Summary Report

Dehydroepiandrosterone

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 NOMINATION

Dehydroepiandrosterone (DHEA; UNII code: B9840IHU4T) was nominated for inclusion on the 503B Bulks List by Triangle Compounding Pharmacy, Inc. for treating vaginal dryness, pain, and irritation via topical, oral, and vaginal routes of administration in various strengths ranging between 1-20mg per dose.

Reasons provided for nomination to the 503B Bulks List include DHEA being an alternative in situations where estrogen therapy is inappropriate and that DHEA is only available as a vaginal suppository and therefore cannot be used for compounding.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of DHEA 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 DHEA; name variations of DHEA were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient(s); strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing DHEA. 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 24, 2019. The search included a combination of (DHEA[TIAB] OR dehydroepiandrosterone[TIAB] OR dehydroisoandrosterone[TIAB] OR androstenolone[TIAB] OR prasterone[TIAB]) AND (humans[MeSH Terms] AND English[lang]) NOT autism AND (oral OR topical OR vaginal) AND (treat*[TIAB] OR therap*[TIAB] OR clinic*[TIAB] OR dryness[TIAB] OR pain[TIAB]). Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to Covidence®, merged, and sorted for removal of duplicate citations.

Study selection

Literature reviews and/or meta-analyses, cost-effectiveness, and epidemiological studies were excluded. DHEA is a component of an FDA-approved product, as a result, articles were excluded if DHEA was utilized as the FDA-approved product or in the same concentration and formulation as the FDA-approved product. Articles were considered relevant based on the identification of a clinical use of DHEA or the implementation of DHEA 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.

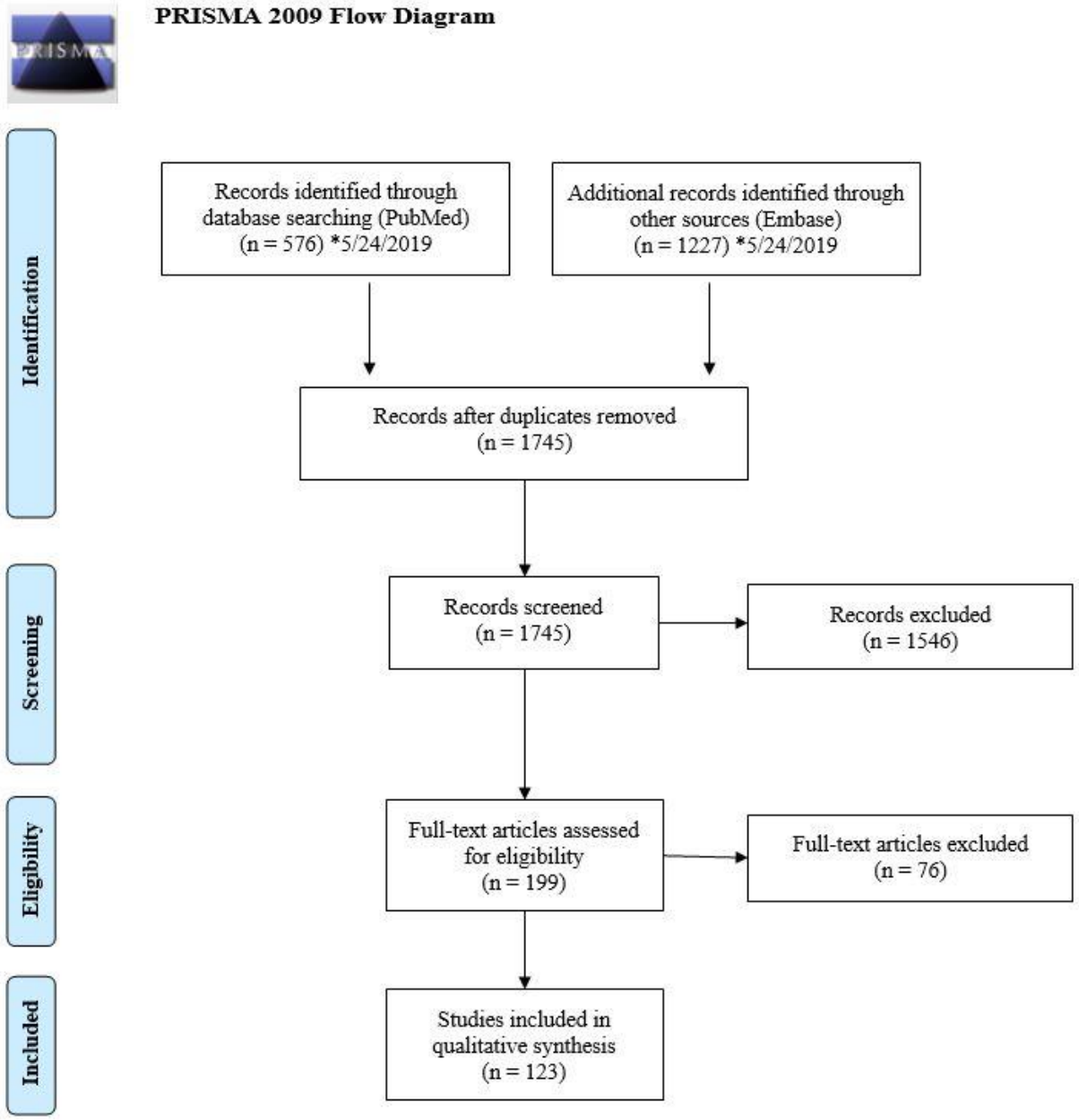
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for DHEA 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 DHEA 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 nomination and the results of the literature review, four (4) medical specialties that would potentially use DHEA were identified: endocrinology, naturopathy, obstetrics and gynecology, and primary care. Semi-structured interviews were conducted with subject matter experts within this/these specialties. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. Two (2) experts were contacted for interviews, of which two (2) accepted and zero (0) declined interviews. One interview was recorded and transcribed via ©Rev.com, while the other 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 endocrinology, naturopathy, obstetrics and gynecology, and primary care, identified from the nominations, were contacted to facilitate distribution of an online survey. A Google™ search was conducted to identify relevant professional associations within each specialty. Associations were included if their members are predominantly practitioners, national associations, and organizations focused on practice within the US. Organizations without practicing physicians and state or regional organizations were excluded. The association's website was searched in order to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used.

An online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to eight (8) 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.

Due to the identification of additional substances relevant to these associations, DHEA was included on a survey with estradiol, estradiol cypionate, estriol, estrone, medroxyprogesterone, pregnenolone, progesterone, testosterone, testosterone cypionate, and testosterone propionate.

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)
Primary Care	American Association 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"
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Obstetrics and Gynecology	American College of Obstetricians and Gynecologists (ACOG)	Declined, survey not approved for distribution
Primary Care	American College of Physicians (ACP)	Failed to respond
	American Academy of Family Physicians (AAFP)	Failed to respond

CURRENT AND HISTORIC USE

Summary of background information

- DHEA is available as an FDA-approved product (see Table 3).
- DHEA is not available as an OTC product in the US.
- There is no current United States Pharmacopeia (USP) monograph for DHEA.
- DHEA is available in Canada, Belgium, the EU, Ireland, Latvia, and the UK. DHEA is approved in the EU as an orphan medication for the treatment of adrenal insufficiency (see Table 4).

Table 3. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	ROA	Status	Approval Date
Prasterone	6.5mg	Insert	Vaginal	Prescription	11/16/2016

Abbreviation: 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
Prasterone	–	–	–	EU	Orphan Medicine	07/28/2003
	6.5mg	Ovule, Pessary	Vaginal	Canada	Prescription	10/30/2019
				Belgium	Medical prescription	01/07/2018
				EU	Prescription	08/01/2018
				Ireland	Prescription-only non-renewable	–
				UK	Prescription-only	01/08/2018
Prasteronum				Latvia	Prescription	01/08/2018

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

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

Summary of literature review

- Total number of studies included: 123 studies (9 descriptive, 90 experimental, and 24 observational studies).
- Most of the studies were from the US (46), followed by the Netherlands (13), and Italy (11).
- The most prevalent indication in the US was osteoporosis and decreased bone mineral density, followed by female sexual dysfunction and vaginal symptoms.
- The most prevalent indication in non-US studies was infertility, followed by adrenal insufficiency/failure (10), and menopause/post-menopause.
- Dosing ranges per ROA:
    - Oral (25mg/2 days-1600mg/day)
    - Gel (3.25-6.5mg/day)
    - Cream (10mg-5g/day)
- Compounded DHEA products were identified from both US (12) and non-US (2) studies.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive[1-9]	9
Experimental[10-99]	90
Observational[100-123]	24

Table 6. Number of studies by country

Country	Number of Studies
Australia[60]	1
Austria[8,68,69]	3
Belgium[99]	1
Canada[51,58]	2
China[21,22,34,52,123]	5
Denmark[23,109,110]	3
France[17,25,59,62-64,114]	7
Germany[18,38,47,100,101]	5
Hong Kong[6]	1
India[11,35,43,94]	4
Israel[70,89,105]	3
Italy[29-31,53,66,73-75,79,106,117]	11
Japan[93]	1
Poland[61]	1
Serbia[5]	1
Singapore[54]	1
Spain[32]	1
Sweden[28,44,116]	3
Switzerland[7]	1
The Netherlands[9,24,39,50,71,80,95-98,118,120,121]	13
United Arab Emirates[57]	1
UK[12,36,40,42,81,107,111,115]	8
US[1-4,10,13-16,19,20,27,33,37,41,45,46,48,49,55,56,65,67,72,76-78,82-88,90-92,102-104,108,112,113,115,119,122]	46
	Total US: 46 Total non-US Countries: 77

Table 7. Number of studies by combinations

No combination products were nominated

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Osteoporosis and decreased bone mineral density[41,45,46,78,87,88,112,113,119]	50-90mg/day	–	Capsule	Oral	6 months-2 years
Female sexual dysfunction[33,37,49] and vaginal symptoms[14-16,103]	75mg/day	–	–	Oral	4-8 weeks
	300mg	–	Capsule		1 day
	3.25-6.5mg/day	–	Gel	Vaginal	12 weeks
Depression and fatigue[4,67,91,92,122]	25-500mg/day	–	Tablet	Oral	4 weeks-6 months
	10mg/day	1%	Cream	Topical	12 months
Autoimmune (Sjogren's syndrome[65], Systemic lupus erythematosus[82-85])	50-200mg/day	–	Capsule	Oral	3-12 months
Cognitive decline[48,56,90]	50-100mg/day	–	Capsule	Oral	4 weeks-1 year
Insulin resistance[86,104,108]	50-300mg/day	–	Capsule	Oral	3 weeks-6 months
Infertility[1,20,102]	75-80mg/day	–	Tablet	Oral	2-7 months
DHEA supplementation[13,27]	50-100mg/day	–	Capsule, Tablet	Oral	3 months
Menopause[55] and post-menopause[72]	25mg/2 days-50mg/day	–	Capsule	Oral	4 weeks-12 months
Adjuvant in tetanus and influenza vaccination in elderly[26]	100mg/day	–	Capsule	Oral	4 days

Atrophic skin tears[2]	50mg/day	–	–	Oral	1 year
Cardiovascular risk factors[19]	50mg/day	–	–	Oral	6 months
HIV replication[10]	100-200mg/day	–	Capsule	Oral	12-24 weeks
Obesity[77]	1600mg/day	–	–	Oral	28 days
Poison ivy dermatitis[3]	25-50mg/day	–	–	Oral	–
Stress[76]	50-75mg/day	–	Capsule	Oral	12 days

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

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Infertility[8,11,42,43,54,57,75,89,94,115,123]	25-75mg/day	–	Capsule, Powder, Tablet	Oral	6 weeks-4 months
Adrenal insufficiency/failure[9,18,23,53,109,110], Addison's disease[28,36,40,111]	25-200mg/day	–	Capsule, Tablet	Oral	8 days-1 year
	10-33mg/m^2	–	–	Oral	1-17 years
Menopause/post-menopause[5,29,31,35,51,66,73,74,117]	10-50mg/day	–	–	Oral	3 months-1 year
	Apply 3-5g/day	10%	Cream	Topical	12 months
Autoimmune (Inflammatory bowel disease[100], Rheumatoid arthritis[118], Sjogren's syndrome[39,116], Systemic lupus erythematosus[21,22,120,121])	50-200mg/day	–	Capsule	Oral	56 days-1 year
Androgen deficiency[44,58,95-97,99,107]	20-100mg/day	–	Capsule, Tablet	Oral	4-12 months
Female sexual dysfunction[24,30,50,60,79,80,98]	10-50mg/day	–	Capsule, Tablet	Oral	140 days-1 year

Anti-aging[6,25,38,59]	50-75mg/day	–	–	Oral	3 months-2 years
	Apply 2x/day	0.1-2%	Cream	Topical	13 weeks-4 months
Osteoporosis and decreased bone density[34,47,61,105]	25-100mg/day	–	Capsule	Oral	6-12 months
DHEA supplementation[12,17,101]	50-75mg/day	–	Capsule, Tablet	Oral	4 months-2 years
Muscle damage[52,63], Type 1 myotonic dystrophy[62]	50-400mg/day	–	Capsule, Tablet	Oral	5 days-12 months
Cognitive decline[81,93]	25-50mg/day	–	Capsule, Tablet	Oral	13 weeks-6 months
Erectile dysfunction[68,69]	50mg/day	–	Capsule	Oral	24 weeks-6 months
Advanced HIV disease[64]	50mg/day	–	Capsule	Oral	4 months
Depression/fatigue[7]	25-50mg/day	–	–	Oral	5-8 months
Metabolic syndrome[32]	100mg/day	–	Capsule	Oral	3 months
Mood disturbances with combined oral contraceptives[71]	50mg/day	–	Tablet	Oral	84 days
Oxidative stress[106]	50mg/day	–	–	Oral	12 weeks
Pulmonary hypertension[114]	200mg/day	–	Tablet	Oral	3 months
Schizophrenia[70]	200mg/day	–	Capsule	Oral	6 weeks

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

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Depression and fatigue[122]	1999	• DHEA compounded with polyunsaturates and silica -based-excipient	Tablet	–
Cognitive decline[56]	2012	• "Compounded"	Capsule	–
DHEA supplementation[27]	1999	• DHEA mixed with wax vegetable oil matrix and compressed with silica -based expedient	Tablet	–
Sjogren's syndrome[65]	2004	• DHEA "produced by Pharmaceutical Development Services, Clinical Center Pharmacy, National Institutes of Health"	Capsule	–
Systemic lupus erythematosus[82-85]	1994-1999	• DHEA powder prepared in capsules "by the Stanford University Hospital pharmacy"	Capsule	–
Vaginal symptoms[14-16,103]	2014-2018	• Bioadhesive containing DHEA, carbomer, squalene, vitamin E, and glycerin	Gel	3.25, 6.5mg/syringe
		• Bioadhesive vaginal moisturizer	–	
		• Bioadhesive containing DHEA, carbomer, squalene, vitamin E acetate USP liquid, distilled water, methylparaben NF powder, propylparaben NF powder, glycerin, and zinc acetate	Gel	3.25mg/0.4mL 6.5mg/0.4mL

Abbreviation: "–", not mentioned.

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Postmenopause[51]	• DHEA with ethanol 29.6%, USP purified water 33.4%, emulsifying wax 16% , light mineral oil 10%, and benzyl alcohol 1%	Cream	10%
Metabolic syndrome[32]	• DHEA-S and cellulosum microcristallinum	Capsule	100mg/capsule

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

Two (2) interviews were conducted. For one interview, the audio recording malfunctioned and as a result, the interview was not recorded.

Table 12. Overview of interviewees

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with DHEA	Interview Summary Response
END_01	MD	Endocrinology and Metabolism Internal Medicine	Academic medical institution	Does not specify	• Does not specify use
OBG_01	MD	Obstetrics and Gynecology	Academic medical institution	Yes	• Does use intravaginal DHEA • Does not see a need for compounded DHEA

Abbreviation: MD, Doctor of Medicine.

Use of DHEA

- One interviewee stated that DHEA is used as a daily intravaginal suppository to improve libido and treat vaginal atrophy.

Compounded DHEA

- One interviewee mentioned that hormones are typically difficult to compound.
    - Uses compounded products for women with low libido not responding to lifestyle changes or commercial treatment.
    - Since there is now an FDA-approved intravaginal DHEA product, the interviewee does not see a need for compounding intravaginal DHEA. There is no documented benefit with oral or topical DHEA.

General use of compounded hormone products

- Both interviewees preferred to use FDA-approved products over compounded hormone therapy.
- One interviewee commented that there are many FDA-approved bioidentical hormones already on the market and therefore less reason to give patients compounded therapy unless very specific circumstances are met (such as allergies). While there may be some women who need specific doses that are not commercially available, there is concern about supraphysiological hormone levels, and it just is not necessary for a majority of menopausal women.

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 to the demonstrably difficult to compound list.[124-134]
    - Information included nomination of DHEA to the list of products that present demonstrable difficulties for compounding,[125] a statement on the use of testosterone therapy in women,[126] patient information for what to expect when taking DHEA,[127] position statements from the Endocrine Society regarding the use of compounded bioidentical hormones,[128,129,132] and position statements from the North American Menopause Society regarding the use of hormone therapy in menopausal patients.[130,131]

Summary of survey results

Table 13. Characteristics of survey respondents [53 people responded to the survey[a]]

Board Certification	MD	ND	No Response
Endocrinology, Diabetes and Metabolism	0	1	0
Fellow of the American Board of Naturopathic Oncology	0	1	0
Naturopathic Doctor	0	6	0
Naturopathic Physician	0	9	0
No Board Certification	1	4	0
No Response	0	0	38

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

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

Types of Products	Respondents, n (N=48[a])
Compounded	29[b]
FDA-approved	6
Over-the-counter	18
Dietary	36
Unsure	0
No response	8

[a]Out of 53 respondents, 48 reported using, prescribing, or recommending multiple types of DHEA product
[b]Eight (8) respondents used in combination (see Figure 2 below for specifics)

Figure 2. Compounded combinations reported in the survey

Active ingredients in combination products:

- DHEA, estriol
- DHEA, estradiol
- DHEA, testosterone
- DHEA, testosterone, estriol, hyaluronic acid, Vitamins E and A
- DHEA, E2, progesterone, testosterone

Forms of combination products:

- Cream
- Suppository

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

Indication	Strength	Dosing Frequency	Dosage Form	ROA	Duration of Treatment	Patient Population
Adrenal insufficiency	5-25mg	Daily	Tablet	Oral	Short term, 90d	All
Andropause Menopause Endocrine disorders	5-50mg	Daily	Capsule, Tablet	Oral	Long-term Ongoing	Elderly males Females 15-99 Adults
	5mg	2 drops 3-4x/day	Drops	Transbuccal		
	25-50mg	Daily	Cream	Transdermal		
Autoimmune disorders[b]	10-100mg	1-2x/day	Capsule	Oral	1-5 years Indefinitely	Autoimmune
DHEA deficiency	5-25mg	Daily	Capsule	Oral	Long-term 6-24 months	Males Females
			Cream	Topical		
Joint pain	5mg	Daily	Capsule	Oral	As long as needed	Deficient patient
Menarche Menstrual disorders[c]	5mg	2 drops 1-4x/day	Drops	Transbuccal	Ongoing	Female early teens Female cycling
Vaginal atrophy	5mg	Daily	Cream, Suppository	Vaginal	1+ months Ongoing	Women
	10mg	Every other day				

Abbreviation: ROA, route of administration
[a]Eight (8) respondents
[b]Lupus, rheumatoid arthritis
[c]Metorrhagia, premenstrual syndrome

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

Indication	Standard Therapy			
	Compounded, n (N=29)	Non-Compounded, n (N=38)	Unsure, n (N=0)	No Response, n (N=8)
Adrenal insufficiency, cortisol deficiency	1	5	0	0
Aging	1	0	0	0
Autoimmune diseases, lupus	1	2	0	0
DHEA deficiency	1	4	0	0
Dysautonomia	1	0	0	0
Erectile dysfunction	0	1	0	0
Fatigue	0	1	0	0
Hormonal imbalance (estrogen, testosterone), andropause, menopause/post-menopause	6	4	0	0
Osteoarthritis, joint pain	2	0	0	0
Osteopenia, osteoporosis	0	1	0	0
Other[b]	0	1	0	0
Vaginal atrophy	1	0	0	0
No response	25	4	0	8

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

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

Theme	Reasons
Availability	• "I am unaware of any FDA-approved product with DHEA. I use it IF FDA-approved product is inadequate to address the issue and/or if patients elect NOT to use the FDA-approved product for some reason." • "More cost effective, easier access"
Customizable	• "Because it can be individualized according to a patient's specific needs." • "No binders, no fillers, ease of use, customizable, quality" • "It is time release; otc products not available in 10 mg caps"

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

	Respondents, n (N=29)
No - Use has remained consistent	5
Yes - I use it LESS often now	0
Yes - I use it MORE often now	0
No Response	24

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

	Respondents, n (N=29)
No	4
Yes[a]	1
No Response	24

[a]Respondent reports stocking non-patient-specific compounded DHEA in physician office, and compounds the product themselves for reasons of convenience and cost-effectiveness.

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

No additional survey respondents provided information for this section

CONCLUSION

DHEA (UNII code: 9840IHU4T) was nominated for inclusion on the 503B Bulks List to treat vaginal dryness, pain, and irritation via various routes of administration. Out of the national medical registers that were reviewed, DHEA is available in Canada, Belgium, the EU, Ireland, Latvia, and the UK.

From the literature review conducted, the most prevalent indication for use of DHEA in the US was osteoporosis and decreased bone mineral density, followed by female sexual dysfunction and vaginal symptoms. The most prevalent indication for use of DHEA in non-US studies was infertility, followed by adrenal insufficiency/failure and menopause/post-menopause.

Interviewees did not see any benefit in using compounded hormonal products over commercially available FDA-approved products. One interviewee did use DHEA to improve libido and treat vaginal atrophy. The other did not specify use. In the supplemental information provided, one document nominated DHEA to the demonstrably difficult to compound list.

Out of the specialty organizations that were approached for survey participation, only the AANP agreed to participate. Out of 53 respondents, 48 reported using, prescribing, or recommending DHEA in practice, of which 29 reported using compounded DHEA. Availability and customization were the reasons provided for using the compounded DHEA over an FDA-approved product. One respondent reported stocking compounded DHEA in their office.

APPENDICES

Appendix 1. References

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Appendix 2. Survey instrument

Dehydroepiandosterone (DHEA)

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 **dehydroepiandrosterone (DHEA)**. 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: Dehydroepiandrosterone (DHEA)

Q1 What type(s) of product(s) do you use, prescribe, or recommend for **dehydroepiandrosterone (DHEA)**? 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: Q14 If What type(s) of product(s) do you use, prescribe, or recommend for dehydroepiandrosterone (DHEA)?... != Compounded drug product

Skip To: Q3 If What type(s) of product(s) do you use, prescribe, or recommend for dehydroepiandrosterone (DHEA)?... = Compounded drug product

Display This Question:

If What type(s) of product(s) do you use, prescribe, or recommend for dehydroepiandrosterone (DHEA)?... = Compounded drug product

Q2 Please list any conditions or diseases for which you use compounded **dehydroepiandrosterone (DHEA)** 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 **dehydroepiandrosterone (DHEA)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- ☐ Single
- ☐ Combination

Skip To: Q6 If Do you use compounded dehydroepiandrosterone (DHEA) as a single agent active ingredient, or as on... != Combination

Display This Question:

If Loop current: Do you use compounded dehydroepiandrosterone (DHEA) as a single agent active ingredient, or as on... = Combination

Q4 Please list all combination products in which you use compounded **dehydroepiandrosterone (DHEA)**.

_____

Page Break

Q5 For which, if any, diseases or conditions do you consider compounded **dehydroepiandrosterone (DHEA)** standard therapy?

_____

Q6 Does your specialty describe the use of compounded **dehydroepiandrosterone (DHEA)** in medical practice guidelines or other resources?

_____

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

_____

Q9 Do you stock non-patient-specific compounded **dehydroepiandrosterone (DHEA)** in your practice location?

- ○ Yes
- ○ No

Skip To: End of Block If Do you stock non-patient-specific compounded dehydroepiandrosterone (DHEA)in your practice locati... = No

Page Break

Display This Question:

If Do you stock non-patient-specific compounded dehydroepiandrosterone (DHEA)in your practice locati... = Yes

Q10 In what practice location(s) do you stock non-patient-specific compounded **dehydroepiandrosterone (DHEA)**? 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 **dehydroepiandrosterone (DHEA)**? 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 **dehydroepiandrosterone (DHEA)**? 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 dehydroepiandrosterone (DHEA)? Please... = Convenience

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded dehydroepiandrosterone (DHEA)? Please... = Emergencies

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded dehydroepiandrosterone (DHEA)? Please... = Other (please describe)

Page Break

Q13 For which, if any, diseases or conditions do you consider **dehydroepiandrosterone (DHEA)** standard therapy?

_____

Q14 Does your specialty describe the use of **dehydroepiandrosterone (DHEA)** in medical practice guidelines or other resources?

_____

End of Block: Dehydroepiandrosterone (DHEA)

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