product.
- Use of state-of-the-art equipment, like the SKAN isolator technology, requires the use of bulk starting materials.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of testosterone 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 testosterone; name variations of testosterone 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 testosterone. 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 April 2, 2019. The search included a combination of (testosterone[TIAB] OR testosteron[TIAB] OR testosteroni[TIAB]) AND (capsule OR cream OR pellet OR sublingual OR subdermal OR anastrozole[TIAB] OR drop OR transdermal OR subdermal OR buccal OR topical OR intranasal OR nasal OR intramuscular OR gel OR solution) AND (clinic*[TIAB] OR treat*[TIAB] OR therap*[TIAB] OR hypogonadism[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 RefWorks®, merged, and sorted for removal of duplicate citations. Covidence® was used for screening purposes.

Study selection

Articles were not excluded on the basis of study design. Testosterone is a component of an FDA-approved product, as a result, articles were excluded if testosterone was utilized as the FDA-approved product or in the same concentration and formulation as the FDA-approved product. Additional exclusion criteria include 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 testosterone or the implementation of testosterone 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.

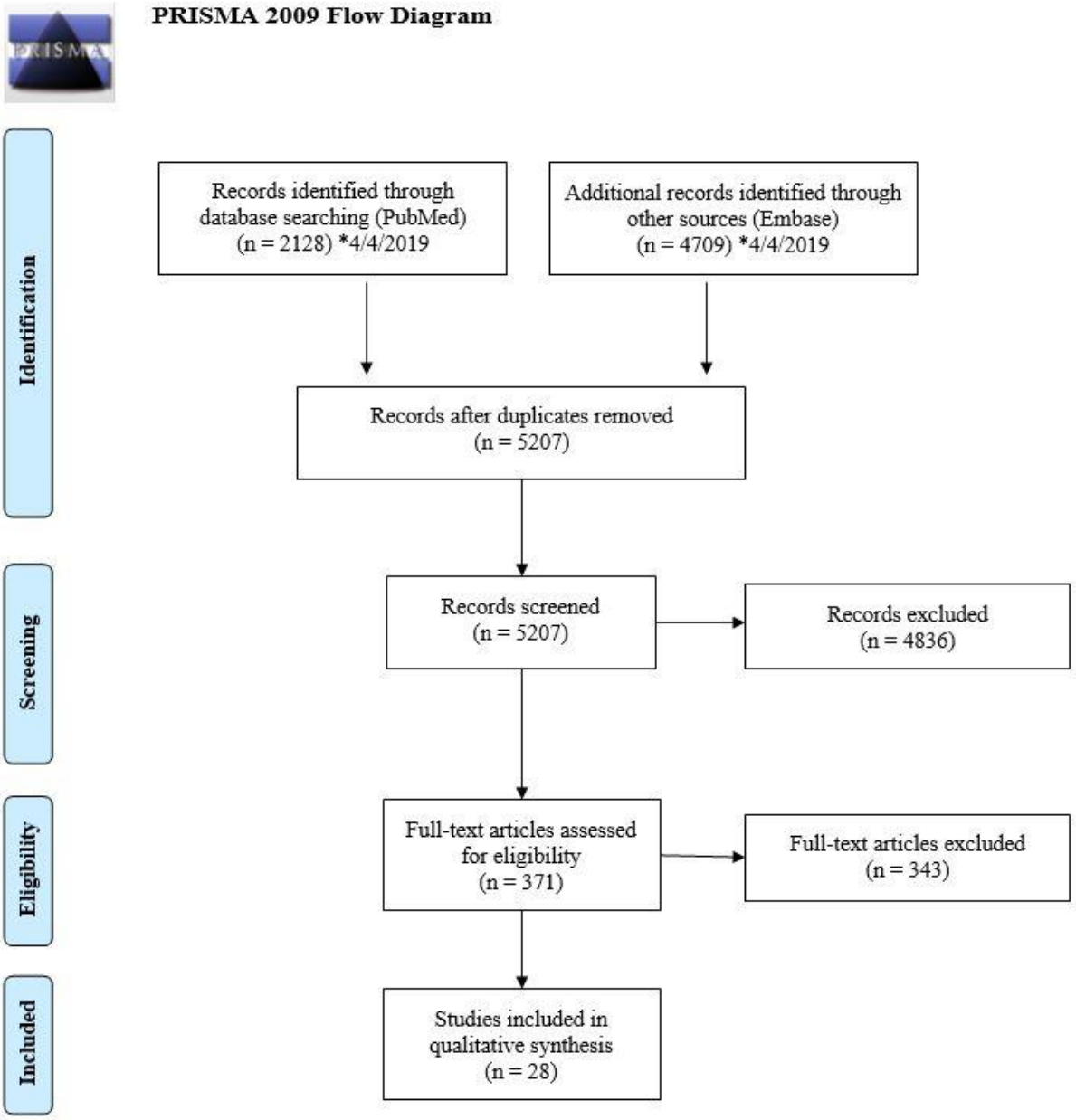
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for testosterone 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 testosterone 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, ten (10) medical specialties that would potentially use testosterone were identified: cardiology, endocrinology, hematology, naturopathy, neurology, obstetrics and gynecology, oncology, ophthalmology, primary care, and urology. 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 and zero (0) declined interviews. Two (2) experts, one specializing in neurology and one (1) in oncology, failed to respond to the interview request. Two (2) 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 cardiology, endocrinology, hematology, naturopathy, neurology, obstetrics and gynecology, oncology, ophthalmology, primary care, and urology, 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 15 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)
Opthalmology	American Academy of Ophthalmology (AAO)
	American Society of Cataract and Refractive Surgery (ASCRS)
	American Society of Retina Specialist (ASRS)
Primary Care	American Academy of Environmental Medicine (AAEM)

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."
Hematology	American Society of Hematology (ASM)	Failed to respond
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
Oncology	American Society of Clinical Oncology (ASCO)	Declined, "they are unable to share survey with members"
Primary Care	American Academy of Family Physicians (AAFP)	Failed to respond
	American College of Physicians (ACP)	Failed to respond
Urology	American Urology Association (AUA)	Declined, "our physicians are inundated with surveys and I'm afraid you won't be able to get the information you need"

CURRENT AND HISTORIC USE

Summary of background information

- Testosterone is available as an FDA-approved product. Testosterone is also available as a topical transdermal and nasal gels, extended-release films, and solutions.
- Testosterone is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for testosterone.
- Testosterone is available in Australia. Testosterone is also available as a topical transdermal and nasal gels, extended-release films, and solutions in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, New Zealand, Saudi Arabia, and the. The EU previously had testosterone available as a transdermal patch, but the marketing authorization was withdrawn at the request of the marketing authorization holder, because the benefits did not outweigh the risk of use.

Table 3. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	ROA	Status	Approval Date
Testosterone	75mg	Pellet	Implantation	Prescription	Approved prior to 01/01/1982

Abbreviations: "–", not mentioned; ROA, route of administration.
[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

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
Testosterone	50mg/mL	Cream	Topical	Australia	Prescription-only medicine	07/11/2014

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.

Summary of literature review

- Total number of studies included: 28 (10 descriptive, 16 experimental, and 2 observational).
- Most of the studies were from the US (8), followed by the UK (6).
- Two (2) studies reported testosterone combined with anastrozole, as the nominated implantable pellet.
- The most common indication for the use of testosterone in the US was decreased libido in female cancer patients. The most common indications from the non-US studies were menopausal and climacteric symptoms.
- Compounded products were identified from the both US and non-US studies in the nominated dosage forms (pellets, creams), but only two (2) were for a nominated indication (breast cancer).

Table 5. Types of studies

Types of Articles	Number of Studies
Descriptive[1-10]	10
Experimental[11-26]	16
Observational[27,28]	2

Table 6. Number of studies by country

Country	Number of Studies
Australia[9,10,16,20]	4
Brazil[27]	1
Canada[23]	1
Egypt[22]	1
India[24,26]	2
The Netherlands[25]	1
UK[7,8,13,14,17,28]	6
US[1,3-6,11,12,15]	8
Multiple Countries • Australia, Germany[21] • US, Greece[2,18,19]	4
	Total US: 11 Total non-US Countries: 20

[a]Studies 2, 18, 19 counted in both US and non-US total.

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Testosterone / Not mentioned – Topical cream[a]	0
	Testosterone / Anastrazole – Implant[2,19]	2
Others found in literature	Testosterone 0.8% / Isosorbide dinitrate 0.5% / Co-dergocrine mesylate 0.06% – Cream[22]	1
	Testosterone / Estradiol • Testosterone 100mg / Estradiol 50-75mg – Implant[13,14,17,28] • Testosterone 80mg / Estradiol 200mg – Implant[27]	5

[a]Nomination identified the need for combination products. However, no information was provided regarding specific combination desired.

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Decreased libido in female cancer paitents[11,15]	0.3-10.4mg/day	0.06-2%	Cream	Transdermal, Vaginal	4 weeks
Androgen receptor (AR)-positive breast cancer[2]	180mg	60mg/pellet	Pellet	Intramammary/Peritumorally	13 weeks
Advanced breast carcinomatosis[6]	750mg	75mg/pellet	Pellet	Subcutaneous	–
Atrial fibrillation, stroke prevention[1]	40mg/day	1%	Liquid	Sublingual/Buccal	–
Hypogonadism in spinal cord injury[3]	1800-2800mg	–	Pellet	Subcutaneous	–
Male contraceptive[12]	40-60mg	20mg/implant	Implant	Subdermal	3 months
Menopausal symptoms in breast cancer survivors[19]	Weight-based	–	Implant	Subcutaneous	3 months – 8 years

Migraine[18]	100-160mg	–	Pellet	Subcutaneous	3 months
Penile growth[4,5]	Apply 1-2x/day	5-10%	Cream	Topical	3-4 weeks

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

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Menopausal/climacteric symptoms[13,14,17,20,21,23,26]	100mg	100mg/pellet	Pellet	Subcutaneous	6 months – 4 years
	2mg/week-10mg/day	1-3%	Cream	Topical, Transdermal	8-12 weeks
Osteoporosis/bone loss prevention[27,28]	80-100mg	–	Implant, Pellet	Percutaneous	1-24 years
Acute intermittent porphyria[8]	100mg	100mg/implant	Implant	Subcutaneous	–
Androgen receptor (AR)-positive breast cancer[2]	180mg	60mg/pellet	Pellet	Intramammary/Peritumorally	13 weeks
Behçet's disease[9]	50-100mg	50-100mg/implant	Implant	Subcutaneous	–
Erectile dysfunction[22]	Apply 1x/day	0.8%	Cream	Topical	1 month
Hypoactive sexual desire disorder[25]	0.5mg	–	Solution	Sublingual	4 weeks
Hypogonadism[10]	8-10mg/kg	–	Pellet	Subcutaneous	18 months
Menopausal symptoms in breast cancer survivors[19]	Weight-based	–	Implant	Subcutaneous	3 months – 8 years
Microphallic hypospadias[24]	2mg/kg/week	–	Cream	Topical	3 weeks
Migraine[18]	100-160mg	–	Pellet	Subcutaneous	3 months
Premenstrual orogenital ulcers[7]	100mg	100mg/implant	Implant	Subcutaneous	–

Vulvovaginal atrophy associated with aromatase inhibitor use[16]	0.9mg/week-0.3mg/day	0.03%	Cream	Intravaginal	26 weeks

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

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
AR-positive breast cancer[2]	2014	• "Compounded"	Pellet	60mg/pellet
Decreased libido in female cancer patients[15]	2014	• "Compounded"	Cream	0.06%

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
AR-positive breast cancer[2]	• "Compounded"	Pellet	60mg/pellet
Erectile dysfunction[22]	• Testosterone with co-dergocrine mesylate and isosorbide dinitrate	Cream	0.8%
Microphallic hypospadias[24]	• Testosterone in a neutral base	Cream	–
Menopausal/climacteric symptoms[26]	• Testosterone in petroleum	Cream	2%

Abbreviation: "–", not mentioned.

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 Testosterone	Interview Summary Response
END_01	MD	Endocrinology and Metabolism Internal Medicine	Academic medical institution	Yes	• Primarily uses FDA-approved products. • No need to administer in the office.
END_03	MD	Endocrinology, Diabetes, and Metabolism	Academic medical institution	Yes	• Primarily uses FDA-approved products. • No need to administer in the office.
OBG_01	MD	Obstetrics and Gynecology	Academic medical institution	Yes	• Primarily uses FDA-approved products. • Does not use testosterone frequently.

Abbreviation: MD, Doctor of Medicine.

Use of testosterone as a compounded product

- Two (2) interviewees reported use of the FDA-approved products the majority of the time.
    - One (1) interviewee said that there are a few patients who want their testosterone prescriptions to be compounded for reasons of skin sensitivity and the lack of products approved for female patients.
        - "The problem is they don't have a woman-specific product and so sometimes you'll end up compounding so they can just do much lower doses, you know, lower concentrations so…getting a…instead of trying to do like a quarter of a package or something of a commercially available gel, they'll do something that they can, that's a little easier to dose with."
    - One (1) interviewee stated that they use compounded products "for women who have low libido that hasn't responded to treatment, hot flashes, and vaginal estrogen, and the lifestyle options that we talk about," for patients with sensitivities or who need a lower dose, and if a preservative-free dosage form is needed.
        - Also stated they do not use testosterones frequently in their practice setting because they "don't have an FDA-approved physiological dose available to me. And so because of that I am always very concerned with compounded products - if I'm going to over dose or under dose, and so we work hard for the loss of libido in other ways to try and improve that."

Testosterone dosage forms

- One (1) interviewee stated they often use a gel for testosterone.
- Two (2) interviewees discussed the use of testosterone as a pellet.
    - One (1) interviewee reported not using the pellets in practice but commented that urology does. They mentioned reasons to use a pellet would be patient preference and concern about transference of gel to children or spouse.
    - One (1) interviewee discussed pellets containing estradiol and testosterone but mentioned "there's a lot of concern that we are giving post-menopausal women very high levels of hormones without any data showing safety or efficacy or need for those high doses."
        - "We just completed an androgen workshop run by the [redacted], and we're working on our guidelines right now, and what we found was that if women who have low libido received physiological dosing of testosterone it may improve libido, but it doesn't have any prevention of breast cancer. It doesn't have prevention of heart disease. It doesn't improve depression, quality of life, and the concern amongst this entire group of people from different major medical organizations was that supraphysiological levels of testosterone, which are in these pellets, may actually increase the risk of breast cancer and heart disease"
        - "And when these women are in clinic and I draw levels, they may have a testosterone level of 300, versus a normal physiological level might be up to 40. And the estradiol levels might be in the 300 range, and I've seen testosterone as high as 700 from these pellets"
        - The interviewee mentioned the side effects associated with using high dose testosterone in female patients, which include "scalp hair loss, balding, facial hair, increased body hair, lowering of the pitch of the voice, increase in larynx size, increased muscle mass, increase in clitoral size, you can get an increase in the bad cholesterol LDL, decrease in the good cholesterol HDL, increase risk of atherosclerosis, and increase risk for liver dysfunction."
        - Contrary to the high doses seen in testosterone pellets, the interviewee stated that testosterone 150mcg/day is enough to improve the sex drive in women.

Testosterone as office stock

- Two (2) interviewees stated that they do not stock medications in the office, and that there is no need to administer in the office.
    - One (1) said that there is no reason they would want to stock compounded testosterone in their office because they would not use it very much and would not trust it to stay stable.

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.[29-39]
    - Information included a statement on the use of testosterone therapy in women,[31] position statements from the Endocrine Society regarding the use of compounded bioidentical hormones,[33,34,37] and position statements from the North American Menopause Society regarding the use of hormone therapy in menopausal patients.[35,36]

Summary of survey results

Table 13. Characteristics of survey respondents [100 people responded to the survey[a]]

Board Certification	DO	MD	ND	NP	No Response
Cardiovascular Disease	0	0	0	1	0
Emergency Medicine	1	0	0	0	0
Endocrinology, Diabetes and Metabolism	0	0	1	0	0
Fellow of the American Board of Naturopathic Oncology	0	0	1	0	0
Family Medicine	0	2	0	0	0
Integrative Medicine	0	1	0	0	0
Internal Medicine	0	1	0	0	0
Naturopathic Doctor	0	0	6	0	0
Naturopathic Physician	0	0	9	0	0
Obstetrics and Gynecology	0	1	0	1	0
Ophthalmology	0	20	0	0	0
Surgery (General)	0	1	0	0	0
Urology	1	1	0	0	0
No Board Certification	0	1	3	0	0
No Response	0	0	0	0	56

Abbreviations: DO, Doctor of Osteopathic Medicine; MD, Doctor of Medicine; ND, Naturopathic Doctor; NP, Nurse Practitioner.

[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=42[a])
Compounded	17[b]
FDA-approved	6
Over-the-counter	0
Dietary	0
Unsure	1
No Response	24

[a]Out of 100 respondents, 42 reported using, prescribing, or recommending multiple types of testosterone product.
[b]Ten (10) respondents used in combination (see Figure 2).

Figure 2. Compounded combinations reported in the survey

Active ingredients in combination products:

- Testosterone, anastrozole
- Testosterone with other hormones:
  - DHEA
  - Estradiol
  - Estriol
  - Progesterone

Table 15. Compounded use of testosterone in practice[a,b]

Indication	Strength	Dosing frequency	Dosage Form	ROA	Duration of Treatment	Patient Population
Andropause, hypogonadism, testosterone deficiency in men	25-200mg	1-2x/day	Tablet	Oral, sublingual	Long-term Varies Every 3-8 months	Middle aged/older males Hypogonadal males Males with testosterone deficiency
	Variable	1-2x/day	Injection	Intramuscular		
	2-125mg	Weekly – 2x/day	Patch, cream, oils	Transdermal		
	100mg/gm					
	100-2200mg	Every 3-6 months	Pellet	Subcutaneous		
Depression	5-200mg	Weekly – daily	Cream	–	1-5 years	Males
			Injection	Intramuscular		
Dry eyes	–	2-3x/day	Eye drop	Topical	1-12+ months	Dry eyes unresponsive to therapy
Estrone dominance	90mg[c]	120 days	Pellet	Subcutaneous	Every 4 months	Females with very high estrone and symptoms of high estrogen
Menopause, post-menopause, testosterone deficiency in women	0.5-10mg	1-2x/day	Capsule, tablet, liposomal tablet	Oral, sublingual	Long-term 1-3 years Every 3-6 months	Adult and aging females Menopause, post-menopause Females with low menopause and local deficiency symptoms Females with testosterone deficiency
	0.25-10mg	1-2x/day Every other day	Cream, suppository, tablet	Topical, transdermal, vaginal		
	1-20mg/mL					
	50-200mg	Every 3-4 months	Pellet	Subcutaneous		
Transgenderism	2-100mg	Weekly – 2x/day	Patch, cream, oils	Transdermal	Long-term	"Trans women"

Abbreviations: "–", not mentioned; ROA, route of administration.
[a]Fifteen (15) respondents.
[b]Quotations are direct from respondents.
[c]Respondent reported using testosterone in combination with Arimidex 10mg.

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

Indication	Standard Therapy			
	Compounded, n (N=17)	Non-compounded, n (N=0)	Unsure, n (N=1)	No Response, n (N=24)
Andropause, hypogonadism, male gonadal failure, testicular hypofunction	6	0	0	0
Depression	1	0	0	0
Erectile dysfunction	2	0	0	0
Fatigue	1	0	0	0
Hypoactive sexual desire disorder	2	0	0	0
Insomnia	1	0	0	0
Insulin resistance	1	0	0	0
Menopause	2	0	0	0
None	2	0	0	0
Obesity	1	0	0	0
Osteoporosis in men	1	0	0	0
Other[b]	1	0	0	0
Testosterone deficiency	7	0	0	0
Transgenderism	1	0	0	0
No Response	2	0	1	24

[a]Some respondents reported more than one indication.

[b]"Not that many."

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

Theme	Reasons
Availability	Dosage forms and strengths • "Injectable" • "No fda approved drop exists" • "Versatility in dosing and route of admin" • "Limited strengths" • "Lack of availability of low dosages" • "Alternate dosage forms, more precise dose adjustments, patient preference" • "Dose and combinations not available in FDA approved drug" • "Dose & combinations not commercially available"
	Treatment of female patients • "No options for women" • "No approved cream for women" • "No FDA approved for women" • "No FDA approved testo treatment for women" • "There is no comparable drug for women and the quality and dosing guidelines for men's testosterone pellets (testapel) don't work"
Cost	Cost to patient • "FDA-approved option is rarely ever covered by patient healthcare plan" • "Expensive"
Efficacy	Improved clinical outcomes • "Better" • "More effective, better results, can more readily titrate to patient need" • "Topical forms for men do not result in optimal levels for most men" • "Methods that bypass the skin (injections or pellets) give much better clinical outcomes" • "Compounded Testosterone pellets have less complications and better efficacy"

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

	Respondents, n (N=17)
No–use has remained consistent	7
Yes–I use it LESS often now • "Less in women" • "Regulated prescription, use only when needed" • "Not needed"	3
Yes–I use it MORE often now • "Men presenting with condition" • "More cases of low T" • "It works and patients fly in from all over the country and world for treatment" • "Increase patient awareness about their conditions and treatment options"	6
No Response	1

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

	Respondents, n (N=17)
No	9
Yes	7
No Response	1

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

	Respondents, n (N=7)
In what practice locations do you stock non-patient-specific compounded testosterone?	
Physician office	7
Outpatient clinic	0
Emergency room	0
Operating room	0
Inpatient ward	0
How do you obtain your stock of non-patient-specific compounded testosterone?	
Purchase from a compounding pharmacy	4
Purchase from an outsourcing facility	3
Compound the product yourself	0
Why do you keep a stock of non-patient-specific compounded testosterone?[a]	
Convenience	5
Emergencies	1
Other (Procedure done in office)	3
Other (Accidental waste)	1
Other (Custom dosing)	2

[a]Some respondents reported more than one (1) reason for stocking non-patient-specific testosterone.

CONCLUSION

Testosterone (UNII code: 3XMK78S470) was nominated for inclusion on the 503B Bulks List for male hypogonadism and testosterone deficiency in females with breast cancer history via sublingual dosage forms, subcutaneous pellets, and topical creams. Testosterone is available as an FDA-approved implantable product, as well as a variety of topical products. It is not available as an OTC product in the US. Testosterone is available in Australia as a topical cream, and in other countries as other topical dosage forms.

From the literature review conducted, the most prevalent indication in US studies was decreased libido in female cancer patients with testosterone as a vaginal cream. The most common indications from non-US studies were menopausal and climacteric symptoms with testosterone as both a subcutaneous pellet and a topical cream. Compounded products were identified from both the US and non-US studies that reflected

the nominated dosage forms (pellets and creams). However, only two (2) of the studies used the compounded product for the nominated indication (breast cancer).

Two (2) interviewees stated that they prefer to use FDA-approved products instead of compounded products for all substances. Reasons to use compounded products generally related to skin sensitivity with commercial products and a lack of products approved for use in female patients. One (1) interviewee expressed concern with patients receiving supraphysiological dosing of testosterone, where the risk outweighs the benefit. Two (2) interviewees stated that they do not stock medications in the office, and that there is no need for them to administer it to patients there. 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.

From the survey responses, 42 out of 100 respondents used testosterone, 17 of which reported using compounded testosterone products. Respondents reported using testosterone in combination with anastrozole, as well as with estradiol, estriol, progesterone, and/or DHEA. Fifteen (15) respondents reported using compounded testosterone for a variety of indications via a variety of ROA. The most common indication respondents used compounded testosterone for was testosterone deficiency in men and women. Reasons for using the compounded testosterone product over an FDA-approved product could be categorized as availability, cost, and efficacy. Respondents were divided regarding the change in frequency of compounded testosterone usage over the past 5 years, with seven (7) respondents reporting use remaining constant, three (3) reporting less frequent use, and six (6) reporting more frequent use. Seven (7) respondents reported stocking compounded testosterone in the physician office. Methods of obtaining stock were via purchase from a compounding pharmacy (4) or from an outsourcing facility (3). The most common reason for keeping non-patient-specific compounded testosterone in the office was convenience.

APPENDICES

Appendix 1. References

1. Eby G. Testosterone as an atrial fibrillation treatment and stroke preventative in aging men: Case histories and hypothesis. *Medical Hypotheses.* 2010;75(2):269-270.
2. Glaser RL, Dimitrakakis C. Rapid response of breast cancer to neoadjuvant intramammary testosterone-anastrozole therapy: neoadjuvant hormone therapy in breast cancer. *Menopause (New York, NY).* 2014;21(6):673-678.
3. Gray KM, Derosa A. Subcutaneous pellet testosterone replacement therapy: the "first steps" in treating men with spinal cord injuries. *The Journal of the American Osteopathic Association.* 2013;113(12):921-925.
4. Jacobs SC, Kaplan GW, Gittes RF. Topical testosterone therapy for penile growth. *Urology.* 1975;6(6):708-710.
5. Klugo RC, Cerny JC. Response of micropenis to topical testosterone and gonadotropin. *The Journal of urology.* 1978;119(5):667-668.
6. Lamar CP, Rezek PR. Testosterone pellet implants for advanced breast carcinomatosis in the female; preliminary report. *Journal of the American Geriatrics Society.* 1958;6(5):397-404.
7. Misra R, Anderson DC. Treatment of recurrent premenstrual orogenital aphthae with implants of low doses of testosterone. *BMJ (Clinical research ed).* 1989;299(6703):834.
8. Savage MW, Reed P, Orrman-Rossiter SL, Weinkove C, Anderson DC. Acute intermittent porphyria treated by testosterone implant. *Postgraduate medical journal.* 1992;68(800):479-481.
9. Sokolovska S, Finlay M, Varigos G, David S. Treatment of behcets disease with subcutaneous testosterone: A case report. *Australasian Journal of Dermatology.* 2015;56((David S.) NHMRC Research Fellow, Monash Health, Melbourne, VIC, Australia):72-73.
10. Zacharin MR, Warne GL. Treatment of hypogonadal adolescent boys with long acting subcutaneous testosterone pellets. *Archives of disease in childhood.* 1997;76(6):495-499.
11. Barton DL, Wender DB, Sloan JA, et al. Randomized controlled trial to evaluate transdermal testosterone in female cancer survivors with decreased libido; North Central Cancer Treatment Group protocol N02C3. *Journal of the National Cancer Institute.* 2007;99(9):672-679.
12. Brenner PF, Bernstein GS, Roy S, Jecht EW, Mishell DR. Administration of norethandrolone and testosterone as a contraceptive agent for men. *Contraception.* 1975;11(2):193-207.
13. Brincat M, Magos A, Studd JW, et al. Subcutaneous hormone implants for the control of climacteric symptoms. A prospective study. *Lancet (London, England).* 1984;1(8367):16-18.
14. Cardozo L, Gibb DM, Tuck SM, Thom MH, Studd JW, Cooper DJ. The effects of subcutaneous hormone implants during climacteric. *Maturitas.* 1984;5(3):177-184.
15. Dahir M, Travers-Gustafson D. Breast cancer, aromatase inhibitor therapy, and sexual functioning: A pilot study of the effects of vaginal testosterone therapy. *Sexual Medicine.* 2014;2(1):8-15.
16. Davis SR, Robinson PJ, Jane F, White S, White M, Bell RJ. Intravaginal testosterone improves sexual satisfaction and vaginal symptoms associated with aromatase inhibitors. *Journal of Clinical Endocrinology and Metabolism.* 2018;103(11):4146-4154.

17. Dow MG, Hart DM, Forrest CA. Hormonal treatments of sexual unresponsiveness in postmenopausal women: a comparative study. *British journal of obstetrics and gynaecology.* 1983;90(4):361-366.

18. Glaser R, Dimitrakakis C, Trimble N, Martin V. Testosterone pellet implants and migraine headaches: a pilot study. *Maturitas.* 2012;71(4):385-388.

19. Glaser RL, York AE, Dimitrakakis C. Efficacy of subcutaneous testosterone on menopausal symptoms in breast cancer survivors. *Journal of Clinical Oncology.* 2014;32(26).

20. Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR. Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. *Menopause (New York, NY).*10(5):390-398.

21. Golebiowski B, Badarudin N, Eden J, et al. The effects of transdermal testosterone and oestrogen therapy on dry eye in postmenopausal women: a randomised, placebo-controlled, pilot study. *The British journal of ophthalmology.* 2017;101(7):926-932.

22. Gomaa A, Eissa M, El-Gebaley A. The effect of topically applied vasoactive agents and testosterone versus testosterone in the treatment of erectile dysfunction in aged men with low sexual interest. *International journal of impotence research.* 2001;13(2):93-99.

23. Martin JS. Application of testosterone cream to the clitoral area vs. to general skin may be Beneficial in Bioidentical Hormone Replacement Therapy (BHRT). *Menopause.* 2015;22(12):1382.

24. Nerli RB, Koura A, Prabha V, Reddy M. Comparison of topical versus parenteral testosterone in children with microphallic hypospadias. *Pediatric surgery international.* 2009;25(1):57-59.

25. Poels S, Bloemers J, van Rooij K, et al. Toward personalized sexual medicine (part 2): testosterone combined with a PDE5 inhibitor increases sexual satisfaction in women with HSDD and FSAD, and a low sensitive system for sexual cues. *The journal of sexual medicine.* 2013;10(3):810-823.

26. Raghunandan C, Agrawal S, Dubey P, Choudhury M, Jain A. A comparative study of the effects of local estrogen with or without local testosterone on vulvovaginal and sexual dysfunction in postmenopausal women. *The journal of sexual medicine.* 2010;7(3):1284-1290.

27. Britto R, Araújo L, Barbosa I, Silva L, Rocha S, Valente AP. Hormonal therapy with estradiol and testosterone implants: bone protection? *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology.* 2011;27(2):96-100.

28. Garnett T, Studd J, Watson N, Savvas M. A cross-sectional study of the effects of long-term percutaneous hormone replacement therapy on bone density. *Obstetrics and gynecology.* 1991;78(6):1002-1007.

29. Citizen petition from TherapeuticsMD, Inc. *Food and Drug Administration.* 2018. https://www.regulations.gov/document?D=FDA-2018-P-4714-0001. Published December 12, 2018. Accessed November 27, 2019.

30. Archer D. Nomination from David Archer. *Food and Drug Administration.* 2018. https://www.regulations.gov/document?D=FDA-2017-N-2562-0016. Published October 9, 2018. Accessed November 22. 2019.

31. Davis SR, Baber R, Panay N, et al. Global consensus position statement on the use of testosterone therapy for women. *J Sex Med.* 2019;16(9):1331-1337.

32. Develen C. Comment from Carolyn Develen. *Food and Drug Administration Notice: Drug Products That Present Demonstrable Difficulties for Compounding Under the Federal Food,*

Drug, and Cosmetic Act. 2018. https://www.regulations.gov/document?D=FDA-2017-N-2562-0017. Published October 9, 2018. Accessed November 27, 2019.

33. Endocrine Society. Comment from Endocrine Society. *Food and Drug Administration Notice: Drug Products That Present Demonstrable Difficulties for Compounding Under the Federal Food, Drug, and Cosmetic Act.* 2017. https://www.regulations.gov/document?D=FDA-2017-N-2562-0006. Published December 14, 2017. Accessed November 22, 2019.

34. Endocrine Society. Compounded bioidentical hormone therapy. *An Endocrine Society Position Statement.* 2019. https://www.endocrine.org/news-and-advocacy/position-statements/compounded-bioidentical-hormone-therapy. Published October 2, 2019. Accessed November 27, 2019.

35. Pinkerton J, Sánchez Aguirre F, Blake J, et al. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause.* 2017;24(7):728-753.

36. Pinkerton JV, Conner EA, Kaunitz AM. Management of menopause and the role For hormone therapy. *Clin Obstet Gynecol.* 2019;62(4):677-686.

37. Santoro N, Braunstein GD, Butts CL, Martin KA, McDermott M, Pinkerton JV. Compounded bioidentical hormones in endocrinology practice: an Endocrine Society scientific statement. *J Clin Endocrinol Metab.* 2016;101(4):1318-1343.

38. Stamoran C. Comment from Catalent Applied Drug Delivery Institute. *Food and Drug Administration Notice: Drug Products That Present Demonstrable Difficulties for Compounding Under the Federal Food, Drug, and Cosmetic Act.* 2018. https://www.regulations.gov/document?D=FDA-2017-N-2562-0011. Published May 7, 2018. Accessed November 27, 2019.

39. Utian W. Comment from Wulf Utian. *Food and Drug Administration (FDA) Proposed Rule: Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act.* 2014. https://www.regulations.gov/document?D=FDA-2013-N-1523-0036. Published July 8, 2014. Accessed November 22, 2019.

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 **testosterone**. 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: Testosterone

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

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

Display This Question:

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

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

Display This Question:

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

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

- ☐ Testosterone / Anastrozole
- ☐ Other (please describe) _____

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

_____

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

_____

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

_____

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

- o Yes
- o No

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

Display This Question:

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

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

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

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

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

_____

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

_____

End of Block: Testosterone

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