UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

WELLNESS PHARMACY, INC., *et al.*, Plaintiffs, v. **XAVIER BECERRA, SECRETARY OF HEALTH AND HUMAN SERVICES,**[1] ***et al.***, Defendants.	Case No. 20-cv-3082 (CRC)

MEMORANDUM OPINION

Evoking Victorian apothecary scales and porcelain mortars and pestles, compounded drugs are formulated by pharmacists to create medicines tailored for individual patients. Federal law generally exempts these extemporaneous mixtures from the vast regulatory framework that governs the development and introduction of new drugs, leaving most regulation to the States. Congress has, however, authorized the Food and Drug Administration to exercise its enforcement powers over pharmacies that engage in the interstate distribution of compounded drugs under circumstances that might indicate large-scale drug manufacturing under the guise of compounding. For over twenty years, pharmacies that specialize in compounding and their industry representatives have jousted with FDA over where and how to draw the line between legitimate compounding and disguised new-drug distribution. This case presents the latest skirmish in this decades-old fight.

[1] Secretary Becerra is automatically substituted for former Secretary Alex Azar. See Fed. R. Civ. P. 25(d).

The plaintiffs here are seven compounding pharmacies located throughout the country. They challenge the recent finalization of a standard Memorandum of Understanding that Congress required FDA to develop in 1997 when it passed Section 503A of the Federal Food, Drug, and Cosmetic Act ("FDCA"). The Final Standard MOU establishes an agreement between individual state pharmacy boards and FDA. The agreement requires States to identify and report information on pharmacies within the State that distribute "inordinate amounts" of compounded drugs interstate, as defined by the MOU. Pharmacies within signatory States may compound drugs exempt from the FDCA's otherwise applicable new-drug laws. Meanwhile, pharmacies located in States that do *not* sign the MOU must comply with a provision of Section 503A known as the five-percent limit, which removes the new-drug exemption for pharmacies that distribute compounded drugs interstate in quantities that exceed five percent of their total prescription orders.

The Final Standard MOU has been years in the making. FDA did not finalize the present MOU until October 2020. In the meantime, the agency exercised its discretion not to enforce the five-percent limit, the violation of which could otherwise subject compounding pharmacies to civil and criminal penalties. FDA recently announced that it intends to extend its forbearance until October 2022. Thus, States have another year to decide whether to sign the Final Standard MOU before their pharmacies will be subject to the five-percent limit and its attendant sanctions.

On the same day that FDA noticed the Final Standard MOU, plaintiffs initiated this lawsuit and moved for partial summary judgment. The complaint advances three counts—two allege procedural violations in FDA's development of the MOU and the third alleges that FDA exceeded its statutory authority under Section 503A in defining several key statutory terms. In the procedural counts, plaintiffs allege that FDA violated Section 503A by not developing the

Final Standard MOU through regulations and that it violated the Regulatory Flexibility Act by failing to conduct an analysis of the MOU's impact on small pharmacies. In the remaining count, plaintiffs contend that FDA exceeded its statutory authority by defining "distribution" in the MOU to include instances of compounding drugs pursuant to a prescription. Defendants cross-moved for summary judgment, arguing that plaintiffs lack standing to bring this lawsuit and that their claims otherwise fail on the merits.

The Court concludes that plaintiffs have standing and that the Final Standard MOU is a legislative rule and thus subject to the Regulatory Flexibility Act's procedural requirements. It will, accordingly, grant plaintiffs' motion for summary judgment and remand the MOU to the agency to either certify that it will not have a significant economic effect on small businesses or prepare a regulatory flexibility analysis. See 5 U.S.C. §§ 603, 604, 605.

I. Background

A. Regulatory Background

1. Statutory framework

FDA strictly regulates the development and introduction of new drugs through an extensive series of laws contained in the FDCA. For instance, each new drug's manufacturer or sponsor must seek FDA approval for the drug via an application that describes how the drug was manufactured, lists all of the drug's ingredients, and contains "full reports of investigations" into the drug's safety and effectiveness for each intended use. 21 U.S.C. § 355(a), (b). Once approved, a new drug is subject to a comprehensive set of current good manufacturing practices—known as "cGMPs"—that govern everything from the drug's ingredients to the quality of its manufacturing facility. See id. §§ 351(a)(2)(B), 355(e). Additionally, all approved

drugs are subject to FDA labeling requirements, which mandate (among other things) that they be labeled with adequate instructions for safe use. See id. § 352(f)(1).

This case involves the application (or lack thereof) of these laws to compounded drugs. "Drug compounding" refers to "the process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient." Thompson v. W. States Med. Ctr., 535 U.S. 357, 360–61 (2002). For example, a pharmacist may compound a drug for a patient who would otherwise be allergic to an ingredient in his or her medication. Though a compounded drug qualifies as a "new drug" under the FDCA, see 21 U.S.C. § 321(p), FDA has historically left regulation of compounded drugs to the States, Thompson, 535 U.S. at 362. Over time, however, FDA grew concerned that some pharmacies were compounding drugs at levels that rendered the pharmacies akin to drug manufacturers. Id.

Acting on this concern, in 1992, FDA issued a Compliance Policy Guide ("CPG") clarifying that "FDA may, in the exercise of its enforcement discretion, initiate enforcement actions against" compounding pharmacies "when the scope and nature of a pharmacy's activity raises the kinds of concerns normally associated with a manufacturer and that results in significant violations of the new drug, adulteration, or misbranding provisions of the Act." Def. Cross-Mot. for Summ. J., ECF No. 36 (hereinafter, "Def. MSJ"), Ex. A (1992 CPG), at 195. The CPG set forth various factors that the agency would consider when evaluating whether to initiate such an enforcement action. Id. The relevant factors included the frequency with which the pharmacy was compounding copies of FDA-approved drugs, the pharmacy's use of commercial-scale manufacturing equipment, and the pharmacy's interstate distribution of an inordinate level of compounded drugs. Id. At the same time, FDA "recogniz[ed] that pharmacists traditionally have extemporaneously compounded . . . reasonable quantities of drugs upon receipt of a valid

prescription" and noted that "[t]his traditional activity [was] not the subject of th[e] CPG." Id. at 193.

Five years later, the 1992 CPG was effectively codified within the FDCA via the Food and Drug Administration Modernization Act. See Pub. L. No. 105-115, 111 Stat. 2296 (1997) ("FDAMA"). Most importantly for present purposes, the FDAMA added Section 503A to the FDCA. See 21 U.S.C. § 353a ("Section 503A"). Section 503A sets forth certain conditions that must be satisfied for compounded drugs to be exempt from the vast regulatory framework that would otherwise govern new drugs. The section begins by providing a general exemption for drugs that are "compounded for an identified individual patient based on the receipt of a valid prescription or a notation[.]" Id. § 353a(a). The statute then imposes *additional* requirements for such compounded drugs that are distributed interstate. Specifically, a drug may be compounded pursuant to Section 503A's general exemption *only if* it falls into one of two categories:

> (B) such drug product is compounded in a State—
>
> (i) that has entered into a memorandum of understanding with the Secretary which addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State; or
>
> (ii) that has not entered into the memorandum of understanding described in clause (i) and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.

Id. § 353a(b)(3)(B). The Court will follow the parties' lead in referring to § 353a(b)(3)(B)(ii) as "the five-percent limit."

After setting out these two categories, subsection (b)(3) provides that "[t]he Secretary shall, in consultation with the National Association of Boards of Pharmacy ["NABP"], develop a

memorandum of understanding for use by the States in complying with subparagraph 353a(b)(3)(B)(i)." Id. Immediately thereafter, § 353a(c)(1), which is entitled "regulations" and subtitled "in general," instructs the Secretary to "issue regulations to implement this section." Id.

2. Development of a standard MOU

Section 503A was to take effect in November 1998. See FDAMA, 111 Stat. 2296. That month, FDA announced that it was developing proposed rules to implement the section. See Unified Agenda of Federal Regulatory and Deregulatory Actions, 63 Fed. Reg. 61,680, 61,707, 61,709–10 (Nov. 9, 1998) ("Fall 1998 Regulatory Agenda"). In particular, FDA said that it was developing proposed regulations "for the interpretation and enforcement of section 503A," which would "delineate the conditions under which compounding is exempt from the manufacturing, misbranding, and new drug provisions of the [FDCA]" and "set forth other definitions and conditions for distinguishing legitimate pharmacy compounding from pharmaceutical drug manufacturing performed under the guise of compounding." Id. at 61,709.

Two months later, FDA noticed its first draft MOU. See Administrative Record ("A.R.") 000001–2 (Federal Register Notice); id. at 000003–19 ("1999 draft MOU").[2] As part of the 1999 draft, the State agency agreed to "take action" regarding "any pharmacy or physician that "distribute[d] inordinate amounts of compounded drugs interstate." Id. at 000014. The draft defined inordinate amount of distribution as occurring when "[t]he number of compounded prescriptions dispensed or distributed interstate" constituted twenty percent or more of the "total number of prescriptions dispensed or distributed (including both intrastate and interstate) by such pharmacy or physician[.]" Id. The 1999 draft MOU excluded from this twenty-percent

[2] Although the draft MOU is dated December 23, 1998, the FDA noticed availability of the draft in January 1999. The Court will therefore refer to this draft as the "1999 draft MOU."

threshold instances of "local" interstate distribution, which FDA defined as sending a compounded drug to an out-of-state patient within fifty miles of the pharmacy. Id. at 000015. FDA announced that it would give States "at least 90 days after the standard MOU is finalized and made available to the States for their consideration and signature" before enforcing the five-percent limit against pharmacies. Id. at 000002. FDA noticed the draft in the Federal Register, and it received over 6,000 comments. Id. at 000030-028485.

Meanwhile, lawsuits across the country began calling Section 503A's validity into doubt. See, e.g., W. States Med. Ctr. v. Shalala, 238 F.3d 1090, 1092-93 (9th Cir. 2001), aff'd sub nom. Thompson v. W. States Med. Ctr., 535 U.S. 357 (2002). In May 2002, the Supreme Court declared that Section 503A's advertising restrictions were unconstitutional but declined to decide whether those provisions were severable from the remainder of the statute. See Thompson, 535 U.S. at 366. Shortly thereafter, FDA announced that it was no longer developing proposed regulations to implement Section 503A, see 67 Fed. Reg. 33,040, 33,045 (May 13, 2002), and that the agency viewed the Supreme Court's decision in Thompson as invalidating Section 503A in its entirety, see Pharmacy Compounding Compliance Policy Guide; Availability, 67 Fed. Reg. 39,409, 39,410 (June 7, 2002).

Ten years later, a nationwide outbreak in fungal meningitis was traced to a contaminated compounded drug produced by a facility in Massachusetts. See Drug Quality and Security Act, Pub. L. No. 113-54, 127 Stat. 587 (2013). The following year, Congress enacted the Drug Quality and Security Act, which, among other things, severed the unconstitutional advertising provisions from Section 503A but left the statute otherwise intact. See id.

With its statutory mandate thus revived, FDA turned back to drafting Section 503A's standard MOU. In 2015, the agency released a second draft, see A.R. 028760–67 ("2015 draft

MOU"); id. at 028752–759 (Federal Register Notice), which differed from the 1999 version in several respects. For starters, it raised the level of distribution that qualified a pharmacy as an inordinate distributor of compounded drugs from twenty to thirty percent of the pharmacy's total prescriptions. Id. at 028763. And in place of a carveout for local interstate distribution, the 2015 draft excluded from this threshold any instances in which a patient picked up a compounded drug in person and then took the drug out of state. Id. Like its predecessor, the 2015 draft MOU was noticed in the Federal Register, and FDA announced that it would not enforce the five-percent limit until States had time to evaluate and sign a finalized MOU. Id. at 028753. The agency also noted that it was "considering whether to propose regulations or issue guidance documents to further its implementation of [S]ection 503A(b)(3)(B)[.]" Id. at 028754 n.2. The 2015 draft MOU received over 3,000 comments. Id. at 028768–30838.

In September 2018, FDA noticed another substantially revised draft MOU. Id. at 030849–857 ("2018 draft MOU"); id. at 030839–848 (Federal Register Notice). The 2018 draft MOU required State agencies only to collect and report information on pharmacies that they identified as distributing inordinate amounts of compounded drugs interstate, id. at 030851–53, whereas prior drafts had required the State to take action against those pharmacies, id. at 000014 (1999 draft MOU); id. at 028762–63 (2015 draft MOU). Through this revision, FDA effectively changed the "inordinate amount" percentage from a *limit* on pharmacies' interstate compounding to a *threshold* that triggered information-gathering and reporting obligations on behalf of the States. Additionally, the 2018 draft increased the threshold for inordinate distribution from thirty percent to fifty percent of a pharmacy's total *compounding* orders (rather than total prescription

orders, compounded or otherwise). Id. at 030851–52.[3] In other words, a pharmacy met the 2018 MOU's threshold when over half of its compounded drugs were shipped out of state. Like its predecessors, the 2018 draft MOU was noticed in the Federal Register and accompanied by an extension of FDA's enforcement discretion of the five-percent limit. Id. at 030839–48. It received approximately forty comments. Id. at 031061–031226.

The following year, FDA sought applications for a three-year pilot project aimed at establishing an information management system for use by State pharmacy regulators, compounders, and FDA. See id. at 031631–50. FDA awarded the grant to NABP in October 2019. See id. at 031651. The pilot project remains ongoing.

3. Final Standard MOU

On October 27, 2020, FDA noticed the Final Standard MOU in the Federal Register. See id. at 031438–446 (Federal Register Notice); id. at 031447–459 (Final Standard MOU). As the Final Standard MOU is at the center of this litigation, the Court will describe it in some detail.

The MOU begins by declaring its purpose:

> This Memorandum of Understanding (MOU) establishes an agreement between the [insert State Board of Pharmacy or other appropriate State agency] and the U.S. Food and Drug Administration (FDA) regarding the distribution of inordinate amounts of compounded human drug products interstate and the appropriate investigation by the [insert State Board of Pharmacy or the appropriate State agency] of complaints relating to human drug products compounded in [insert State] and distributed outside such State. This is the MOU provided for by section 503A(b)(3)(B)(i) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 353a)[.]

[3] FDA explained that this change responded to comments to the 2015 draft, which noted that the prior calculation disfavored "specialty compounding pharmacies that engage in interstate distribution and only distribute compounded drug products[.]" Id. at 030843.

Id. at 031447 (internal footnotes omitted). It continues with a "background" section, which summarizes the statutory provisions governing compounded drugs. See id. at 031447–48. In particular, the MOU notes that Section 503A(b)(3) of the FDCA "directs FDA to develop a standard MOU in consultation with the National Association of Boards of Pharmacy" and declares that "[t]his MOU is the standard MOU developed by FDA for this purpose." Id. at 031448.

The MOU then details the substance of agreement. See id. at 031448–55. Relevant here, it declares that a pharmacy has distributed an inordinate amount of compounded drugs interstate when:

> the number of prescription orders for compounded human drug products that the pharmacy distributed interstate during any calendar year is greater than 50 percent of the sum of:
>
> (i) the number of prescription orders for compounded human drug products that the pharmacy sent out of (or caused to be sent out of) the facility in which the drug products were compounded during that same calendar year; plus
>
> (ii) the number of prescription orders for compounded human drug products that were dispensed (e.g., picked up by a patient) at the facility in which they were compounded during that same calendar year.

Id. at 031450–51; see also id. at 031452 (Figure 1). In other words, a pharmacy meets the "inordinate amounts" threshold when over half of its annual compounded drug orders are distributed interstate. On an annual basis, States that sign the MOU are required to identify pharmacies that meet this threshold through "surveys, reviews of records during inspections, data

submitted to an Information Sharing Network, or other mechanisms available to the [State]." Id. at 031452.[4]

For each pharmacy that exceeds the 50-percent threshold, States are further required to gather and report four categories of information: (1) "the total number of prescription orders for sterile compounded human drugs distributed interstate;" (2) "the names of States in which the pharmacy is licensed;" (3) "the names of States into which the pharmacy distributed compounded human drug products;" and (4) "whether the State inspected for and found during its most recent inspection that the pharmacy distributed compounded human drug products without valid prescription orders for individually identified patients." Id. at 031452. The MOU instructs States to gather this information "using data submitted to an Information Sharing Network or other available mechanisms." Id.

B. Procedural Background

Plaintiffs are seven compounding pharmacies located in Alabama, Wisconsin, Colorado, Pennsylvania, California, Utah, and New York. Compl. ¶¶ 8–14. On the same day that FDA noticed its Final Standard MOU, plaintiffs commenced this action and moved for partial summary judgment. The complaint names as defendants the Secretary of Health and Human Services, the Commissioner of Food and Drugs, and FDA. Id. ¶¶ 15–17. In Count I, plaintiffs allege that FDA's issuance of the Final Standard MOU violates Section 503A's "shall issue regulations" command and should therefore be set aside as agency action undertaken "without observance of procedure required by law" under 5 U.S.C. § 706(2)(D). Compl. ¶¶ 87–92. In

[4] As described above, the MOU is an agreement with the "State Board of Pharmacy or other appropriate State agency." A.R. 031447. For ease of reference, the Court refers to this entity as the State.

Count II, plaintiffs maintain that FDA failed to conduct an analysis of the Final Standard MOU's impact on small entities as required by the Regulatory Flexibility Act. Compl. ¶¶ 93–97 (citing 5 U.S.C. § 604(a)).[5] And in Count III, they contend that FDA exceeded its statutory authority by defining "distribution of compounded human drug products interstate" and "inordinate amounts" to include interstate "dispensing," which plaintiffs understand to mean compounding drugs pursuant to a prescription.[6] Id. ¶¶ 98–101.

Plaintiffs moved for summary judgment on all three counts in their Complaint on February 10, 2021. See Mot. for Summ. J., ECF No. 26 (hereinafter, "Pl. MSJ"). A compounding industry group and a collection of other compounding pharmacies followed with amicus briefs in support of plaintiffs. See Amicus Br. by Alliance for Pharm. Compounding, *et al.*, ECF No. 39; Amicus Br. by Infuserve America, Inc., *et al.*, ECF No. 41. Defendants then cross-moved for summary judgment on March 3, 2021. See Def. MSJ. Not to be outdone, a coalition of manufacturers of FDA-approved drugs filed an amicus brief in support of defendants. See Amicus Br. of the Campaign for Responsible Compounding, ECF No. 43. After

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[5] In addition to an allegation under the RFA, Count II alleges that "[t]he Final Standard MOU is a substantive rule for which prior notice-and-comment rulemaking was required by 5 U.S.C. § 553." Compl. ¶ 95. However, plaintiffs declined to brief this argument and abandoned it at oral argument. Oral Arg. Tr. 19:11–15 (explaining that plaintiffs' "position is that FDA did consider 30,000 comments, and that if [they] brought a notice and comment challenge, it could have been subject to a harmless error [analysis]. And, therefore, [plaintiffs] brought the procedural claims that have actually injured us[.]").

[6] This case involves several semantic disputes, one of which is worth noting at the outset. The term "dispensing," in plaintiffs' view, refers to the provision of compounded drugs pursuant to a prescription. Compl. ¶ 2; see also, e.g., Oral Arg. Tr. 09:22–10:01. Defendants, meanwhile, understand "dispensing" to encompass providing a compounded drug to a patient *in person*, regardless of whether that drug was compounded pursuant to a prescription. See, e.g., A.R. 031443–44; id. at 031450; Oral Arg. Tr. 58:24–59:19. The intended meaning of the term thus varies in the record depending on which party is using it.

briefing on the cross-motions had concluded, Colorado, in which plaintiff Belmar Pharmacy is located, executed a Final Standard MOU with FDA.

The Court heard oral argument on the cross-motions on July 14, 2021. Following the hearing, plaintiffs moved to file a supplemental declaration in support of their theory of standing. See Mot. for Leave to File Supp. Decl., ECF No. 54. Defendants' opposed the motion. See Mem. in Opp. to Mot. for Leave to File Supp. Decl., ECF No. 57. All the motions are ripe for the Court's resolution.

II. Standard of Review

When evaluating cross-motions for summary judgment under the Administrative Procedure Act ("APA"), "the Rule 56 standard does not apply." Alfa Int'l Seafood v. Ross, 264 F. Supp. 3d 23, 36 (D.D.C. 2017). The court instead "sits as an appellate tribunal" and "[t]he entire case on review is a question of law." Id. (quoting Am. Biosci., Inc. v. Thompson, 269 F.3d 1077, 1083 (D.C. Cir. 2001)). The APA provides that a court must "hold unlawful and set aside agency action, findings, and conclusions" that are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," 5 U.S.C. § 706(2)(A), in excess of statutory authority, id. § 706(2)(C), or "without observance of procedure required by law," id. § 706(2)(D). Within this "narrow" standard of review, "a court is not to substitute its judgment for that of the agency," Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983), and "will defer to the [agency's] interpretation of what [a statute] requires so long as it is rational and supported by the record," Oceana, Inc., v. Locke, 670 F.3d 1238, 1240 (D.C. Cir. 2011) (cleaned up).

III. Analysis

FDA first argues that the Court lacks subject matter jurisdiction over this case because plaintiffs failed to establish standing and their claims are not ripe. It next contends that plaintiffs fail on the merits because FDA complied with Section 503A and was not subject to the Regulatory Flexibility Act when developing the MOU. Finally, FDA maintains that the final standard MOU constitutes a reasonable interpretation of Section 503A that should be upheld under Chevron, U.S.A., Inc. v. Nat. Res. Def. Council, Inc., 467 U.S. 837 (1984).

The Court first assures itself of its jurisdiction and then turns to the merits.

A. Jurisdiction

FDA argues that the Court should dismiss this action because plaintiffs lack standing and their claims are not ripe. The Court takes these arguments in turn.

1. Standing

Article III extends federal jurisdiction to cases and controversies. U.S. Const. art. III, § 2. "For a legal dispute to qualify as a genuine case or controversy, at least one plaintiff must have standing to sue." Dep't of Com. v. New York, 139 S. Ct. 2551, 2565 (2019). Standing is a claim-specific inquiry. Competitive Enter. Inst. v. F.C.C., 970 F.3d 372, 382 (D.C. Cir. 2020). At the same time, the Court need not conclude that each individual plaintiff has standing where, as is the case here, all plaintiffs "raise the same issues." Grocery Mfrs. Ass'n v. E.P.A., 693 F.3d 169, 175 (D.C. Cir. 2012). If one plaintiff has standing, then the Court has "established [its] jurisdiction to consider the merits" of plaintiffs' claims. Id.; see also R. Labor Execs. Ass'n v. United States, 987 F.2d 806, 810 (D.C. Cir. 1993) ("[I]f one party has standing in an action, a court need not reach the issue of standing of other parties when it makes no difference to the merits of the case.").

To have Article III standing, a "plaintiff must have (1) suffered an injury in fact, (2) that is fairly traceable to the challenged conduct of the defendant, and (3) that is likely to be redressed by a favorable judicial decision." Spokeo, Inc. v. Robins, 578 U.S. 330, 136 S. Ct. 1540, 1547 (2016). The first two elements—injury in fact and traceability—are at issue here. As plaintiffs have alleged the same theories of injury for all three claims, the Court first evaluates whether these injuries satisfy the injury-in-fact element of Article III and then turns to whether they are fairly traceable to each claim.

a. Injury in fact

"To establish injury in fact, a plaintiff must show that he or she suffered an invasion of a legally protected interest that is concrete and particularized and actual or imminent, not conjectural or hypothetical." Id. at 1548 (cleaned up). While the imminence and redressability elements of standing are relaxed for procedural-rights plaintiffs, the injury-in-fact and causation requirements are not. Ctr. for L. & Educ. v. Dep't of Educ., 396 F.3d 1152, 1157 (D.C. Cir. 2005).

A plaintiff can establish standing based on future injures if they "satisfy either the certainly impending' test or the 'substantial risk' test." New Jersey v. Env't Prot. Agency, 989 F.3d 1038, 1047 (D.C. Cir. 2021) (quoting Attias v. Carefirst, Inc., 865 F.3d 620, 626–27 (D.C. Cir. 2017)). Plaintiffs advance two theories of injury here: (1) should their States sign the Final Standard MOU, plaintiffs claim that they will incur compliance costs as a result of the MOU's information-gathering and reporting requirements; and (2) should their States *not* sign the MOU, plaintiffs maintain that compliance with Section 503A's five-percent limit will force them to curtail business or close their pharmacies.

Starting with compliance costs for pharmacies in MOU states, plaintiffs argue that they will have to expend time and money gathering and reporting information because of two sets of conditions imposed by the Final Standard MOU. *First*, on an annual basis, the State must "identify, using surveys, reviews of records during inspections, data submitted to an Information Sharing Network, or other mechanisms available . . . pharmacies that distribute inordinate amounts" of compounded drugs interstate. A.R. 031452. This requirement extends to all pharmacies located in MOU States—not only those that are otherwise flagged as inordinate distributors of compounded drugs. *Second*, for those pharmacies that the State identifies as "distributing inordinate amounts" of compounded drugs interstate, the State must "identify, using data submitted to an Information Sharing Network or other available mechanisms during that same calendar year[,]" additional information and then report that information to FDA. Id. Specifically, the State must collect and report: (1) "the total number of prescription orders for sterile compounded human drugs distributed interstate;" (2) "the names of States in which the pharmacy is licensed;" (3) "the names of States into which the pharmacy distributed compounded human drug products;" and (4) "whether the State inspected for and found during its most recent inspection that the pharmacy distributed compounded human drug products without valid prescription orders for individually identified patients." Id.

Defendants rejoin that that compliance costs associated with these requirements are too speculative to count as injuries-in-fact. See Def. MSJ at 18–19; Def. Reply Mem., ECF No. 48, at 6–8. They argue that it is not yet known which States will sign the MOU and that pharmacies in MOU States might not incur any costs given that the MOU obligates the *States* (rather than the *pharmacies*) to collect and report the relevant information. Def. MSJ at 18. The Court is not persuaded. As explained below, plaintiffs have established a substantial risk that some of their

States will choose to sign the MOU and pass on its information-gathering burdens to them. Plaintiffs' compliance-cost theory of injury therefore qualifies as an Article III injury in fact.

FDA has indicated that it expects all but five States to sign the MOU. See Human Drug Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act, 85 Fed. Reg. 28,961, 28,962 (May 14, 2020). Indeed, Colorado executed an MOU on June 29, 2021, effective immediately. See Notice of Subsequent Event, ECF No. 51. The president and CEO of plaintiff Belmar Pharmacy, which is located in Colorado, has submitted a declaration attesting that "[t]he data-sharing requirements that would likely be imposed upon us by the Colorado State Board of Pharmacy as a result of the Final Standard MOU would result in greater compliance costs." Hill Decl. ¶ 7. Mr. Hill further avers that "the assessment, compilation, reporting, and error-correction obligations would absolutely require the hiring of an additional full-time pharmacist." Id. ¶ 8. In fact, *every* pharmacy in this case submitted a declaration attesting to its expectation that the individual pharmacies (rather than the States) would be responsible for complying with the reporting requirements of the MOU. See Besteman Decl. ¶¶ 7–9 (attesting that pharmacy will have to hire a new employee to undertake the data-gathering and reporting processes required by the MOU if plaintiff's State chooses to sign); Bray Decl. ¶¶ 7–9 (same); Harbin Decl. ¶¶ 7–10 (same); Stuart Decl. ¶¶ 6–8 (same); Patel Decl. ¶¶ 7–11; Mansour-Awad Decl. ¶¶ 7–10 (same).

These statements are not mere speculation. Multiple declarants indicate that they were informed by officials within their respective State Boards of Pharmacy that pharmacies will be shouldering the compliance costs. See, e.g., Stuart Decl. ¶ 7 (averring that the Executive Director of the California State Board of Pharmacy indicated at a committee meeting in January 2021 "that the Board does not have the resources to collect this data itself and will pass the

burden of aggregating and reporting this burden to the pharmacies"); Harbin Decl. ¶ 7 (averring that Wellness Pharmacy's "assigned compliance officer from the Alabama Board of Pharmacy" informed Mr. Harbin that "he would require Wellness Pharmacy to provide these categories of data upon inspection" should Alabama sign the MOU); Bray Decl. ¶ 7 (averring that MedQuest Pharmacy has "been informed that responsibility for [the information-gathering and reporting] process will be imposed on us by the Utah Board of Pharmacy and [the pharmacy's] licensing agency"). These statements are corroborated by comments made by regulators in a California State Board of Pharmacy meeting. See Cal. State Bd. of Pharmacy, Recording of Enforcement Committee Meeting Webcast (Part 2) at 27:55–28:26 (Jan. 20, 2021), available at https://www.youtube.com/watch?v=oQoo6bZckug (California State Board Executive Officer stating that "we will probably be recommending at the staff level that some of these reporting obligations actually get pushed to the licensees that are actually performing the compounding" and that "the NABP as part of their deployment of the [information-sharing] system was envisioning actually the compounding pharmacies doing a lot of the reporting").

Defendants do not contest the pharmacies' averments. They merely point out that States may rely on the NABP information-sharing network, which might "further minimize any potential information collection burden on States and pharmacies." Def. MSJ at 15. But the NABP information-sharing network is currently in a three-year pilot and, in defendants' own telling, "requires ongoing research to evaluate the system as well as a final report and assessment of the project." Id. at 9. And defendants nowhere explain *how* the NABP information-sharing network might reduce pharmacies' information-gathering and reporting obligations. Meanwhile, a "Frequently Asked Questions" of the NABP's webpage indicates that the system relies on information input by the *pharmacies* rather than the State agency. See Frequently Asked

Questions, NABP (including answers to questions such as, "Can the state solely rely on pharmacies entering information into the Information Sharing Network to identify pharmacies that distribute inordinate amounts of compounded human drug products interstate under the MOU?" and "How do compounding pharmacies submit the requested data?") available at https://nabp.pharmacy/members/compounding-pharmacy-information-sharing-project/faqs/ (last visited Sept. 20, 2021). The existence of the NABP information-sharing pilot project does not render plaintiffs' theory of injury speculative.

Moreover, plaintiffs have submitted declarations indicating that neither the pharmacies nor their regulators currently maintain information required by the Final Standard MOU in *any* format. See Mansour-Awad Decl. ¶ 8; Bray Decl. ¶ 7 ("discern[ing] and report[ing] the categories of information that are currently not required by our regulators but are required by the Final Standard MOU . . . will undoubtedly come at a sizable cost"); Besteman Decl. ¶ 7 ("we do not currently report that type of data to our regulators in the ordinary course of business"); Harbin Decl. ¶ 9 ("Adding the never-before-requested layer of information to our compliance practices would increase my reporting-compliance employee's workload by approximately four to six hours each workday."). Regardless of whether the State relies on an information-sharing network, pharmacies in MOU States will *at least* be required to start maintaining the information called for by the MOU for purposes of accurate collection and reporting. In sum, plaintiffs in States that sign the MOU have demonstrated a substantial risk that the MOU will cause them financial injuries stemming from its information collection and reporting obligations.

The Court next considers whether plaintiffs have established injury in fact based on Section 503A's five-percent limit. Again, any pharmacy located in a State that declines to sign the Final Standard MOU with FDA must abide by Section 503A's five-percent limit. See 21

U.S.C. § 353a(b)(3)(B)(ii). All plaintiffs have filed affidavits attesting that compliance with this limit would spell doom for their pharmacies. See Besteman Decl. ¶¶ 4–6 (compliance with the five-percent limit will drastically curtail if not ruin plaintiff's business); Bray Decl. ¶¶ 4–6 (same); Harbin Decl. ¶¶ 4–6 (same); Stuart Decl. ¶¶ 4–5 (same); Patel Decl. ¶¶ 4–6; Mansour-Awad Decl. ¶¶ 4–6 (same). Defendants argue that this injury, too, is overly speculative because it is unknown which States will sign the MOU. They also point out that FDA has announced its intent to extend its enforcement discretion of the five-percent limit until October 2022. See Notice of Subsequent Event, ECF No. 56. Thus, States have another year to decide whether to sign the MOU without subjecting their pharmacies to penalties associated with the five-percent limit.

For plaintiff Wellness Pharmacy in Alabama, the injuries associated with the five-percent restriction are clearly not speculative. That is because Alabama has *already* indicated that it will not sign the MOU. Wellness's president, Mr. Harbin, has attested to his understanding that "both the Alabama Board of Pharmacy . . . and [the] State's Attorney General are unconvinced that the Board has the requisite the authority to sign the Final Standard MOU." Harbin Decl. ¶ 3. The FDA's website confirms that Alabama is not participating in the MOU due to "[l]egal or [t]echnical reasons." See FDA Compounding MOU Project, NABP, available at https://nabp.pharmacy/members/compounding-pharmacy-information-sharing-project/#mou-map (last visited September 20, 2021).

Like his co-plaintiffs, Mr. Harbin anticipates that the five-percent restriction "would have a devastating effect on both the financial condition of [his] business and the wellbeing of [his] patients" because "the majority of prescriptions dispensed by Wellness Pharmacy are dispensed outside of Alabama[.]" Id. ¶ 4. Consequently, Mr. Harbin predicts that he would have to

"downsize [his] staff" or "close [his] business entirely." Id. Wellness Pharmacy has thus established an Article III injury based on Section 503A's five-percent limit.

In sum, plaintiffs fall into one of two groups. Either they will operate in a non-MOU State and face the five-percent limit and its corresponding economic injuries, or they will operate in an MOU-State and face the various compliance costs associated with its terms. Either injury suffices for Article III's injury-in-fact requirement.

b. Traceability

Defendants also maintain that the plaintiffs' injuries are not fairly traceable to the alleged legal violations. The Court first addresses this dispute as it relates to plaintiffs' procedural claims before turning to their statutory-authority claim.

"To establish traceability in a procedural-injury case, an adequate causal chain must contain at least two links: (1) a connection between the omitted procedure and a government decision and (2) a connection between the government decision and the plaintiff's particularized injury." Hawkins v. Haaland, 991 F.3d 216, 224 (D.C. Cir. 2021) (cleaned up). "The first link does not require the plaintiff to show that but for the alleged procedural deficiency the agency would have reached a different substantive result." WildEarth Guardians v. Jewell, 738 F.3d 298, 306 (D.C. Cir. 2013). All that is necessary is "some sort of connection between the procedural requirement at issue and the substantive action of the agency[.]" City of Waukesha v. E.P.A., 320 F.3d 228, 234–35 (D.C. Cir. 2003) (citing Fla. Audubon Soc. v. Bentsen, 94 F.3d 658, 668 (D.C. Cir. 1996)).

Count One of the complaint alleges that the Final Standard MOU imposes costly information-gathering and reporting obligations on the individual pharmacies. The substantive action (the Final Standard MOU) is thereby directly connected to the procedural requirement that

plaintiffs claim was omitted (the development of that MOU through regulations). Count Two alleges that FDA was required to conduct an analysis of the Final Standard MOU under the Regulatory Flexibility Act. Among other things, a Regulatory Flexibility Act analysis "must include an explanation for the rejection of alternatives designed to minimize significant economic impact on small entities[.]" U.S. Telecom Ass'n v. F.C.C., 400 F.3d 29, 42 (D.C. Cir. 2005). Plaintiffs aver that compliance with the terms of the Final Standard MOU will require hiring a new employee, which they say is a sizable burden for their pharmacies, considering that some are comprised of only twenty to thirty employees. See Mansour-Awad Decl. ¶ 2; Stuart Decl. ¶ 2. Plaintiffs' allegation under the Regulatory Flexibility Act is thus connected to the financial injuries stemming from compliance with the Final Standard MOU.

Defendants contend that the causal chain is broken by the independent decision-making of the States, given that FDA "ultimately has no control over any given State's decision to sign (and if so, how that State intends to carry out its agreed upon information and collection sharing)." Def. MSJ at 20. Not so. When a plaintiff's theory of standing depends on third-party decisions, it is her burden "to adduce facts showing that those choices have been or will be made in such manner as to produce causation and permit redressability of injury." Lujan v. Defs. of Wildlife, 504 U.S. 555, 562 (1992). "[M]ere 'unadorned speculation'" does not suffice. Am. Freedom L. Ctr. v. Obama, 821 F.3d 44, 49 (D.C. Cir. 2016) (quoting Nat'l Wrestling Coaches Ass'n v. Dep't of Educ., 366 F.3d 930, 938 (D.C. Cir. 2004)). Instead, the plaintiff must establish the third-party's conduct by a "substantial likelihood[.]" Competitive Enter. Inst., 970 F.3d at 384 (cleaned up). Courts may "consider a variety of evidence" when evaluating whether plaintiffs have carried this burden, "including the agency's own factfinding, affidavits submitted

by the parties, evidence in the administrative record," and "arguments firmly rooted in the basic laws of economics[.]" Id. at 382 (cleaned up).

As described above in the context of injury in fact, plaintiffs have submitted extensive evidence that States will sign the MOU and then pass along its information-gathering and reporting obligations to the pharmacies. Indeed, Colorado, in which plaintiff Belmar Pharmacy is located, has already signed the MOU. Additionally, all plaintiffs have submitted declarations attesting to their conviction that they will be required to undertake information-gathering and reporting obligations. See Bestman Decl. ¶¶ 7–9; Bray Decl. ¶¶ 7–9; Harbin Decl. ¶¶ 7–10; Stuart Decl. ¶¶ 6–8; Patel Decl. ¶¶ 7–11; Hill Decl. ¶¶ 7–11; Mansour-Awad Decl. ¶¶ 7–10. Certain declarants claim to have been told as much by their State Boards of Pharmacy, see Stuart Decl. ¶ 7; Harbin Decl. ¶ 7; Bray Decl. ¶ 7, and others have averred that they will shoulder a cost *regardless* of the State's implementation procedure because they simply lack the requisite information in their current practice, see Mansour-Awad Decl. ¶ 8; Bray Decl. ¶ 7; Stuart Decl. ¶ 7; Besteman Decl. ¶ 7; Harbin Decl. ¶¶ 7, 9. Taken together, this evidence carries plaintiffs' burden to prove that the States are substantially likely to pass along compliance costs imposed by the Final Standard MOU.

As to Count III, plaintiffs argue that FDA exceeded its statutory authority "by defining 'distribution of compounded human drug products interstate' and 'inordinate amounts' to include interstate dispensing of compounded human drug products." Compl. ¶ 100. (Again, plaintiffs construe "dispensing" to mean sending compound drugs to a customer pursuant to a prescription.) FDA's definitional choice, plaintiffs contend, will subject them to the five-percent limit and its attendant economic harms. By contrast, plaintiffs' preferred reading of the statute—that the FDA may regulate only the distribution of compound drugs without a prescription—

would not trigger the five-percent limit. The Court takes no position on the merits of plaintiffs' argument. But, assuming *arguendo* that they are correct, their alleged theory of injury stemming from the five-percent limit is directly traceable to the allegation lodged in Count III.

Defendants counter that the five-percent limit is statutory, so any injury caused by that restriction is attributable to Congress rather than FDA. Def. MSJ at 2, 19–20; see 21 U.S.C. § 353a(b)(3)(B)(ii) (five-percent limit). The Court disagrees. In developing the MOU, FDA defined "[d]istribution of compounded human drug products interstate'' to encompass any instance in which the "pharmacy or physician has sent (or caused to be sent) a compounded drug product out of the state in which the drug was compounded." A.R. 031443. Again, plaintiffs contend that *dispensing*—in the sense of sending out compounded drugs pursuant to a prescription—should be excluded from the meaning of *distribution*. FDA explicitly rejected that interpretation in the notice accompanying the Final Standard MOU. It explained:

> We received a number of comments on the 2015 draft standard MOU and the 2018 revised draft standard MOU stating that distributing and dispensing are mutually exclusive activities, such that if a drug product is distributed, it is not also dispensed, and vice versa. Some comments asserted, in particular, that a compounded drug product should not be considered to be "distributed" when it is provided pursuant to a prescription . . . . After considering these comments and the public health objectives of section 503A(b)(3)(B) of the FD&C Act, FDA considers that when a drug is picked up at the facility in which it was compounded, dispensing, but not distribution, occurs *for purposes of 503A(b)(3)(B).*

A.R. 031443–44 (emphasis added). Later on, FDA again rejected plaintiffs' distinction between dispensing and distribution by reference to how Congress identified those terms in Section 503A(b)(3)(B):

> Section 503A(b)(3)(B) of the FD&C Act does not define "distribution" to exclude dispensing . . . . Indeed, with respect to comments suggesting that drugs dispensed pursuant to prescriptions could not also be "distributed," we note that, in section 503A(b)(3)(B), Congress specifically contemplated that prescription orders could

> be 'distributed' when it directed the Agency to count the number of prescription orders that pharmacists and prescribers distributed.

Id. at 031444. At oral argument, defendants represented that they were unsure how FDA might interpret distribution for purposes of the five-percent restriction. See Oral Arg. Tr. at 42:23–43:02. But FDA has specifically declared that "Section 503A(b)(3)(B) of the FD&C Act," which contains the five-percent limit, "*does not define 'distribution' to exclude dispensing*." A.R. 031444. Meanwhile, the agency has nowhere indicated that it may interpret the terms otherwise.

For this reason, plaintiffs' declarations are consistent in stating that they will be injured by the five-percent limit "*as calculated by the FDA*." Harbin Decl. ¶ 4 (emphasis added); see also Bestman Decl. ¶ 5 ("[t]he 5-percent limit . . . *as that limit is calculated by FDA*, would have a grave impact on our overall business") (emphasis added); Bray Decl. ¶ 4 ("the effect on my business and our patients would be catastrophic if subjected to the 5-percent limit . . . *as that limit is calculated by FDA*") (emphasis added); Stuart Decl. ¶ 4 ("[t]he impact of the 5-percent limit . . . *as that limit is calculated by FDA*, would have dire consequences for our business") (emphasis added); Patel Decl. ¶ 5 ("[i]f subjected to the 5-percent limit . . . *as calculated by FDA*," plaintiff's "pharmacy will experience what is certain to be a precipitous decrease in revenue") (emphasis added); Hill Decl. ¶ 4 ("there is not a shred of doubt" that "the 5-percent limit . . . *as that limit is calculated by FDA*" would require plaintiff's pharmacy "to close its doors"); Mansour-Awad Decl. ¶ 5 ("the 5-percent limit . . . *as that limit is calculated by FDA*" will require "shutter[ing] the business . . . or drastically downsiz[ing]") (emphasis added).

Mr. Harbin of Wellness Pharmacy in Alabama, which has indicated that it will not sign the Final Standard MOU, explains that Wellness Pharmacy "does not send compounded drug products to patients without first receiving a patient-specific prescription, which is the act of

dispensing." Supp. Harbin Decl. at ¶ 2, ECF No. 54-1.[7] Therefore, his pharmacy would be in compliance with the five-percent restriction should FDA adopt plaintiffs' view that "distribution" is the act of sending out compounded drugs *without* a prescription. Id. That is so because Wellness Pharmacy *never* sends out compounded drugs without a prescription, which, again, plaintiffs' view as the only activity governed by the five-percent restriction. Id. Injuries associated with the five-percent restriction thus result from FDA's *interpretation* of the five-percent restriction in the MOU rather than the statutory restriction itself. Consequently, those injuries are attributable to the agency rather than Congress.

2. Ripeness

FDA also contends that plaintiffs' claims are not prudentially ripe. When evaluating whether a case is prudentially ripe, courts consider two factors: (1) "the fitness of the issues for judicial decision," and (2) "the hardship to the parties of withholding court consideration."

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[7] At oral argument, the Court asked plaintiffs' counsel whether they would be compliant with the five-percent restriction notwithstanding the Final Standard MOU. Oral Arg. Tr. 13:5–8. Counsel answered in the affirmative, explaining that "it's in the complaint . . . that they dispense pursuant to a patient-specific prescription. So notwithstanding [the MOU] definitions, . . . which include dispensing in the definition of 'distribution,' they would be compliant[.]" Id. at 13:9–14. Three days later, plaintiffs moved to file Mr. Harbin's supplemental declaration, which reiterates the point. Defendants oppose the motion, arguing that it is untimely without good cause. See Def. Opp. to Pl. Mot. for Leave to File Supp. Decl., ECF No. 55, at 2. The Court will consider the declaration. Plaintiffs may submit evidence after filing their opening briefs where "the parties reasonably, but mistakenly, believed that the initial filings before the court had sufficiently demonstrated standing[.]" Twin Rivers Paper Co. LLC v. Sec. & Exch. Comm'n, 934 F.3d 607, 614 (D.C. Cir. 2019) (cleaned up). As described above, every plaintiff in this case submitted a declaration averring that its injuries stemming from the five-percent restriction are dependent on FDA's interpretation of that provision. Likewise, plaintiffs' declarations and complaint allege that each pharmacy *dispenses* compounded drugs out of state pursuant to a prescription. Compl. ¶¶ 8–14. It was reasonable for plaintiffs to believe that they had sufficiently demonstrated that injuries associated with the five-percent restriction are traceable to FDA's interpretation of that provision. The Supplemental Harbin Declaration merely clarifies this point in response to the Court's questioning at oral argument.

Conservation Force, Inc. v. Jewell, 733 F.3d 1200, 1206 (D.C. Cir. 2013) (quoting Abbott Labs. v. Gardner, 387 U.S. 136,149 (1967)). The "basic rationale" for the prudential ripeness doctrine is "is to prevent the courts . . . from entangling themselves in abstract disagreements over administrative policies, and also to protect agencies from judicial interference until an administrative decision has been formalized and its effects felt in a concrete way by the challenging parties." Abbott Labs., 387 U.S. at 148–49. "[T]here is also a 'usually unspoken' underlying rationale relating to the doctrine of mootness: a claim may be unripe where 'if we do not decide [the claim] now, we may never need to.'" Alcoa Power Generating Inc. v. F.E.R.C., 643 F.3d 963, 967 (D.C. Cir. 2011) (quoting Devia v. Nuclear Regul. Comm'n, 492 F.3d 421, 424 (D.C. Cir. 2007)) (second alteration in original).

a. Fitness

An issue's "fitness" for judicial resolution "depends on whether it is purely legal, whether consideration of the issue would benefit from a more concrete setting, and whether the agency's action is sufficiently final." Devia, 492 F.3d at 424 (internal quotation marks omitted).

Again, plaintiffs bring three claims—one count alleging that FDA was statutorily required to develop the MOU through regulations, see Compl. ¶¶ 87–92, one count alleging that FDA failed to conduct an RFA analysis under 5 U.S.C. § 604(a), Compl. ¶¶ 93–98, and one count that FDA exceeded its statutory authority under Section 503A, Compl. ¶¶ 98–101. The first two counts are purely procedural challenges that require no further factual development for resolution. Nat'l Ass'n of Home Builders v. U.S. Army Corps of Eng'rs, 417 F.3d 1272, 1281, 1286 (D.C. Cir. 2005) ("Home Builders I") (claim that rule violated RFA's procedural requirements was ripe "at the time the alleged failure occurred, *i.e.*, when the [agency] issued the [rule] without complying with those procedures") see also Gen. Elec. Co. v. E.P.A., 290 F.3d

377, 380 (D.C. Cir. 2002) (claim that document was a legislative rule improperly issued without notice-and-comment was "largely a legal, not a factual, question, turning as it does in this case primarily upon the text of the [d]ocument"). Plaintiffs' claim that FDA exceeded its statutory authority in developing the MOU likewise satisfies the fitness prong. Home Builders I, 417 F.3d at 1281–82 (claim that agency "exceeded its statutory authority in drafting" permits under the Clean Water Act "easily satisfie[d]" the fitness prong of ripeness).

Defendants nonetheless contend that this case is not ripe because "[i]t is not yet known" which States "will sign the Final Standard MOU." Def. MSJ at 13. This argument is unpersuasive. As discussed in the injury-in-fact context, plaintiff Belmar Pharmacy is *already* subject to the terms of the MOU because it is located in Colorado, which has executed a Final Standard MOU. See Notice of Subsequent Event, ECF No. 51; see also MOU 225-21-014 (July 2, 2021, available at https://www.fda.gov/about-fda/compounding-mous/mou-225-21-014. On the other side of the coin, plaintiff Wellness Pharmacy is located in Alabama, which FDA has indicated will *not* sign the Final Standard MOU for "legal or technical" reasons. See NABP, MOU Participation, available at https://nabp.pharmacy/members/compounding-pharmacy-information-sharing-project/ (last visited Sept. 20, 2021). So, while the complete roster of MOU- and non-MOU states has yet to materialize, these developments have fixed the legal consequences of the MOU for at least some plaintiffs.

Regardless, the fitness prong is concerned with whether judicial "consideration of the issue would *benefit* from a more concrete setting[.]" Devia, 492 F.3d at 424 (emphasis added). Though defendants have pointed out some degree of factual uncertainty, they have not identified any reason to delay judicial review until that uncertainty disappears completely. The Circuit rejected a similar ripeness argument in Home Builders I, where the plaintiffs challenged the

conditions contained in general permits developed for certain development projects by the Army Corps of Engineers. 417 F.3d at 1281. The Corps argued that the claims were unripe because plaintiffs had not yet applied an individual permit, which, if approved, would render them unaffected by the conditions in the general permits. Id. at 1282. The Circuit disagreed because "[n]o further factual development [was] necessary to evaluate the [plaintiffs'] challenge." Id. So too here.

b. Hardship

Given the Court's conclusion that plaintiffs' challenges are fit for judicial review, it need not consider the hardship prong of the ripeness inquiry. See Teva Pharms. USA, Inc. v. Sebelius, 595 F.3d 1303, 1310 (D.C. Cir. 2010); see also Nat'l Ass'n of Home Builders v. U.S. Army Corps of Engineers, 440 F.3d 459, 465 (D.C. Cir. 2006) (where "there are no significant agency or judicial interests militating in favor of delay, lack of hardship cannot tip the balance against judicial review") (cleaned up). The Court nonetheless concludes that plaintiffs have demonstrated that hardship would result from delayed judicial consideration. The focus of the hardship prong is "not whether the parties have suffered any direct hardship, but rather whether *postponing* judicial review would impose an undue burden on them or would benefit the court." Vill. of Bensenville v. F.A.A., 376 F.3d 1114, 1120 (D.C. Cir. 2004). Defendants contend that this case would not be ripe until after the deadline has passed for States to sign the MOU, or (later still) until some point *after* States have ironed out the implementation of the MOU's terms. The Court disagrees.

Delaying judicial consideration until either point would put plaintiffs in an untenable position. In non-signatory States, a delay would force plaintiffs to either shutter their businesses, see Harbin Decl. ¶ 5, or risk civil and criminal penalties by flouting applicable laws, see 21

U.S.C. § 331(a) (prohibiting the "introduction or delivery for introduction into interstate commerce of any . . . drug . . . that is adulterated or misbranded"); id. at § 333(a) ("Any person who violates a provision of section 301 [of the FDCA, 21 U.S.C. § 331] shall be imprisoned for not more than one year or fined not more than $1,000, or both."). "To use the Supreme Court's words, we 'normally do not require plaintiffs to bet the farm' by violating the law in order to challenge the constitutionality of the regulating agency." State Nat'l Bank of Big Spring v. Lew, 795 F.3d 48, 54 (D.C. Cir. 2015) (quoting Free Enter. Fund v. Public Co. Acct. Oversight Bd., 561 U.S. 477, 490 (2010)). Meanwhile, pharmacies located in signatory States (such as Belmar Pharmacy in Colorado) would be forced to continue expending resources on the MOU's information-gathering and reporting requirements until other States determine whether they will sign and, if so, the manner in which they will comply with the MOU's terms. Plaintiffs have thus satisfied the hardship prong of ripeness.

B. Merits

Having assured itself of its jurisdiction to hear this case, the Court turns to the merits of plaintiffs' allegations. In the first two counts, plaintiffs allege that FDA failed to promulgate the MOU by regulations as required by Section 503A and failed to conduct an analysis of the MOU's impact on small entities as required by the Regulatory Flexibility Act. Compl. ¶¶ 87–92 (Count I), ¶¶ 93–97 (Count II). And in Count III, plaintiffs contend that FDA exceeded its statutory authority by defining "distribution of compounded human drug products interstate" and "inordinate amounts" to include sending compounded drugs interstate pursuant to a prescription. Id. ¶¶ 98–101. Because the Court concludes that the MOU is subject to the Regulatory Flexibility Act, it will remand the rule to the agency without deciding the remaining counts.

The Regulatory Flexibility Act requires an agency issuing a final rule to either conduct "an analysis of the rule's impact on small businesses," Nat'l Tel. Co-op. Ass'n v. F.C.C., 563 F.3d 536, 538 (D.C. Cir. 2009), or to "certify" that there will be "no impact for those small businesses that are subject to the regulation," Cement Kiln Recycling Coal. v. E.P.A., 255 F.3d 855, 869 (D.C. Cir. 2001) (internal quotation marks omitted). See 5 U.S.C. § 605. Defendants do not dispute that plaintiffs qualify as small businesses under the Act and that they are "subject to" the MOU under § 605(b).

Nor do defendants contend that they conducted a regulatory flexibility analysis or certified an analysis to be unnecessary. Instead, defendants pin their hopes on the contention that the MOU is an interpretive rule and is therefore not subject to the requirements of the Act. See Nat'l Ass'n for Home Care v. Shalala, 135 F. Supp. 2d 161, 164 (D.D.C. 2001) ("[I]nterpretive rules, because they are exempted from the APA's notice and comment procedures, are exempted from the RFA's strictures as well."). Plaintiffs counter that the MOU falls within the Regulatory Flexibility Act's compass because it is a legislative rule. Plaintiffs have the better of this dispute.

"The line between interpretive and legislative rules is fuzzy and enshrouded in considerable smog." Nat. Res. Def. Council v. Wheeler, 955 F.3d 68, 83 (D.C. Cir. 2020) (internal quotation marks omitted). That said, "a basic taxonomy" emerges from the D.C. Circuit's decisions on the divide. Id. On one hand, "[a] legislative rule is one that has legal effect or, alternately, one that an agency promulgates with the intent to exercise its delegated legislative power by speaking with the force of law." Id. (cleaned up). On the other hand, "[a]n interpretive rule . . . derives a proposition from an existing document, such as a statute, regulation, or judicial decision, whose meaning compels or logically justifies the proposition." Id. (cleaned up). Whereas legislative rules "effect a substantive change in existing law or

policy," interpretive rules "clarify a statutory or regulatory term, remind parties of existing statutory or regulatory duties, or merely track preexisting requirements and explain something the statute or regulation already required." Mendoza v. Perez, 754 F.3d 1002, 1021 (D.C. Cir. 2014) (cleaned up).

The Final Standard MOU falls on the legislative side of the line. By defining key statutory terms in Section 503A that have binding legal consequences, FDA has evinced its intent to speak with the force of law in the MOU. For starters, the MOU defines "distribution" to incorporate the act of sending compounded drug products interstate pursuant to a prescription. See A.R. 031450–51. This same term is used in § 353a(b)(3)(B)(ii), which, in non-MOU States, limits pharmacies' compounded drug "distribut[ion]" to five-percent of their "total prescription orders dispensed or distributed[.]" Determining what activity counts as "distribut[ion]" for purposes of calculating this five-percent threshold matters, because violation of that restriction carries civil and criminal penalties. See 21 U.S.C. §§ 303, 331(a), 333(a); see also A.R. 028750, (guidance document advising that any pharmacy that compounds in violation of Section 503A may be subject to criminal prosecution).

The declarations submitted in this case illustrate the legal consequences created by the MOU. Take plaintiff Wellness Pharmacy. It has been operating a compounding business for fifty-seven years in Alabama, which has indicated that it will not sign the Final Standard MOU. Harbin Decl. ¶¶ 2–3. Under plaintiffs' view of "distribution"—which *only* encompasses instances in which a compounded drug has been sent out *without* a prescription—Wellness Pharmacy would be compliant with Section 503A *regardless* of whether Alabama signs because it *exclusively* sends out drugs pursuant to prescriptions. See Supp. Harbin Decl. ¶ 2. Under FDA's interpretation, however, all compounding orders that Wellness Pharmacy ships out of

state will be counted towards the five-percent restriction under § 353a(b)(3)(B)(ii). Because out-of-state prescription orders constitute the majority Wellness Pharmacy's business, Harbin Decl. ¶ 4, the pharmacy would quickly find itself in violation of § 353a(b)(3)(B)(ii) and subject to its corresponding penalties.

Resisting the conclusion that the Final Standard MOU carries legal consequences, defendants urge the Court to instead treat the MOU as an interpretive rule. In doing so, they insist that the MOU "does not impose any penalties or define any violations of the law," Def. Reply at 16 n.7, that by its terms it "does not create or confer any rights," A.R. 031448, and that its defined terms are limited to the "purposes of th[e] MOU," id. at 031456.[8] This argument is unavailing. As discussed in the context of standing, FDA explained its interpretation of "distribution" versus "dispensing" as follows:

> FDA considers that when a drug is picked up at the facility in which it was compounded, dispensing, but not distribution, occurs *for purposes of 503A(b)(3)(B)* . . . . FDA is not persuaded by comments urging the Agency to interpret "distribution" and "dispensing" to be entirely separate activities *for purposes of section 503A(b)(3)(B) of the FD&C Act*. These comments . . . generally conclude that distribution does not include the transfer of a drug pursuant to a prescription.

A.R. 031443–44 (emphases added). In other words, FDA explicitly rejected plaintiffs' interpretation of distribution, *not only* for the MOU *but also* "*for purposes of [§] 503A(b)(3)(B)*."

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[8] As FDA concedes, an MOU (at least in the abstract) cannot be "neatly categorized" within the APA's taxonomy of interpretive rules, legislative rules, and policy statements. See Oral Arg. Tr. at 41:06-07. The case law bears this out. Contrast W. Virginia Mining and Reclamation Ass'n v. Snyder, No. 91–0123–W(S), 1991 WL 331482 (N.D. W. Va. 1991) (MOU was a legislative rule) with Ranchers Cattlemen Action Legal Fund United Stockgrowers of Am. v. Vilsack, 6 F.4th 983, 991 n.8 (9th Cir. 2021) (MOU was not a legislative rule); Reynolds Metals Co. v. Rumsfeld, 564 F.2d 663 (4th Cir. 1977) (same); and Defs. Of Wildlife v. Tuggle, 607 F. Supp. 2d 1096 (D. Ariz. 2018) (same). Accordingly, Courts must look to the substance of an MOU, rather than its label, when categorizing it as either an interpretive or legislative rule.

A.R. 031444 (emphasis added). Section 503A(b)(3)(B), importantly, contains the five-percent limit. See 21 U.S.C. § 353a(b)(3)(B)(ii).

Regardless, the MOU's definition of an inordinate amount of interstate distribution necessarily extends beyond the four corners of the agreement. That is so because that language is precisely what defines the scope of FDA's authority to develop a standard MOU in the first instance. Section 503A instructs the Secretary to develop an MOU that "addresses *the distribution of inordinate amounts of compounded drug products interstate*." 21 U.S.C. § 353a(b)(3)(B)(i) (emphasis added). In the MOU, FDA has thus simultaneously defined the phrase for the purposes of *both* the MOU *and* delineating its authority to develop that MOU under Section 503A. And by developing the MOU, FDA has implemented its authority under § 353a(b)(3)(B)(i) to entitle certain pharmacies to distribute compounded drugs exempt from the FDCA's new drug laws. Legislative rules "are those that grant rights, impose obligations, or produce other significant effects on private interests." Home Builders I, 417 F.3d at 1285. The Final Standard MOU does precisely that.

This point is underscored by defendants' position that the five-percent restriction is enforceable under § 353a(b)(3)(B)(ii) regardless of whether a Final Standard MOU exists under § 353a(b)(3)(B)(i). Oral Arg. Tr. 42:4–9. In defendants' telling, compounding drugs in excess of § 353a(b)(3)(B)(ii)'s five-percent limit was necessarily illegal for *all* pharmacies from 1997 through the issuance of the Final Standard MOU in October 2020. Through the Final Standard MOU, FDA has exercised its authority under Section 503A to entitle certain pharmacies to lawfully exceed this limit for the first time in over two decades. Far from having clarified a pre-existing rule or policy, the Final Standard MOU has thereby "effect[ed] a substantive change in

existing law or policy[.]" POET Biorefining, LLC v. Env't Prot. Agency, 970 F.3d 392, 407 (D.C. Cir. 2020).

To be sure, "even a consequential, conduct-altering rule remains interpretive so long as it can fairly be viewed as interpreting—even incorrectly—a statute or regulation." Id. at 408. An agency thus performs an interpretative function when it has "derive[d] a proposition from an existing document whose meaning compels or logically justifies the proposition." Mendoza, 754 F.3d at 1021 (cleaned up). By contrast, "[a]n agency performs a legislative function when it makes reasonable but arbitrary (not in the 'arbitrary or capricious' sense) rules that are consistent with the statute or regulation under which the rules are promulgated but not derived from it, because they represent an arbitrary choice among methods of implementation." Cath. Health Initiatives v. Sebelius, 617 F.3d 490, 495 (D.C. Cir. 2010). The Final Standard MOU rests in the latter camp.

Tellingly, defendants have not argued that Section 503A compels or logically justifies the MOU and its interpretation of "distribute" and "inordinate amounts." Any such argument would fail. Most importantly, the MOU reduces the phrase "inordinate amounts" to a numeric 50-percent threshold. "When agencies base rules on arbitrary choices they are legislating," and "[a] rule that turns on a number is likely to be arbitrary in this sense." Cath. Health Initiatives, 617 F.3d at 495 (quoting Hoctor v. U.S. Dep't of Agric., 82 F.3d 165, 171 (7th Cir. 1996)). Section 503A nowhere suggests that inordinate amounts of interstate distribution means anything greater than 50 percent. While this figure may well be *consistent* with the statutory language, it is nonetheless an arbitrary choice. Nor does Section 503A compel FDA's present interpretation of what instances of compounding should be counted towards that 50-percent figure.

The realm of potential options available to FDA is perhaps best illustrated by the various MOUs that the agency has proposed over the years. In 1999, the initial draft of the MOU concluded that a pharmacy distributed an inordinate amount of compounded drugs interstate when the number of compounded drugs dispensed or distributed interstate constituted 20 percent of the pharmacy's dispensed or distributed drugs. A.R. 000014. However, "local" interstate distribution, in which a compounded drug was given to an out-of-state patient located within fifty miles of the pharmacy, was excluded from that 20-percent figure. Id. at 000015.

Sixteen years later, FDA raised this threshold to 30 percent and removed the carve-out for "local" distribution, having determined that "special calculations to address interstate distribution between contiguous States or over short distances [were] not needed." Id. at 028755. Instead, the 2015 draft MOU excluded instances in which patients picked up compounded drugs in person and subsequently carried them interstate. Id. Three years later, FDA changed course again, increasing the threshold from 30 percent to 50 percent of the pharmacy's total compounded (but not non-compounded) drug orders. Id. at 030851.

Finally, in the present draft, FDA settled on the following definition: a pharmacy has distributed an inordinate amount of compounded drugs interstate when the number of compounded drugs distributed interstate is greater than 50 percent of the total number of compounded drug orders sent out of the pharmacy *plus* the total number of compounded drugs "dispensed (e.g., picked up by a patient) at the facility[.]" Id. at 031450-51. In other words, FDA has concluded that a pharmacy is an inordinate interstate distributor of compounded drugs if over half of the pharmacy's total compounding business is interstate. Additionally, FDA determined that—unlike prior draft MOUs—the threshold for inordinate distribution should be

based on the pharmacy's annual rather than monthly business in order to account for any "significant monthly fluctuations[.]" Id. at 031443.

The Final Standard MOU constitutes one choice among many available to FDA when implementing Section 503A. Its ultimate decision has significant binding legal consequences for plaintiffs and pharmacies across the country, and it signals a substantive change in the current legal regime governing interstate compounding.[9] The Final Standard MOU is therefore a legislative rule. As a result, FDA was required to comply with the Regulatory Flexibility Act before issuing it. It did not. The Court, accordingly, will remand the MOU to FDA to either prepare a regulatory flexibility analysis, 5 U.S.C. §§ 603–604, or to certify that the MOU "will not . . . have a significant economic impact on a substantial number of small entities," id. § 605(b). See id. § 611(A). The Court will request a progress report from the agency within sixty days.

[9] To be clear, this ruling says nothing on the merits of Count One, which claims that Section 503A required the Secretary to develop the Final Standard MOU by issuing regulations. That claim would require the Court to accept plaintiffs' argument that Section 503A's general admonition that "[t]he Secretary shall issue regulations to implement this section," 21 U.S.C. § 353a(c)(1), overrides—and is exclusive of—the statute's more specific instruction that "[t]he Secretary shall, in consultation with the National Association of Boards of Pharmacy, develop a standard memorandum of understanding for use by the States," id. § 353a(b)(3)(B)(ii). Nor does the Court express an opinion on the statutory-authority claim presented in Count Three. Additionally, the Court's conclusion that the Final Standard MOU constitutes a legislative rule does not require FDA to now conduct notice-and-comment rulemaking. As stated previously, plaintiffs have abandoned their notice-and-comment claim in recognition of the fact that FDA *did* in fact develop the Final Standard MOU through several rounds of notice and comment. See Oral Arg. Tr. 19:11–17 ("Our position is that FDA did consider 30,000 comments, and that if we brought a notice and comment challenge, it could have been subject to a harmless error [test]. And, therefore, we brought the procedural claims that have actually injured us[.]").

IV. Conclusion

For the foregoing reasons, the Court will grant Plaintiffs' Motion for Summary Judgment in part. A separate Order will follow.

CHRISTOPHER R. COOPER
United States District Judge

Date: September 21, 2021

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August 17, 2020

By Electronic Mail

U.S. Food & Drug Administration
Department of Health and Human Services
Compounding of Human Drug Products Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act; Establishment of a Public Docket
Docket No. FDA-2015-N-0030

RE: The National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy"

To Whom It May Concern:

We hereby submit this comment to the U.S. Food & Drug Administration ("*FDA*" or "*Agency*") on behalf of a coalition of traditional compounding pharmacies and FDA-registesred outsourcing facilities (the "*Coalition*") and request that FDA reject the conclusions and recommendations published by The National Academies of Sciences, Engineering, and Medicine ("*NASEM*") in its report titled *The Clinical Utility of Compounded Bioidentical Hormone Therapy: A Review of Safety, Effectiveness, and Use* (the "*Report*"). FDA cannot adopt the Report or rely on it in any way, because the Report patently fails to represent an independent perspective and is rooted in striking biases. As such, the adoption thereof not only threatens to violate the statutory requirements for federal advisory committees set forth in the Federal Advisory Committee Act ("*FACA*"), but will also prohibit ***millions*** of men and women across the U.S. from receiving the treatment they need.[1]

This Report is evidence of yet another public attempt by FDA to discredit critical and life-sustaining compounded hormone therapies in the eyes of the public in favor of FDA-approved hormone therapies. FDA's disdain for compounded hormone therapies appears to have begun in 2002, after a finding by the Women's Health Initiative that FDA-approved hormone medications raised the risk of heart disease, blood clots, and certain cancers.[2] To overcome the negative press, FDA engaged in a series of

[1] The NASEM Committee acknowledges four times throughout its Report that compounded hormone therapy is used by millions of men and women. *See* National Academies of Sciences, Engineering, and Medicine, *The clinical utility of compounded bioidentical hormone therapy: A review of safety, effectiveness, and use*, pages 1, 18, 219, 227, (2020) (hereinafter referred to as the "*Report*").

[2] S*ee* Hormone Therapy Trials (HT), Women's Health Initiative, https://www.whi.org/about/SitePages/HT.aspx (last visited August 17, 2020) ("The WHI Hormone Therapy Trials (HT) were designed to test the effects of postmenopausal hormone

public endeavors designed to discredit compounded bioidentical hormone replacement therapy ("*cBHRT*"), which included initiating enforcement action against seven pharmacies that compounded cBHRT in 2008.[3] Two days after initiating such enforcement actions, FDA responded favorably to a Citizen's Petition submitted by a commercial manufacturer of FDA-approved hormone replacement therapy products asking that FDA take action against compounders of cBHRT.[4] In addition, FDA published press releases and participated in a press conference touting its position against cBHRT. In doing so, FDA garnered cross-country news headlines such as, "*FDA Warns Against Bio-Identical Hormone Therapy*,"[5] "*FDA cracks down on makers of 'bioidentical' hormones*,"[6] and "*FDA Warns Pharmacies On Hormone Claims*,"[7] among so many others.

Notwithstanding FDA's attempts to discredit cBHRT, physicians across the country continued to see the benefits of cBHRT and its positive effects on their patients, particularly with women suffering from a broad range of menopause symptoms. Over the next ten years, more and more physicians around the country began treating their patients with cBHRT. As a result, in fall 2018, FDA commissioned NASEM to appoint an ad hoc committee (the "*NASEM Committee*") to examine the clinical utility of treating patients with cBHRT. The NASEM Committee held a series of open and closed sessions from March 2019 to April 2020, to examine data, research, and stakeholder input in order to form conclusions and recommendations regarding the clinical utility of cBHRT (the "*Study*"). On July 1, 2020, the NASEM Committee published its Report, wherein it concluded that there is a lack of high-quality clinical evidence to demonstrate the safety and effectiveness of cBHRT and, accordingly, that there is insufficient evidence to support the overall clinical utility of cBHRT as treatment for menopause and male hypogonadism symptoms.[8] In light of this supposed dearth of evidence to support the marketed claims for the clinical utility of cBHRT, the NASEM Committee recommended restricted use of cBHRT, assessments of their difficulty to compound, and additional education, state and federal regulatory oversight, and research.[9]

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therapy on women's risk for coronary heart disease (primary analyses) and on hip and other fractures and breast cancer (secondary analyses). The effects of hormone therapy on endometrial cancer was also evaluated in women with a uterus.).

[3] On January 7, 2008, FDA issued Warning Letters to seven compounding pharmacies (Panorama Compounding Pharmacy, Saint John's Medical Plaza Pharmacy, Murray Avenue Apothecary, Pharmacy Compounding Specialties, Reed's Compounding Pharmacy and Pacifica Pharmacy) based on the Agency's determination that these pharmacies were providing false and misleading information about compounding with estriol.

[4] On January 9, 2008, two days after initiating enforcement action against seven compounding pharmacies, FDA responded to Wyeth Pharmaceuticals' Citizen Petition.

[5] Steven Reinberg, *FDA Warns Against Bio-Identical Hormone Therapy*, The Washington Post, January 9, 2008.

[6] Liz Szabo and Julie Appleby, *FDA Cracks Down On Makers Of 'Bioidentical' Hormones*, USA Today, January 10, 2008.

[7] Anna Wilde Mathews and Sarah Rubenstein, *FDA Warns Pharmacies On Hormone Claims*, Wall Street Journal, January 10, 2008.

[8] Report, at 9. Please note that despite the dozens of disease states that physicians prescribe cBHRT to address, the NASEM Committee only considered two disease states to be of "substantial patient interest:" menopause and male hypogonadism symptoms.

[9] In total, the NASEM Committee made six recommendations to FDA: (1) Restrict the use of compounded bioidentical hormone therapy (cBHRT) preparations; (2) Review select bioidentical hormone therapies and dosage forms as candidates for the U.S. Food and Drug Administration (FDA) Difficult to Compound List; (3) Improve education for prescribers and pharmacists who market, prescribe, compound, and dispense compounded bioidentical hormone therapy (cBHRT) preparations; (4) Additional federal and state-level oversight should be implemented to better address public health and clinical concerns regarding the safety and effectiveness of compounded bioidentical hormone therapy (cBHRT); (5) Collect and disclose conflicts of interest;

The Report is just the latest chapter in a long battle initiated by FDA against compounders that specialize in cBHRT and the physicians and patients they serve. From its inception, the Study was not independent and demonstrated extraordinary bias, including gender bias. Accordingly, as set forth in greater detail below, FDA must reject the Report in its entirety for the following reasons:

- **FDA stacked the deck against the compounding industry by steering the NASEM Committee to conclude that cBHRT has no clinical utility and may be too difficult to compound**. FDA unfairly and inappropriately influenced the NASEM Committee's conclusions and recommendations to discredit cBHRT because it is not FDA-approved. The Federal Food, Drug, And Cosmetic Act ("*FDCA*") via the Drug Quality Security Act ("*DQSA*") exempts compounds like cBHRT from the new drug approval process, meaning FDA cannot evaluate compounded medication for its perceived clinical utility (i.e., for safety and effectiveness). FDA cannot therefore circumvent its governing federal statute and effectively force cBHRT through new drug approval via this commissioned Study.

- **The Study was predicated on multiple forms of bias**. In a review of who comprised the NASEM Committee, the materials the NASEM Committee chose to consider, and the organizations that provided data for the Study, it is clear that the scales were tipped far in favor of Big Pharma. The NASEM Committee also heavily relied on studies that it claimed demonstrated "methodologic rigor," which have traditionally used the male body as the default and excluded women, and are therefore rooted in striking gender bias. These multiple forms of bias seriously call into question the credibility of the Report and the NASEM Committee's conclusions and recommendations.

- **FDA's adoption or use of the Report violates FACA**. FACA requires membership of an advisory committee to be fairly balanced, and it also prohibits a federal agency from managing or controlling an advisory committee. In this case, FDA so heavily influenced the NASEM Committee and its conclusions and recommendations that FDA, in essence, managed and controlled the NASEM Committee. Jane Axelrad's involvement, as well as the active measures FDA took to control the outcome of the Study, demonstrate FDA's undue influence over the NASEM Committee and its results. Accordingly, FDA may not adopt the Report without violating FACA.

Nonetheless, even if FDA accepts the Report at face value and considers adopting the recommendations therein, we strongly discourage FDA from engaging the Pharmacy Compounding Advisory Committee ("*PCAC*") for any evaluation of whether a bioidentical hormone in any form, including pellet form, should be a candidate for FDA's Difficult to Compound List. It appears that PCAC itself is in violation of FACA for failing to be fairly balanced in the points of view represented and the functions it performs and is therefore in no position to be evaluating whether hormone therapies or categories thereof should be included on FDA's Difficult to Compound List. Further, should PCAC place

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and (6) Strengthen and expand the evidence base on the safety, effectiveness, and use of compounded bioidentical hormone therapy (cBHRT) preparations. Report, at 5.

certain bioidentical hormones and pellets on the Difficult to Compound List, this will have devastating effects on the health and wellbeing of the ***millions*** of patients treated with cBHRT.

We therefore urge FDA to disregard the Report in its entirety, as FDA cannot follow any of the NASEM Committee's recommendations without running afoul of FACA, acknowledging its undue influence over the Study, and endorsing the Report's clear gender and other biases.

I. FDA Stacked The Deck Against The Compounding Industry By Steering The NASEM Committee To Conclude That cBHRT Has No Clinical Utility And May Be Too Difficult To Compound.

FDA can neither accept the NASEM Committee's conclusions nor adopt its recommendations because FDA unfairly influenced the NASEM Committee in order to achieve its goals of discrediting cBHRT. FDA steered the NASEM Committee to conclude that cBHRT has no clinical utility and may be too difficult to compound. FDA did so in the following key ways: (1) by influencing the NASEM Committee's definition of "clinical utility" in such a way that it effectively forces compounds through the new drug approval process, a process from which compounds are statutorily exempt; (2) by furthering its public campaign designed to discredit cBHRT; and (3) by indirectly encouraging the dominance of presenter and Report reviewer Jane Axelrad—who, as the former FDA lead on compounding for 21 years, ***is*** FDA on compounding issues.

First, FDA's influence over the NASEM Committee's definition of "clinical utility" holds compounded cBHRT to new drug approval standards that compounds were never designed to meet and effectively allows FDA to inappropriately practice medicine. As a result of the ***FDA***-submitted literature, including peer-reviewed articles, consumer surveys, and formal position statements and guidelines, the NASEM Committee chose to define "clinical utility" as, "a multidimensional construct that reflects evidence about ***safety, effectiveness***, therapeutic need, and patient preference concerning benefit-risk balance."[10] This definition mirrors the language in Section 355 of the FDCA, which sets out requirements for drugs that go through FDA's new drug approval process. Specifically, Section 355 states that an application for new drug approval must contain, among other things, "full reports of investigations which have been made to show whether or not such drug is ***safe for use and whether such drug is effective in use*** . . . ." 21 U.S.C. § 355(b)(1)(A) (emphasis added). In other words, both the Committee's definition of "clinical utility" and FDA's threshold for new drug approval require the same evidence of ***safety and effectiveness***.

Compounded medication is not just a poor fit for new drug approval but is, in fact, wholly exempt from FDA's new drug approval requirements. Drugs compounded in compliance with Section 503A and Section 503B of the FDCA are statutorily exempt from compliance with Section 355. 21 U.S.C. § 353a(a); 21 U.S.C. § 353b(a). As a result, compounded medications need not, do not, and ***cannot***, provide the kind of "safety and effectiveness" data normally expected for FDA new drug approval. FDA, the industry, and the Courts have long acknowledged that compounded medications are not designed to go through FDA's new drug approval process, as "it would not make sense to require compounded drugs created to meet the unique needs of individual patients to undergo the testing required for the new drug approval process."

[10] Report, at x (emphasis added).

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Thompson v. W. States Med. Ctr., 535 U.S. 357, 369 (2002).[11] Nevertheless, in defining "clinical utility" as it did, and in using that definition as the guiding principle throughout the Report, the NASEM Committee, under clear direction from FDA, fashioned a threshold that compounded preparations, and cBHRT in particular, ***cannot meet***. It can come as no surprise then that the NASEM Committee reached the conclusions that it did—namely, that there is a lack of high-quality clinical evidence, akin to studies submitted in the new drug approval process, to demonstrate the safety and effectiveness of cBHRT.

Additionally, the NASEM Committee's definition of "clinical utility" allows FDA to practice medicine—which the Agency is well aware it cannot do. As set out above, at FDA's influence, the NASEM Committee defined "clinical utility" as a construct that reflects evidence about, among others, "***therapeutic need***."[12] The NASEM Committee clarified that, "[i]n the context of this report, therapeutic need relates to the treatment of menopausal and male hypogonadism symptoms."[13] In other words, at the request and sponsorship of FDA, the NASEM Committee is evaluating whether a certain medication (i.e., cBHRT) treats two specific disease states—***this is the practice of medicine***, and the practice of medicine lies wholly outside the scope of FDA's purview. Physicians—not FDA—are to determine which medication is appropriate to prescribe to best treat their patients. In commissioning NASEM to examine the "clinical utility" of treating patients with cBHRT, FDA effectively inserted itself into the decision-making process between a physician and his or her patient and called into question physicians' judgement as to the use of cBHRT for treatment.

Numerous courts have held that ***FDA does not have the legal authority to regulate the practice of medicine*** and even FDA has, in the past, acknowledged that it has no such authority.[14] During FDA's 2008 challenge to cBHRT, Kathleen Uhl, then Assistant Commissioner, Office of Women's Health at

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[11] *See also Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 398 (5th Cir. 2008); *United States v. Franck's Lab, Inc.*, 816 F. Supp. 2d 1209, 1243 (M.D. Fla. 2011), order vacated, appeal dismissed, No. 11-15350 (11th Cir. Oct. 18, 2012).

[12] Report, at x (emphasis added).

[13] *Id.* at 4.

[14] "In the legislative debates that led up to the enactment of the Food, Drug, and Cosmetic Act of 1938 (FDCA), Congress expressed a concern that the statute not interfere with the practice of medicine. In the course of passing the Drug Amendments of 1962, Congress reiterated this point." Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 U. Kan. L. Rev. 149, 173 (2004) (citing Ch. 675, 52 Stat. 1042 (codified as amended at 21 U.S.C. §§ 301-397 (2000)); S. Rep. No. 87-1552, at 1998 (1962) ("[T]he ... [Act] should not interfere with the professional function of the physician. FDA clearance would assure physicians that a drug effectively produces certain physiological actions, but the physician, not the FDA, would determine whether these specific physiological effects would be useful or beneficial with respect to particular patients."); 78 Cong. Rec. 2728 (1934) (statement of Sen. Copeland) (responding to fears that the proposed legislation would interfere with the "prerogatives of the doctor" by emphasizing that the revised bill "makes certain that the medical practitioner shall not be interfered with in his practice")). Further, FDA has also stated in proposed rulemaking that, "[t]hroughout the debate leading to the enactment [of the FDCA], there were repeated statements that Congress did not intend the Food and Drug Administration to interfere with medical practice and references to the understanding that the bill did not purport to regulate the practice of medicine as between the physician and the patient." *United States v. Evers*, 643 F.2d 1043, 1048 (5th Cir. 1981) (quoting 37 FR 16503). FDA has acknowledged during the course of proposing a rule to address labeling of prescription drugs that "it is clear that Congress did not intend the Food and Drug Administration to regulate or interfere with the practice of medicine . . . ." 37 FR 16,503, 16,504 (Aug. 15, 1972). And, Dr. Janet Woodcock, former Director of FDA's Center for Drug Evaluation and Research, testified before Congress that "FDA does not generally regulate the practice of pharmacy or the practice of medicine—the States traditionally have regulated both the prescribing and dispensing of drugs." *Drugstores on the Net: The Benefits and Risks of On-Line Pharmacies: Hearing Before the Subcomm. on Oversight & Investigations of the House Comm. on Commerce*, 106th Cong. 99 (1999) (statement of Dr. Janet Woodcock, Director of the FDA's Center for Drug Eval. & Research).

FDA, stated that "the discussion is really between the woman and her health care provider to make a decision what the appropriate therapy for treatment of her menopausal symptom" and "what's the appropriate therapy for each individual women is really a conversation between her and her doctor."[15] So, even in the context of prescribing cBHRT, FDA ***knows*** it must step out of the room. Physicians are free to prescribe cBHRT if, in their professional medical judgment, they determine that it is appropriate to treat their patients. By commissioning the Study, FDA is circumventing its defined authority and calling into question physicians' endorsement of cBHRT for the treatment of their patients.

Further, FDA continued its targeted public media campaign designed to influence the Report as well as the public's perception of cBHRT. FDA has been critical of cBHRT for many years and, as stated above, prior to commissioning the Study, had engaged in a concerted campaign ***against*** compounders of cBHRT. At least as early as 2008, FDA, without any report of adverse events related to cBHRT, began such campaign by initiating enforcement actions against pharmacies compounding cBHRT on a seemingly arbitrary basis.[16] With no reports of adverse events related to cBHRT, many industry stakeholders easily concluded that FDA took action against compounders not because there were issues with the actual compounded medication, but because of the citizen petition filed by Big Pharma giant, and manufacturer of FDA-approved hormone replacement therapies, Wyeth Pharmaceuticals, which requested that FDA halt the compounding of estrogen medications that contain estriol. Nearly 77,000 comments were submitted in response to this petition, almost all in opposition to Wyeth Pharmaceutical's requests, yet FDA sided with Big Pharma and issued Warning Letters to seven compounding pharmacies. The industry was left with the impression that FDA's actions were triggered by a pharmaceutical company with a commercial interest in suppressing compounding.

Then most recently, in September 2019, FDA published a press release in the middle of the Study that mischaracterized adverse event reporting for cBHRT and implied that the compounding of cBHRT is inherently risky. This press release highlighted FDA's concern over 4,202[17] allegedly adverse events associated with cBHRT that had never been reported to FDA, yet the press release grossly mischaracterized these so-called "adverse events" in order to suggest that cBHRT was unsafe and/or ineffective. Even assuming all 4,202 alleged adverse events were serious and/or unexpected, there remains no evidence that these events were not previously reported and since fully addressed by the offending company. Rather, there seems to be no other explanation for these very public, mischaracterized allegations and their timing other than to perpetuate an unfounded view in the public arena that cBHRT is unsafe. That is, FDA used the press release to reference its own Study, stating that it had contracted with NASEM to "conduct a Study on the ***risks*** associated with compounded hormone products." Right in the middle of its own commissioned and supposedly independent Study, FDA publicly announced its position that cBHRT is risky, complete with mischaracterizations masquerading as evidence to back it up. As FDA was the sponsor of the Study, with several current and former FDA members continually weighing in during the Study presentations or via press releases, what choice did the NASEM Committee have but to

[15] Transcript of FDA Press Conference on FDA Actions on Bio-Identical Hormones, FTS HHS, FDA, January 9, 2008.
[16] In response to the question of whether FDA received adverse event reports or reports of harm to patients as a result of cBHRT, Kathy Anderson, Deputy Director, Division of New Drugs and Labeling Compliance of FDA responded, "[w]ith respect to your answer about whether we received any adverse event reports, we have not." *Id.*
[17] Please note that the medical marketing and training company FDA associated with this number of alleged adverse events was unable to verify how or where FDA obtained this number, as this company's records do not reflect 4,202 events in its tracking system.

conclude that there is a public health concern regarding the prescribing, compounding, dispensing, and use of cBHRT?

Finally, the dominance of Jane Axelrad, FDA's lead on pharmacy compounding from 1991-2016, as a presenter, participant in Study meetings, and Report reviewer, evidences that FDA drove the Report's conclusions.[18] Although Ms. Axelrad retired from FDA after 25 years in April 2016, she launched her own consulting firm Axelrad Solutions and has since used her platform to continue to call for tighter restrictions on the compounding industry. Her participation in and influence over the Study are problematic and strain credulity on the entire Report. Specifically, Ms. Axelrad's presentation advocated for the NASEM Committee to find certain cBHRT and pellet therapies too difficult to compound—an assertion that was at the time, and remains, wholly outside the scope of the Study's charge.

Public information about the NASEM Committee meetings does not indicate who requested that Ms. Axelrad present information claiming cBHRT is too difficult to compound, why she introduced this topic into the Study, and/or why the NASEM Committee found it appropriate for the topic to be considered, despite it being outside of the Study's directive.[19] Nevertheless, Ms. Axelrad's presentation resulted in the NASEM Committee's second recommendation that PCAC should evaluate estradiol, estrone, estradiol cypionate, estriol, dehydroepiandrosterone, pregnenolone, progesterone, testosterone, testosterone cypionate, testosterone propionate, and all compounded bioidentical hormone therapy preparations formulated in pellet dosage form as candidates for FDA's Difficult to Compound List.[20]

Ms. Axelrad's view that cBHRT should be deemed "too difficult to compound" cannot be considered independent. Her opinion cannot be separated from FDA because it is identical to the position she took as FDA's compounding lead during meetings with PCAC. During public PCAC meetings, on behalf of FDA, Ms. Axelrad asserted that compounders are not equipped to compound certain medications based on their alleged level of difficulty.[21] The medications she had to be referring to were substances that had already been nominated to the public docket FDA had opened in 2013, and thus already on FDA's, and Ms. Axelrad's, radar.[22] Among the nominations received by the Agency, ***nine*** were hormones or categories of hormones that the NASEM Committee suspiciously recommended PCAC to review. That is, of the 11 hormones or categories of hormones the NASEM Committee recommended PCAC to review, ***nine were already nominated for FDA's Difficult to Compound List in 2014 when Ms. Axelrad served***

[18] In joining a Compounding Expert Committee meeting with the United States Pharmacopeia on October 23-24, 2013, Ms. Axelrad was introduced by the Chair of the Compounding Expert Committee as "the FDA lead on pharmacy compounding."
[19] To ascertain the full scope of the communications between FDA and Ms. Axelrad regarding the NASEM study and positions she held about cBHRT while at the Agency, we have served FDA with a FOIA request, enclosed herein as Exhibit 1. We will supplement this Comment as we receive additional information.
[20] Report, at 239.
[21] In presenting to PCAC in 2015, less than one year before she left FDA, Ms. Axelrad stated the following: "[W]e have seen drugs and categories of drugs that even drug manufacturers have difficulty getting right . . . . So I think that there may be certain drugs on the list that we don't think that even a highly skilled compounding operation could do successfully . . . . [W]e want to eliminate risks to public health that might be associated with compounding difficult-to-compound drugs that we don't think, in most cases, can be compounded safely or provide a safe and effective product." Thursday, June 18, 2015 PCAC meeting, pages 67–92.
[22] Nominations to the Difficult to Compound List or comments submitted in response to FDA's December 4, 2013 Federal Register notice were submitted to docket FDA-2013-N-1523.

as the FDA lead on compounding.[23] Ms. Axelrad cannot tell the NASEM Committee that hormones are too difficult to compound—the same position she took while at FDA—and maintain any kind of independence from the Agency.

Ms. Axelrad's participation, as an extension of FDA, also violated NASEM rules. Not only was she a presenter and active participant in Study meetings, but she was also chosen as a Study reviewer, a role in which she reviewed the Report and suggested changes. NASEM's Policies explicitly state that, "[s]ponsors are not given an opportunity to suggest changes in reports," i.e., NASEM's Policies forbid sponsors from serving as reviewers to NASEM's reports.[24] Here, FDA clearly served as a reviewer of this Report (and presenter and participant in the Study), via Ms. Axelrad. Ms. Axelrad's role (or, more accurately, FDA's inappropriate role in its Study) standing alone completely invalidates the Report.

II. The Report Is Heavily Rooted In Bias And, As Such, Presents Faulty Conclusions Upon Which The Agency Cannot Rely.

Notwithstanding FDA's influence, the NASEM Committee's makeup, the materials it considered, and the organizations from whom it sought data weighed heavily in favor of Big Pharma. Moreover, the materials the NASEM Committee considered, and the data of which the NASEM Committee claims to need more, are rooted in striking gender bias. As a result, the Report lacks credibility and the NASEM Committee's conclusions and recommendations must be disregarded.

(a) *The NASEM Committee Was Comprised Of Individuals Biased Against The Compounding Industry, Which Caused Them To Rely On The Wrong Data.*

First, the NASEM Committee lacked the expertise and clinical experience necessary to evaluate cBHRT, and this caused the NASEM Committee to analyze data and literature that fell far outside of the scope of, and which was sometimes irrelevant to, the Study's charge.[25] The NASEM Committee was comprised of 12 members with a shared goal to assess the ***clinical utility*** of ***compounded*** hormone medications. However, despite their impressive resumes, not a single member of the NASEM Committee had any stated first-hand expertise or experience in studying, compounding, ***or*** prescribing compounded

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[23] Of the hormones and categories thereof recommended for PCAC review, estradiol, estrone, estradiol cypionate, dehydroepiandrosterone, pregnenolone, progesterone, testosterone, testosterone cypionate, and all compounded bioidentical hormone therapy preparations formulated in pellet dosage form were already nominated to the Difficult to Compound List in 2014.

[24] Our Study Process https://www.nationalacademies.org/about/our-study-process (last visited August 17, 2020).

[25] Although compliance with United States Pharmacopeia ("*USP*") general chapters is not the focus of this section, we wanted to highlight another example of where the NASEM Committee relied upon faulty data. The NASEM Committee alleged in its Report that there was inconsistent oversight of compounding pharmacies with respect to USP compliance. To make this claim, the NASEM Committee relied upon outdated and incorrect information from The Pew Charitable Trusts and the National Association of Boards of Pharmacy. Report, pages 64-65. For example, the Report includes a map that claims that New Hampshire law contains no data with respect to USP <795> compliance, yet New Hampshire regulations currently state, "[t]he board shall require all compounders engaging in compounding in all situations to adhere to and comply with the current edition of the United States Pharmacopeia including but not limited to Chapters 795 (USP 795) and 797 (USP 797) . . . ." N.H. Code Admin. R. § 404.01(b). Similarly, the Report's map also claims that Utah law contains no data with respect to USP <795> compliance, yet the Utah Pharmacy Practice Act states, "[f]acilities shall follow USP-NF Chapter 795, compounding of non-sterile preparations . . . ." Utah Admin. Code r. R156-17b-614a(3)(a). These are only two small examples that demonstrate that NASEM Committee relied on false data to form its conclusions.

medications, much less cBHRT. However, a strong majority of the members had some explicit connection to Big Pharma. For example:[26]

- **Lesley H. Curtis, Ph.D.**: Dr. Curtis is a health services researcher who oversees a portfolio of products that use observational data to address questions related to, among others, pharmacoepidemiology, which studies the utilization and effects of drugs in large numbers of people. Dr. Curtis is a Professor and Chair of Population Health Sciences and Interim Director of the Duke Clinical Research Institute at Duke University, which **has a number of professional connections with pharmaceutical companies**, but it has **not conducted trials on bioidentical hormone replacement therapy products**;

- **Susan S. Ellenberg, Ph.D.**: Dr. Ellenberg is a Professor of Biostatistics, Medical Ethics, and Health Policy at the University of Pennsylvania Perelman School of Medicine who **works closely with several pharmaceutical companies, including Merck, Bristol-Myers Squibb, and Marinus Pharmaceuticals**;

- **Adel H. Karara, Ph.D., FCP**: Dr. Karara is a Professor of Pharmaceutical Sciences at University of Maryland, Eastern Shore, where he teaches in the areas of pharmaceutics, biopharmaceutics, and pharmacokinetics. Prior to joining academia, Dr. Karara **held senior positions in the pharmaceutical industry, including positions at Roche, Berlex, and Novartis**. While at Berlex, Dr. Karara **provided new drug approval support FDA-approved hormone therapies such as Yasmin, ClimaraPro, Menostar, and Angeliq**;

- **Robert B. MacArthur, Pharm.D., M.S.**: Dr. MacArthur is the **only Doctor of Pharmacy on the NASEM Committee** and the only member to potentially have any compounding experience, though not first-hand experience. Dr. MacArthur is currently the Pharmacy Director at The Rockefeller University Hospital and the President of Orphan Drug Services, Inc., which provides drug development and statistics services to pharmaceutical companies. **His work experience includes large pharma (Sandoz and Novartis), small to mid-size pharma (Systems Medicines, CTI, Aeson Therapeutics, Cancer Prevention Pharmaceuticals, and others), commercial phase 1 units (LAB, Inc., others), and GMP drug manufacturing (Pii Inc. US, PharmMaterials UK, and others)**. In academia, his work enabled studies, which includes compounding novel oral and injectable products for first-in-human/phase I/ II/III studies; and

- **David R. Rubinow, M.D.**: Dr. Rubinow is the Meymandi Professor and Chair of the Department of Psychiatry at the University of North Carolina at Chapel Hill's School of Medicine. **Dr. Rubinow has professional and financial interests in Sage Therapeutics**, a pharmaceutical company that primarily manufactures and distributes medications to treat central nervous system disorders.

Despite their long lists of personal achievements, the Committee members lacked the requisite experience in prescribing, preparing, and dispensing compounded medications. Further, not a single Committee

[26] For complete biographies of all 12 NASEM Committee members, *see* Report at 269–76.

member is a current physician that treats patients with any compounded hormone therapies. Experience in compounding and prescribing hormone therapies is ***crucial*** to understanding the clinical utility of compounded bioidentical hormone therapies. The Committee's lack of appropriate expertise, in and of itself, is enough to raise serious questions regarding the conclusions and recommendations reflected in the Report.

Nevertheless, even if the NASEM Committee members were appropriately qualified to oversee the Study, their shared experience in and ties to Big Pharma inherently caused the NASEM Committee to seek out data and studies akin to those conducted by Big Pharma, skewing the results of the Study and the conclusions reached by the NASEM Committee. Despite stakeholders submitting ***thousands*** of research articles and observational data points for the NASEM Committee's review, the NASEM Committee only "identified a total of ***13 studies*** related to cBHRT that were of adequate ***methodologic rigor*** for inclusion in its review of safety and effectiveness of these preparations."[27] These 13 studies, which formed the basis of the NASEM Committee's analysis of the clinical utility of cBHRT, ***only focused on five compounded bioidentical hormone variations***.[28] Such a narrow focus on only 13 studies, which only consider a small fraction of the therapies that are needed to treat patients, blatantly ignores the variability inherent in compounding bioidentical hormones. For example, one compounding pharmacy that presented to the NASEM Committee has "compounded over 149,000 unique hormone formulations using fewer than 10 hormones."[29] There is no way that 13 studies can act as a representative sample of the ***hundreds of thousands*** of compounded bioidentical hormone variations.

Moreover, in cherry-picking the 13 studies, the NASEM Committee inexplicably ignored the medical judgment of a series of reputable physicians who routinely treat their patients with cBHRT for a myriad of conditions.[30] Rebecca Glaser, M.D., David Rosensweet, M.D., and Pamela Smith, M.D., M.P.H., M.S. all provided insightful presentations rooted in scientific evidence to the NASEM Committee regarding their decisions to treat their patients with cBHRT. Further, seventeen physicians, many of whom are Fellows of The American Congress of Obstetricians and Gynecologists, also submitted statements that they regularly, and ***safely***, exercise their medical judgment to prescribe cBHRT for their male and female patients to treat a variety of life-threatening medical conditions, such as decline in brain function, depression, heart disease, heart failure, fibrocystic breast disease, ovarian cysts, autoimmune disorders, bone health, neurodegenerative diseases, breast cancer, insulin resistance, cholesterol issues, Alzheimer's, and dementia, among others. Yet, the NASEM Committee completely disregarded medical experts in this very field, and, in the face of a wealth of observational data, chose to somehow conclude that there is no clinical utility to cBHRT.

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[27] During the NASEM Committee's Q&A on the Report on July 1, 2020, when asked what it would like to see with respect to evidence to support the clinical utility of cBHRT products, the NASEM Committee stated it wanted more observational studies and evidence to support safety and efficacy, despite the thousands of articles and observational studies that were already submitted during the study's course. *See also* Report, at 140 (emphasis added).

[28] It is important to note that none of the 13 studies reported adverse events.

[29] Report, at 95.

[30] We hereby incorporate all arguments and all exhibits contained in our letter to the NASEM Committee submitted on November 7, 2019. This letter is enclosed herein for reference as Exhibit 2.

ReedSmith

(b) *The Data Relied Upon By The NASEM Committee, And The Additional Data It Seems To Be Seeking, Are Rooted In Gender Bias.*

It is perhaps even more troubling that the NASEM Committee appears to have overlooked the gender bias that impedes the independent and credible nature of the very studies the NASEM Committee determined it needed in order to evaluate the clinical utility of cBHRT. The NASEM Committee claimed that it needed well-designed, double-blind, randomized, placebo-controlled trials—that is, studies like those required in FDA's new drug approval—in order to evaluate the safety and effectiveness of cBHRT, and that the lack of such studies hindered its ability to evaluate cBHRT's clinical utility. But even if a plethora of such studies existed for the NASEM Committee's review, that information still would not allow it to make an informed decision on the safety and effectiveness of cBHRT. This is because these kinds of controlled studies frequently exclude women, and women are the very patient population at the heart of this Study and are the very patient population that will be most severely impacted if FDA adopts the Report. In only considering 13 studies and asking for more controlled trials, the NASEM Committee made conclusions and recommendations for women's health based on data and information that left women out of the conversation.

Based on the Coalition's limited engagement with the NASEM Committee during its Study, it was clear that there was a dearth of understanding of the difference between male and female hormones, which is critical to determining which trials (e.g., observational versus controlled) will be most informative for the Study. In this case, due to the highly individualized nature of hormones and compounded hormone therapies, cBHRT is a poor fit for controlled trials (as are all compounds, as Congress recognized when it exempted compounds from these trials via the DQSA) and, accordingly, observational data fills this gap.[31] Female hormones are particularly idiosyncratic and are fundamentally more complicated and misunderstood than male hormones—biological facts that make women a poor fit for double-blind, randomized, placebo-controlled trials.[32] Big pharmaceutical companies that can afford these trials often see female candidates for their studies as risky—women can get pregnant and the risk of fetal concern is often too much to bear for the Study sponsor. In a 2014 report, researchers at the Brigham and Women's

[31] We would like to reiterate that stakeholders submitted ***thousands*** of research articles and observational data points for the NASEM Committee's review throughout the course of the Study, which were largely ignored.

[32] For example, there is a common misconception that female bodies do not produce much, if any, testosterone, but this is far from the truth. Testosterone is the most abundant and biologically active hormone throughout a woman's lifespan. Testosterone levels drop in the years prior to, and during, menopause, which causes similar symptoms of deficiency for women as it does in men (yet, it occurs earlier in a woman's life compared to a man's). This can lead to new onset mood disorders (or worsen existing ones), apathy, impaired glucose metabolism (which leads to weight gain), insult resistance/diabetes, fatigue, muscle wasting, bone loss, cognitive impairment, migraine headaches, low libido, and other sexual function disorders. *See* Rebecca Glaser and Constantine Dimitrakakis, *Testosterone therapy in women: Myths and misconceptions*, Maturitas 74(3), P230-234 (2013) ("[Testosterone] is the most abundant biologically active female hormone, [Testosterone]T is essential for physical and mental health in women . . . ."). *See also* Amy Westervelt, *The medical research gender gap: how excluding women from clinical trials is hurting our health*, The Guardian, 30 April 2015 ("According to the Institute of Medicine, every cell in our bodies has a sex, which means men and women are different at a cellular level. That also means that diseases, treatments, and chemicals might affect the sexes differently. And yet there's a long and storied tradition of ignoring gender when it comes to health research. For several reasons, female subjects have historically been excluded from toxicology or biomedical research . . . .").

Hospital in Boston chronicled the exclusion of women from health research and its impact on women's health:

> The science that informs medicine – including the prevention, diagnosis, and treatment of disease – ***routinely fails to consider the crucial impact of sex and gender***. This happens in the earliest stages of research, when ***females are excluded from animal and human studies or the sex of the animals isn't stated in the published results***. Once clinical trials begin, researchers frequently do not enroll adequate numbers of women or, when they do, fail to analyze or report data separately by sex. This hampers our ability to identify important differences that could benefit the health of all.[33]

Thus, these hormone studies are more often conducted with male candidates, and the data is later extrapolated to female patients.[34] The individualized, complicated, inherently idiosyncratic nature of female hormones is completely disregarded in these scenarios in favor of the "easier" male model. Caroline Criado Perez, author of *Invisible Women: Data Bias in A World Designed For Men*, specifically notes the presence of the male-default data bias in FDA drug trials. One issue that has gone utterly unaddressed, Perez states, is whether the drugs are tested in women at different stages of their menstrual cycles, which can impact the drug's effectiveness.[35] It is ironic, to say the very least, for the NASEM Committee to determine cBHRT lacks studies of adequate methodologic rigor when these types of studies routinely exclude women, and when they do include women, utterly fail to take into account the impact of hormone fluctuations on a drug's effectiveness.

As a result, women and their physicians have been utterly excluded from NASEM's evaluation of what is best for women's bodies.[36] The NASEM Committee relied on methodologies of data evaluation that exclude women and their unique hormonal make up, and ignored the medical judgment of reputable leading physicians that routinely prescribe cBHRT to treat scores of patients. Then, when it came to patients, the NASEM Committee actively disregarded patient choice—dismissing women's opinions of their own well-being as "preference" and rendered this "preference" as non-instrumental to forming its conclusions. Specifically, the Study concluded, "[b]ased on a limited number of studies, patients (largely women) taking cBHRT are thought to be simultaneously 'pushed away' from FDA-approved [bioidentical hormone therapy] and 'pulled toward' cBHRT by conflicting psychosocial forces."[37] Instead of validating the physician's recommended treatment for the patient and the patient's right to follow the advice of her physician, the NASEM Committee made the gendered assertion that women are too influenced by social

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[33] Sex-Specific Medical Research Why Women's Health Can't Wait, A Report of the Mary Horrigan Connors Center for Women's Health & Gender Biology at Brigham and Women's Hospital, 2014, page 5.

[34] Mark Glezerman, *Women are dying because most medical research is done on men*, New York Post, August 16, 2016 ("Yet the vast majority of clinical research on diseases and medications is performed on men, which means that half of the population is treated based on data that doesn't necessarily apply to them."); Caitlin Hoff, *Taking on Gender Bias in Clinical Trials*, National Women's Health Network, February 26, 2019 ("For decades, health research was done on men and the results were assumed to apply to women. Women were treated as if they were just smaller versions of a male body.").

[35] Caroline Criado-Perez, *Invisible Women: Exposing Data Bias in a World Designed for Men* 203–04 (2019).

[36] Holdcroft, Anita, *Gender bias in research: how does it affect evidence based medicine?*, Journal of the Royal Society of Medicine vol. 100,1 (2007): 2-3. ("The evidence basis of medicine may be fundamentally flawed because there is an ongoing failure of research tools to include sex differences in study design and analysis. The reporting bias which this methodology maintains creates a situation where guidelines based on the study of one sex may be generalized and applied to both.").

[37] Report, at 8.

factors to make an informed decision about ***their own healthcare***. The fact that the NASEM Committee is advocating for safety and effectiveness data akin to new drug approval funded by Big Pharma is merely another way for FDA to ignore and gloss over the unique needs of women and make the male body the default model—a way that represents a dismissive and patronizing attack on women's health and women's right to their quality of life.

III. If FDA Adopts The Conclusions And Recommendations In The Report, FDA Will Be In Violation Of The Federal Advisory Committee Act.

As set forth above, FDA so heavily influenced the NASEM Committee and its conclusions and recommendations that FDA, in essence, managed and controlled the NASEM Committee. Ms. Axelrad's involvement, as well as the active measures FDA took to control the outcome of the Study, demonstrate FDA's undue influence over the NASEM Committee and its results. Accordingly, FDA may not adopt the conclusions and recommendations in the Report without violating FACA.

It is through the enactment of FACA in 1972 that Congress formally recognized the importance and value of federal advisory committees. For years, federal advisory committees have played a critical role in shaping policies for and providing advice to the federal government. Thanks to the role that advisory committees play, the public is given an opportunity to engage in important governmental issues and the government, as well as the public, are given access to expertise on a broad range of issues affecting federal policies and programs. Federal agencies that engage advisory committees must adhere to the requirements established by FACA. In particular for our purposes here, FACA requires membership of an advisory committee to be fairly balanced and prohibits a federal agency from managing or controlling a committee created by NASEM. Specifically, "[a]n agency may not use any advice or recommendation provided by the National Academy of Sciences . . . that was ***developed by use of a committee created by that academy under an agreement with an agency***, unless (1) the committee was not subject to any ***actual management or control by an agency*** or an officer of the Federal Government . . . ." 5 U.S.C. APP. 2 § 15(a)(1) (emphasis added). In other words, FDA cannot use any conclusions or recommendations provided by NASEM if they are the result of a NASEM Committee that was unduly influenced by FDA.

It is abundantly clear that FDA had management and control over the NASEM Committee. First, the involvement of Ms. Axelrad, former FDA lead on pharmacy compounding, in the Study evidences that FDA had a strong command over the outcome it wanted. She participated in and presented during the Study and reviewed the Report in violation of NASEM's own policies, and likely suggested articles for the NASEM Committee's review.[38] Second, FDA on its own submitted data, such as articles and references, for the Study's consideration and influenced the definition the NASEM Committee used for "clinical utility." FDA forced the NASEM Committee to evaluate cBHRT under a new drug approval standard knowing full well that cBHRT, as compounded medication, was neither suited for nor could ever meet such a standard. Finally, FDA submitted data on alleged adverse events involving cBHRT in order to unduly influence the NASEM Committee's perception that cBHRT is inherently risky and that its use should be restricted. The adverse event information was, as stated above, heavily mischaracterized and gave a false impression about the prevalence of incidents involving cBHRT and their severity. FDA

[38] "Furthermore, during the National Academies' external review process, additional articles were suggested by reviewers of the report." Report, at 257.

pumped the NASEM Committee with one-sided information in order to ensure that the NASEM Committee came to the conclusions it did.

In sum, as a result of FDA's involvement, the NASEM Committee fell subject to severe management and control by the very agency that commissioned what should have been an independent Study. Therefore, FDA's adoption of any of the conclusions or recommendations in the Report is a violation of FACA.

IV. We Strongly Caution FDA Against Adopting The NASEM Committee's Recommendation That PCAC Review Certain Bioidentical Hormone Therapies And Pellets As Candidates For FDA's Difficult To Compound List.

Even if the Report is taken at face value and FDA considers adopting its conclusions and recommendations, we strongly discourage FDA from adopting the NASEM Committee's recommendation that PCAC review certain bioidentical hormone therapies and pellets as candidates for FDA's Difficult to Compound List. PCAC is an advisory committee that operates in violation of FACA and is therefore in no position to evaluate whether hormone therapies or categories thereof should be included on FDA's Difficult to Compound List. Further, PCAC's involvement threatens to remove viable hormone treatment options for millions of patients who cannot be treated by FDA-approved bioidentical hormone therapies, which will have a devastating impact on the health and well-being of these patients.

To start, PCAC is a federal advisory committee that operates in violation of FACA. FACA requires that "membership of the advisory committee . . . be ***fairly balanced in terms of the points of view represented*** and the functions to be performed by the advisory committee . . . ." 5 U.S.C. APP. 2 § 5(b)(2) (emphasis added). For a ***compounding*** committee whose purpose is to provide "advice on scientific, technical, and medical issues ***concerning drug compounding*** under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act, and, as required, any other product for which the Food and Drug Administration has regulatory responsibility, and make appropriate recommendations to the Commissioner of Food and Drugs," only ***two of its 12 voting members*** actually have compounding listed as their expertise, yet PCAC claims in the FACA database that "[m]embers are ***authorities in the fields of pharmacy compounding***, pharmaceutical manufacturing, pharmacy, medicine, and related specialties."[39] This is clearly not the case.

PCAC needs to adequately represent the interests and needs of providers and patients who use and depend on compounded medications. Compounding is often practiced in community settings, and it is therefore vital that voting members of PCAC have a thorough understanding of compounding in a community setting in order to appropriately advise FDA. As PCAC stands, this advisory committee is ***not*** "fairly balanced in terms of the points of view represented" and is therefore in stark violation of FACA. 5 U.S.C. APP. 2 § 5(b)(2).

The implications of an imbalanced advisory committee are that the individuals who comprise the committee may not be in the best position to properly evaluate whether certain bioidentical hormone

[39] HHS 5220 Pharmacy Compounding Advisory Committee, Committee Detail, https://www.facadatabase.gov/FACA/apex/FACAPublicCommittee?id=a10t0000001gzugAAA (last visited August 17, 2020).

therapies and pellets should be candidates for FDA's Difficult to Compound List. As a result, critical bioidentical hormone therapies are at risk of being placed on a list that removes them as treatment options for the millions of patients across the U.S. who rely on them. Not only that, but if compounders cannot prepare certain bioidentical hormone therapies, they run the risk of going completely out of business, which will have a devastating impact on the compounding industry and the patients they serve.

Moreover, to the extent FDA is considering a way to further evaluate the safety of estradiol, estrone, estradiol cypionate, estriol, dehydroepiandrosterone, pregnenolone, progesterone, testosterone, testosterone cypionate, and testosterone propionate, we want to emphasize that the NASEM Committee ***did not*** conclude that these substances are not ***safe***. This distinction is critical because not only do these bioidentical hormones not belong on the Difficult to Compound List, but they do not have identified safety risks that would require them to be placed in Category 2 of FDA's 503B Bulks List.[40]

V. Conclusion.

In conclusion, we request that FDA ***reject*** the NASEM Committee's Report and all the conclusions and recommendations therein, in favor of keeping cBHRT, a critical, life-saving therapy, available for the ***millions*** of patients that rely on this therapy.

Very truly yours,

/s/ Rachael G. Pontikes

Rachael G. Pontikes
For Reed Smith LLP

RGP:rl

[40] Category 2 of the 503B Bulks List represents bulk drug substances that were nominated with sufficient supporting information for FDA to evaluate them, but FDA identified significant safety risks relating to the use of these substances in compounding pending further evaluation. FDA has stated it would consider taking action against an outsourcing facility for compounding drug products with this bulk drug substance under its general enforcement policies.

EXHIBIT 1

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July 24, 2020

Via Online Access Portal

Food and Drug Administration
Division of Freedom of Information
Office of the Executive Secretariat, OC
5630 Fishers Lane, Room 1035
Rockville, MD 20857

RE: Freedom of Information Act Request

To Whom It May Concern:

We are submitting the following Freedom of Information Act ("*FOIA*") request to the U.S. Food & Drug Administration ("*FDA*").

A. Requestor's name, address, and telephone number.

Rachael Pontikes
10 South Wacker Drive
40th Floor
Chicago, IL 60606
(312) 207-2857

B. A description of the records being sought. The records should be identified as specifically as possible. A request for specific records that are releasable to the public can be processed much more quickly than a request for "all information" on a particular subject. Also fees for a more specific and limited request will generally be less.

I request the following records:

- All communications* between FDA (including, but not limited to, FDA's Center for Drug Evaluation and Research ("*CDER*")) and the National Academies of Sciences, Engineering, and Medicine (including, but not limited to, Leigh Jackson), from January 1, 2016, to the present regarding the following subjects:

* For purposes of this FOIA request, the term "communications" includes, but is not limited to, e-mail messages, letters, memoranda, and calendar invitations and notations.

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  - Bioidentical hormones;
  - Compounded bioidentical hormone therapy (otherwise known as "cBHT" or "cBHRT");
  - Difficult to compound;
  - Clinical utility ;
  - Pharmacy Compounding Advisory Committee (otherwise known as "PCAC");
  - Jane Axelrad; or
  - Axelrad Solutions LLC.

- All communications between FDA (including, but not limited to, FDA's CDER) and Jane Axelrad from May 1, 2016, to the present regarding the following subjects:

  - National Academies of Sciences, Engineering, and Medicine (otherwise known as "NASEM");
  - Bioidentical hormones;
  - Compounded bioidentical hormone therapy (otherwise known as "cBHT" or "cBHRT");
  - Difficult to compound;
  - Clinical utility; or
  - Pharmacy Compounding Advisory Committee (otherwise known as "PCAC").

- All communications between FDA (including, but not limited to, FDA's CDER) and Axelrad Solutions LLC from December 6, 2016, to the present regarding the following subjects:

  - National Academies of Sciences, Engineering, and Medicine (otherwise known as "NASEM");
  - Bioidentical hormones;
  - Compounded bioidentical hormone therapy (otherwise known as "cBHT" or "cBHRT");
  - Difficult to compound;
  - Clinical utility; or
  - Pharmacy Compounding Advisory Committee (otherwise known as "PCAC").

- All communications between FDA (including, but not limited to, FDA's CDER) and the Pharmacy Compounding Advisory Committee, from November 27, 2013, to the present regarding the following subjects:

  - Bioidentical hormones;
  - Compounded bioidentical hormone therapy (otherwise known as "cBHT" or "cBHRT");
  - Difficult to compound;
  - Clinical utility;
  - National Academies of Sciences, Engineering, and Medicine (otherwise known as "NASEM");
  - Jane Axelrad; or
  - Axelrad Solutions LLC.

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C. A statement concerning willingness to pay fees, including any limitations.

I will pay all fees associated with this request. If the agency estimates that those fees will exceed $1,000.00, please contact me before proceeding further.

Very truly yours,

Rachael G. Pontikes

Rachael G. Pontikes
For Reed Smith LLP

RGP:rl

EXHIBIT 2

ReedSmith
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through partnership
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November 7, 2019

VIA EMAIL
VIA UPS

Ms. Leigh Miles Jackson
Study Director
The National Academies of Sciences,
Engineering, and Medicine
Keck Center
Keck 765
500 Fifth St. NW
Washington, DC 20001

Re: Study on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy"

Dear Ms. Jackson:

We write on behalf of a coalition of six compounding facilities that serve thousands of patients and physicians throughout the United States every month (the "*Coalition*"). We understand that the National Academy of Sciences, Engineering, & Medicine ("*NASEM*") has been engaged by the Food & Drug Administration ("*FDA*") to conduct a study on the *Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy"* (the "*Study*"). The purpose of the Study is three-fold:

(1) review the current and historic uses of compounded Bioidentical Hormone Replacement Therapy ("*BHRT*") to treat patients;

(2) understand the physical and chemical characteristics of compounded BHRT preparations; and

(3) review and assess the available evidence regarding the safety and effectiveness of compounded BHRT preparations.

Ultimately, we understand that the committee comprised to conduct the Study (the "*Committee*") will summarize the aforementioned information and issue a report containing recommendations regarding the clinical utility of compounded BHRT preparations; the safety and effectiveness of compounded BHRT preparations; and the patient populations that would benefit from compounded BHRT preparations in lieu of FDA-approved drug products.

In an effort to aid the Committee, the Coalition seeks to present information targeting the three-fold purpose of the Study. In order to assess the overall clinical utility of compounded BHRT, the

Coalition will present an overview of the current and historic uses of compounded BHRT to treat patients, and the reasons why FDA-approved BHRT preparations cannot adequately meet patient need. In addition, the Coalition will present evidence demonstrating that compounded BHRT preparations are safe, effective, and do not present demonstrable difficulties to compound consistently.

In light of the information below, the Coalition believes the Committee should find that: (1) compounded BHRT preparations are clinically necessary to treat the patient population; and (2) compounded BHRT preparations are safe, effective and do not present demonstrable difficulties to compound. Although we understand that the Committee will be conducting a hearing on the Study on November 12, 2019, we respectfully request that the Coalition be granted a separate meeting with the Committee to present our key experts and answer any questions the Committee may have.

I. Compounded BHRT Preparations Are Critically Necessary For The Treatment Of A Variety Of Conditions.

The Committee recognizes that in order to assess the overall clinical utility of compounded BHRT, it is first important to understand the current and historic uses of compounded BHRT to treat patients, and the reasons why FDA-approved BHRT drug products cannot adequately meet patient need. Accordingly, in order to assist the Committee in preparing its report, we have first set forth below a brief history of compounding in general and where compounding sits in the overall regulatory scheme for drug products. We further provide an overview of the current and historic uses of compounded BHRT and then, finally, we explain why FDA-approved BHRT drug products cannot adequately meet patient need.

The Coalition has provided a representative sample of statements from physicians and a nurse practitioner who regularly prescribe compounded BHRT preparations to their patients.[1] These physicians and nurse practitioner support compounded BHRT preparations being made available to their patients. We have summarized these statements in this submission; however, we encourage the Committee to read these statements and reach out to the practitioners for further comment. And, we must also make the Committee aware that there are scores of other physicians and prescribers eager to provide further informative statements like the ones enclosed herein.

As set forth below, physicians recognize that the available FDA-approved BHRT drug products are not offered in the variety of dosage forms and strengths necessary to treat a patient population that needs personalized hormone therapies. Compounded BHRT preparations fill the gaps left by FDA-approved drug products but, due to the nature of hormone therapy, these compounded BHRT preparations cannot go through the new drug approval process. In addition, there are certain patients and patient populations that simply cannot be treated with the current slate of FDA-approved BHRT drug products. Accordingly, compounded BHRT preparations are medically necessary for the treatment of a variety of conditions and patient access to this medication must be preserved and protected.

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[1] *See* Group Exhibit 1, which comprises signed statements from the following: Jeffrey R. Baker, MD, MS; George Benson Branning, MD; David A. Brownstein, MD; Angela DeRosa, DO, MBA, CPE; Bruce Dorr, MD, FPMRS; Christine Farrell, MSN, FNP-C; Laura Grant, MD; Arlene Jacobs, MD; Steven A. Komadina, MD; Daniel Elias Melville, MD; John Joseph Peet, MD, FACOG; John J. Pierce, DO; Cory Stephen Rice, DO; Ann Elizabeth Stanger, MD; G. DeAn Strobel, MD, FACOG; Allan Warshowsky, MD, FACOG, ABIHM; and David Watson, MD, FACOG.

(a) Compounded Medication Is A Traditional Component Of The Practice Of Pharmacy.

Pharmacy compounding is a vital, medically necessary, longstanding, and integral part of the delivery of health care in the United States. Compounded drugs have historically filled the interstitial spaces where, in the physicians' judgment, there is no suitable commercially manufactured drug product available to treat a patient. This unavailability occurs for many reasons. For example: (1) there is no manufactured product to accomplish a desired or preferred medical objective; (2) a commercially available product, while available, is nonetheless not suitable because of patient allergies; drug delivery format, e.g., tablet, injectable, patch, suppository, etc.; flavoring; combination with other drugs, etc.; and (3) a manufactured drug also may not come in the dosage appropriate for a particular patient, e.g., pediatric versus adult dosage.

Without compounding, physicians run the risk that a patient's specific and unique medical need will go untreated. Pharmacies compound and dispense drugs pursuant to prescriptions to treat cancer, autism, premenstrual syndrome, menopause, andropause, infertility, pain management, and every other conceivable condition or illness. Without compounded drugs to treat conditions for which no manufactured drugs exist (or for which manufactured drugs exist, but for patient-specific reasons are unsuitable), certain drug therapies or regimens would be unavailable altogether. Therefore, after physicians determine that there is no suitable commercially manufactured drug available, these physicians prescribe pharmacy compounds.

As a traditional component of pharmacy practice, the States—and more specifically, State boards of pharmacy—have historically had oversight of most aspects of pharmacy compounding practices through State laws regulating the practice of pharmacy. All 50 States address compounding in some form and impose rigorous registration, inspection, and safety requirements. State pharmacy laws have registration requirements for resident and non-resident pharmacies or pharmacists; set forth the professional standards for pharmacies and pharmacists; establish labeling and purity requirements for drugs, including compounded drugs; establish licensure procedures for pharmacists and resident and non-resident pharmacies; and establish certain training and education requirements for pharmacists and other pharmacy providers.

While States have historically regulated compounding as a traditional part of pharmacy practice, the federal government has historically regulated commercial drug manufacturing and distribution. When enacted in 1938, the Food, Drug, and Cosmetic Act ("*FDCA*") did not address drug compounding. Rather, while FDA was given authority to regulate drug manufacturing, the historic practice of traditional pharmacy compounding remained regulated by State law. Under the FDCA, drug manufacturers are required to comply with a series of conditions appropriate for the production of one-size-fits-all drugs, like new drug approval ("*NDA*") requirements, labeling requirements, and the requirement that drugs be prepared in facilities that comply with current Good Manufacturing Practices ("*cGMPs*"). Compounding pharmacies, on the other hand, prepare unique medications for the particularized medical need of a patient or patient population when a physician determines a commercially available drug is not suitable for treatment. The FDCA requirements for manufactured drugs were not designed for these specialized medications.

In 2013, however, Congress, through a series of legislative measures, exerted limited federal oversight over traditional compounding pharmacies and created a new registration for a certain type of compounding facility called an "outsourcing facility." These legislative actions culminated in the Drug Quality and Security Act ("*DQSA*") of 2013. Under Section 503A of the DQSA, traditional compounding pharmacies, or Section 503A compounding pharmacies as they are commonly called, remain primarily regulated by the States but are required to meet certain limited criteria under the statute. They need not register with FDA, but can be subject to FDA inspection. Section 503B of the DQSA, in turn, requires compounding facilities that choose to operate as outsourcing facilities to register with FDA and comply with certain conditions. Section 503B outsourcing facilities are subject to risk-based inspections by FDA and must comply with cGMP standards as well as other requirements set forth in the DQSA.

Section 503A compounding pharmacies and Section 503B outsourcing facilities play a vital role in ensuring that patient needs are met in those cases where FDA-approved drug products cannot meet patient medical need. Without access to the compounded medications prepared by these facilities, public health would suffer.

(b) Current And Historic Uses Of Compounded BHRT Preparations To Treat Patients.

The need for compounded forms of hormone medication cannot be understated. This is especially true for compounded BHRT preparations, which have played an important role in treating a wide variety of medical conditions and symptoms in male and female patients for decades. Bioidentical hormones are plant-derived hormones that, when used by the human body, are molecularly and structurally identical to those hormones endogenously produced by the human body and circulated in the human bloodstream.[2] Treatment with compounded BHRT has consistently proven to be a safe and effective alternative to the one-size-fits-all approach of FDA-approved bioidentical hormone therapies, as they can be custom compounded to match each patient's unique needs and body chemistry.

Compounded bioidentical hormone therapy was first introduced in the 1980s to treat menopause symptoms. Dr. Jonathan Wright researched alternatives to commercially available conjugated estrogens by analyzing the estrogens he found were naturally produced by female bodies: estradiol, estrone, and estriol. He then compounded a product known as "Triest," which combined those three estrogens into a topical cream.[3] Subsequent hormone testing revealed that estrone may not be needed—thus, "Biest" was formed, which is a compounded topical cream made of estradiol and estriol and remains one of the most popular and effective compounded bioidentical hormone therapies today.

However, the real catalyst to the increase in treatment with compounded BHRT is attributed to the early termination and results of the Women's Health Initiative ("*WHI*") trials on estrogen and progestin. Designed in 1991 and completed between 1993 and 2005, WHI conducted two parallel studies (estrogen plus progestin and estrogen only) of hormone therapies to assess the effects of hormone therapy on

[2] Santoro N, Braunstein, et al., Compounded Bioidentical Hormones in Endocrinology Practice: An Endocrine Society Scientific Statement, J Clin Endocrinol Metab. 2016 Apr; 101(4):1319 (defining the term "bioidentical" to mean hormones that have "the same molecular structure as a hormone that is endogenously produced and circulates in the human bloodstream . . . .").

[3] For further information, *see* Jonathan V. Wright, Natural Hormone Replacement: The Safe and Natural Menopause Treatment Alternative, 41 (1997).

cardiovascular disease and breast cancer.[4] Media coverage of the initial results of the estrogen plus progestin trial indicated that the risks of cardiovascular disease, breast cancer, and venous thromboembolism, among others, were not outweighed by the benefits of this treatment. In response to these results, many female patients and physicians sought alternative hormone treatments.[5]

Thus, in 2004, BHRT therapies re-emerged into the market as an alternative to synthetic, conjugated estrogen therapies.[6] Compounded forms of BHRT soon followed as an effective way to individualize symptom management and optimize the clinical experience for patients. Today, compounded BHRT is used by physicians and other medical professionals around the country to treat at least the following conditions and symptoms:[7]

Male and Female Patients	Male Patients Only	Female Patients Only
1. Adrenal dysfunction 2. Anxiety 3. Autoimmune diseases (thyroid, arthritis) 4. Bone density/bone health 5. Brain dysfunction 6. Cardiometabolic disease 7. Cardiovascular disease 8. Chronic pain 9. Coronary heart disease 10. Depression 11. Diabetic control 12. Heart disease/failure 13. Incontinence 14. Insomnia 15. Joint pain 16. Low testosterone/low hormone levels 17. Mental illness	1. Andropause 2. Erectile dysfunction	1. Cervical dysplasia 2. Chronic pain 3. Endometriosis 4. Fibrocystic breast disorder 5. Fibroids 6. Fibromyalgia 7. Heavy vaginal bleeding 8. Inadequate luteal phase in infertility patients 9. Interstitial cystitis 10. Menopause symptoms (vaginal dryness, low libido, hot flashes, night sweats, vaginal atrophy)

[4] For further information on the two trials conducted by the Women's Health Initiative, *see* Hormone Therapy Trials (HT), Women's Health Initiative, https://www.whi.org/about/SitePages/HT.aspx (last visited November 7, 2019) ("The WHI Hormone Therapy Trials (HT) were designed to test the effects of postmenopausal hormone therapy on women's risk for coronary heart disease (primary analyses) and on hip and other fractures and breast cancer (secondary analyses). The effects of hormone therapy on endometrial cancer was also evaluated in women with a uterus.).

[5] Garnet L. Anderson, Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial, JAMA 291(14) (2004) ("The WHI estrogen plus progestin trial was halted in July 2002 after a mean 5.2 years of follow-up because health risks exceeded benefits. Coronary heart disease (CHD), stroke, and venous thromboembolic disease were all increased in women assigned to active treatment with estrogen plus progestin. Breast cancer was also increased while colorectal cancer, hip fracture, and other fractures were reduced. The lack of benefit for CHD was supported by the Heart and Estrogen/progestin Replacement Study (HERS), which also tested CEE plus MPA in women with known coronary artery disease at baseline.").

[6] Ravdin PM, et al., The Decrease in Breast-Cancer Incidence in 2003 in the United States, N Engl J Med 2007; 356:1670-1674 (describing the negative impact the WHI trials had on prescriptions for commercially available hormone replacement therapies).

[7] For further information, *see* the physicians' and nurse practitioner statements attached hereto as Group Exhibit 1.

18. Neurodegenerative diseases (Alzheimer's, Parkinson's) 19. Obesity 20. Osteopenia/osteoporosis 21. Sexual health		11. Musculoskeletal issues 12. Ovarian cysts 13. Perimenopausal hormone deficits 14. Perimenopause 15. Phase related to estrogen dominance and progesterone deficiency 16. PMDD 17. PMS 18. Polycystic ovarian disease 19. Post-TAH/BSO patients with estrogen dominant side effects 20. Vaginal health

(c) FDA-Approved BHRT Drug Products Cannot Meet The Needs Of Every Patient.

FDA-approved BHRT drug products cannot meet the needs of every patient while compounded BHRT preparations are better suited to meet patient needs. As a threshold matter, it is important to understand that the nature of hormone therapy is idiosyncratic and, therefore, requires frequent blood test monitoring and symptom evaluation to ensure that patients are not only getting dosed correctly, but are absorbing the medication in the most effective way possible. All patients are different and, therefore, each patient has different sensitivities, tolerances, and reactions to hormone therapy that must be monitored throughout treatment so that dosages and/or combinations of hormones can be adjusted appropriately.[8]

FDA-approved BHRT drug products cannot accommodate the individualized nature of hormone therapy. Commercially available hormone therapies are not available in all dosage forms, strengths, and combinations required for treatment and, accordingly, many patients experience inconsistencies in treatment and unwanted side effects from these drugs. In addition, there are certain patient populations

[8] Statement from Dr. Watson, Exhibit 1-Q ("All patients are different, and therefore each patient has different sensitivities, tolerances, and reactions to hormone therapy that must be monitored throughout treatment so that the dosages and/or combinations of hormones can be adjusted appropriately. The commercially available BHRT does not, in my experience and medical judgment, allow me to effectively treat my patients the same way and to the same degree to that of compounded BHRT."); Statement from Dr. Strobel, Exhibit 1-O ("In my professional medical judgment, I prefer to treat my patients with compounded BHRT instead of the commercially available BHRT because hormone therapy requires a constant reassessment and adjustment of the hormone dose and the medication. It is impossible to treat patients with a one-size-fits-all hormone therapy treatment.").

that simply cannot be treated by an FDA-approved BHRT drug.[9] Physicians recognize the clinical utility of compounded BHRT to fill the gaps in treatment left by FDA-approved BHRT, and to provide for a more consistent, tailored manner of hormone treatment that significantly reduces, if not eliminates, common side effects.

(i) *Compounded BHRT Preparations Can Be Prepared In A Wider Variety of Dosage Forms, Strengths and Combinations.*

Compounding offers patients a variety of dosage strengths, forms, and combinations that would not otherwise be available to them if patients were relegated to only the commercially available hormone therapies. The following chart sets forth the dosage forms available in an FDA-approved BHRT drug product, compared to the dosage forms that can be prepared by a Section 503A compounding pharmacy or Section 503B compounding facility:

Dosage Form Available	**Commercially Available BHRT Drug Products**	**Compounded BHRT Preparations**
Oral	• Capsules (powder filled) • Capsules (oil based) • Tablets	• Capsules (powder filled) • Capsules (lactose free) • Capsules, semi-solid filled • Capsules, oil-filled • Tablet triturates • Troches and mini-troches, soft • Troches and mini-troches, hard • Buccal tablets • Soft linguets • Liquids (syrups, suspensions, emulsions) • Sublingual drops (oil)
Vaginal	• Gel • Creams • Inserts • Rings • Tablets	• Suppositories/inserts - Water-soluble - Lipid-soluble • Creams • Solutions (Poloxamer, etc.)
Topical/Transdermal	• Gels • Patches • Mini-patches (dots) • Topical emulsion • Spray solution	• Creams • Gels • Microemulsion gels • Lotions, clear • Lotions, opaque • Lotions (aqueous, nonaqueous) • Suspensions
Injection	• Aqueous	• Aqueous

[9] Statement from Dr. Grant, Exhibit 1-G (describing how commercially available bioidentical micronized progesterone is contraindicated in patients with a peanut allergy because it contains peanut oil); Statement from Dr. Jacobs, Exhibit 1-H (describing how there is no commercially available bioidentical testosterone approved for treatment in women).

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	• Oils (sesame, castor)	• Nonaqueous (e.g., sesame oil, castor oil, grapeseed oil, CoSolvents)
Nasal	No commercially available option.	• Drops • Sprays • Solutions • Suspensions
Rectal	No commercially available option.	• Enema - Gels - Suspensions - Emulsions

As is abundantly clear from the chart, patients can obtain compounded BHRT preparations in a much wider variety of dosage forms and combinations than those available to them from an FDA-approved BHRT drug product. Compounded BHRT preparations permit more choice, and can be prepared in a much more effective manner to better treat the patient population.

Moreover, with compounded BHRT preparations, medical providers are able to adjust and optimize a patient's medication dosage forms and strengths rather than relegating their patients to cookie-cutter, commercially available BHRT drug products that do not work for them. For example:

- **Progesterone** – FDA-approved bioidentical progesterone only comes in two dosage forms—an oral peanut oil-filled gel cap that cannot be titrated, or vaginal gel—whereas compounded progesterone can be prescribed in any strength and in any form needed to best treat the patient.[10] Patients often require slight adjustments in strength of hormone therapy in order to receive the optimal benefits of therapy—the two commercially available progesterone products do not allow physicians to make these precise adjustments to the dosage strengths that are required in order to optimize treatment.[11] This is especially necessary because, in physicians' experience, only approximately half of the patient population being treated with commercially available progesterone can tolerate the hormone because the side effects are so severe that they cause patients to discontinue treatment.[12] The side effects of commercially available progesterone include mood changes, headaches, nausea, bloating, menstrual cramps, fluid retention and irritability.[13]

[10] Statement from Dr. Brownstein, Exhibit 1-C (describing the limitations in dosage form and strength of FDA-approved bioidentical progesterone and explaining a medical professional preference to treat patients with bioidentical progesterone compounded in a gel, cream, or troche depending on which form is best absorbed by the specific patient).
[11] Statement from Dr. Baker, Exhibit 1-A ("Safe and effective use of hormone therapy is idiosyncratic and requires ongoing reassessment of patient health, readjustment of hormone combinations, and readjustment of dosage strengths to effectively treat the patients that need this therapy.").
[12] Statement from Dr. Peet, Exhibit 1-K ("Only approximately half of the patients treated with commercially available progestins can tolerate the hormone because the side effects are so severe that they cause patients to discontinue the treatment.").
[13] Statement from Dr. Peet, Exhibit 1-K ("The side effects of commercially available progestins include mood changes, headaches, nausea, bloating, menstrual cramps, fluid retention, and irritability."); Statement from Dr. Grant, Exhibit 1-G ("Oral micronized progesterone in doses potent enough to protect the uterine endometrium, can give many patients CNS side effects, such as dizziness and fatigue."); Statement from Dr. Strobel, Exhibit 1-O (describing the risks and side-effect profile of

Prometrium, in particular, is a commercially available progesterone medication available as an oral capsule. It contains sensitive oils that can denature the progesterone during shipping and delivery of the medication. Additionally, the capsule contains peanut oil, so those patients with peanut allergies cannot be treated with it.[14] Finally, only approximately 80% of the patient population treated with Prometrium can tolerate the medication because of the side effects. If left to only Prometrium, approximately 20% of patients needing progesterone treatment would be left untreated without the availability of compounded forms of progesterone. On the other hand, compounded progesterone sublingual troches and oral capsules can be tolerated by the overwhelming majority of patients with no side effects.[15]

- **Estrogens** – There are a limited number of FDA-approved bioidentical hormone therapies containing estrogens and they are only approved in a few dosage strengths and forms. Women need estrogen doses adjusted constantly depending on life events and health changes. Oral estrogens represent the most frequently used route of administration but can produce wide ranges in serum levels due to the large variation in intestinal absorption and liver metabolization.[16] As a result, medical providers cannot optimize patients' estrogen status without the availability of compounded bioidentical estrogens, which allows them to tailor the dosage strength and dosage form. For example, many physicians prefer to treat their patients with estrogen compounded into a cream, gel, drops, troche, or a vaginal suppository, depending on what the individual patient can best absorb. Compounded Estrogen allows for changes in dosage forms while FDA-approved estrogen drug products cannot.[17]
    - **Estradiol** – One form of estrogen, Estradiol, is necessary for the treatment of postmenopausal patients. There are several options for Estradiol if the patient is under 60 years of age and healthy. However, in physician

commercially available progestin therapy); Statement from Dr. Warshowsky, Exhibit 1-P (describing how patients with a peanut allergy cannot tolerate commercially available progesterone).

[14] Statement from Dr. Peet, Exhibit 1-K and Statement from Dr. Warshowsky, Exhibit 1-P (describing how the heat-sensitive oils in Prometrium can denature the progesterone).

[15] Statement from Dr. Peet, Exhibit 1-K ("[O]nly approximately 80% of the patient population treated with Prometrium can tolerate the medication because of the progestin-type side effects."); Statement from Dr. Jacobs, Exhibit 1-H (describing how commercially available progesterone is "not as well absorbed by patients and often cause negative side effects, such as abnormal bleeding and inadequate improvement of symptoms," and how many patients better tolerate progesterone taken in different dosage forms); Statement from Dr. Baker, Exhibit 1-A ("Compounded progesterone in topical creams or oral troches are able to bypass many of these side effects.").

[16] J.P. Devogelaer et al., Long-term effects of percutaneous estradiol on bone loss and bone metabolism in postmenopausal hysterectomized women, 28 Maturitas Journal of the Climacteric & Postmenopause 243 (1998).

[17] Statement from Dr. Grant, Exhibit 1-G (describing how, although bioidentical estrogens are commercially available in several dosage forms, these products are sometimes not absorbed or tolerated well by patients, which make the product ineffective with respect to that patient); Statement from Dr. Brownstein, Exhibit 1-C ("There are a limited number of FDA-approved bioidentical hormones therapies and they are only approved in a few dosage strengths. Women need estrogen doses adjusted constantly depending on life events and health changes."); Statement from Dr. Stanger, Exhibit 1-N (describing how bioidentical estriol is not commercially available and therefore must be compounded in order to treat certain conditions like vaginal dryness).

experience, only approximately ***half*** of patients are able to absorb transdermal formulations.[18] If the patient desires to continue transdermal administration, often a compounded, stronger version of the BHRT is required in order to appropriately treat the patient. Oral estradiol increases the risk of blood clotting disorders. Compounded transdermal estradiol and compounded estradiol in subcutaneous pellets reduce this risk as well as the risk of heart attack and stroke.[19]

Estrogel, in particular, is an FDA-approved bio-identical Estradiol topical gel that is typically prescribed to female patients in doses of one pump (1 gram) per day; however, most female patients require more than one pump to effectively treat their symptoms. Most patients cannot absorb two pumps (2 grams) of Estrogel in a consistent manner because of the amount of surface area on the body that the topical cream needs to cover. In these instances, physicians prescribe compounded bio-identical Estradiol in a more concentrated dose. With double the strength in one pump, patients get a better treatment that is tailored to what they actually need and their compliance with the prescribed dose is higher than if patients had to use two pumps of Estrogel each day.[20]

- **Testosterone** – There are only a limited number of FDA-approved bioidentical testosterone dosage strengths, and there is no FDA-approved bioidentical testosterone for treatment in women alone, or in ***both*** men and women. Compounded testosterone allows physicians to not only effectively treat male and female patients, but allows them to adjust the dosage strength or combination of hormones slightly depending on the health status of the patient.[21]

  Physicians prescribe compounded testosterone for women in creams, sublingual troches, and subcutaneous pellets. Compounded testosterone as a subcutaneous pellet, in particular, delivers more constant serum levels with fewer peaks and troughs compared to creams and troches. The vast majority of female patients being treated with compounded testosterone pellets for androgen deficiencies have all androgen deficiencies resolved without any side effects.[22]

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[18] Statement from Dr. Strobel, Exhibit 1-O ("[O]nly approximately ***half*** of patients are able to absorb the transdermal formulations which means that the available strengths often are not sufficient.").

[19] Statement from Dr. Peet, Exhibit 1-K (describing the risks of blood clotting disorders such as deep vein thrombosis and risk of pulmonary embolism with oral estradiol).

[20] Statement from Ms. Farrell, Exhibit 1-F (describing the issues many patients experience with Estrogel).

[21] Statement from Dr. Grant, Exhibit 1-G ("Currently, there are no bioidentical testosterone products available for women commercially. Therefore, custom compounded testosterone products are the only option available."); Statement from Dr. Stanger, Exhibit 1-N ("[C]ompounded bioidentical testosterone is very important for women, as there is currently no bioidentical testosterone FDA-approved for treatment in women."); Statement from Dr. Brownstein, Exhibit 1-C ("There are only a limited number of FDA-approved testosterone dosage strengths, and there is no FDA-approved testosterone for treatment in both men and women.").

[22] Statement from Dr. Peet, Exhibit 1-K ("prefer to prescribe compounded testosterone as a subcutaneous pellet because pellets deliver more consistent serum levels with less peaks and troughs compared to the creams and troches. The more peaks in serum levels cause more side effects (acne, abnormal hair growth, oily skin, fluid retention); the more troughs in serum levels means

> Moreover, Androgel, the commercially available testosterone for men, does not absorb as well in male patients—rather, the serum levels spike too high and cause side effects or drop too low and are ineffective. The serum level spikes and troughs both occur within 24 hours of application of the gel. Similar risks are associated with commercially available injectable testosterone for men—the serum level spikes are too high and cause acne, hair loss, fluid retention, and elevated red blood cell count; or the serum level troughs are too low and are less effective. Accordingly, physicians prescribe compounded testosterone for men in creams and subcutaneous pellets, which deliver more consistent results with less side effects.[23]

There are myriad other instances where the FDA-approved product does not adequately meet patient needs and compounded BHRT preparations are better suited for certain patient populations. Physicians recognize that compounded BHRT preparations more effectively treat their patients and, accordingly, consistently prescribe compounded BHRT preparations as part of their overall treatment regimen.

In addition to obtaining a more tailored approach, compounded BHRT preparations also promote patient compliance. It is worth considering that patients treated with the synthetic hormones contained in FDA-approved drug products suffer severe side effects such as weight gain, cognitive issues, and acne, which often leads to patient non-compliance with hormone therapy. Patients will often simply not refill their prescription once they experience these side effects.[24] With compounded BHRT preparations, physicians can perform blood tests on their patients and adjust their medications over time during the course of treatment to ensure that patients receive the most precise dosage forms and strengths tailored to their needs and current circumstances.[25] Compounded BHRT preparations tailored to the patient eliminate the side effects associated with synthetic hormones and, accordingly, ensure patient compliance with treatment protocols.[26]

(ii) *Compounded BHRT Preparations Cannot Go Through New Drug Approval*

It is important to note that compounded BHRT preparations cannot go through new drug approval. As set forth in the attached physician statements, in order to appropriately treat patients with hormone medications, a physician will first perform a blood test on a patient, and then, once those results are

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the treatment is less effective."); Statement from Dr. Jacobs, Exhibit 1-H (describing how having the ability to treat patients with compounded pellet therapy avoids the peaks and troughs of absorption often caused by treatment with transdermal creams and troches).

[23] Statement from Dr. Peet, Exhibit 1-K (describing the serum level issues he has observed in patients being treated with Androgel).

[24] Statement from Dr. Rice, Exhibit 1-M ("When patients were treated with synthetic hormones, they suffered severe side effects such as weight gain, cognitive issues, and acne, which often led to patient noncompliance with the hormone therapy. Specifically, patients would return often having never refilled their prescription after the first prescription fill."); Statement from Dr. Stanger, Exhibit 1-N ("The more tolerable the medication, the greater the patient compliance with the treatment regimen.").

[25] Statement from Dr. Jacobs, Exhibit 1-H ("With compounds, I am able to perform blood tests on my patients every 5-6 weeks to evaluate and reevaluate how the patients is responding to the hormone therapy."); Statement from Dr. Stanger, Exhibit 1-N (describing how her standard of practice is to evaluate blood tests on patients every three months to once a year, which allow her to consistently monitor hormone levels of patients and adjust hormone treatment dosages accordingly); Statement from Dr. Brownstein, Exhibit 1-C (describing how compounded BHRT is necessary to be able to make "precise adjustments to the dosage strengths that are required in order to optimize treatment.").

[26] Statement from Dr. Rice, Exhibit 1-M (describing side effects associated with synthetic hormone treatment).

obtained, prescribe compounded BHRT in the dosage form and strength tailored to the patient's needs. That patient is then monitored throughout the course of treatment and the physician will make tweaks to the compounded BHRT preparation based upon the patient's continued progress. As a result, compounded BHRT preparations are prescribed in a myriad of different combinations, dosage forms and strengths.

There is no way, accordingly, that all of the different dosage forms, strengths and combinations of compounded BHRT preparations can go through new drug approval. New drug approval takes millions of dollars and years of clinical study before a new drug makes its way to market. New drug approval does not allow for incremental changes in medication over the course of treatment. Each change to a compounded BHRT preparation is in a small amount and may be different depending on what a patient's blood test shows. Physicians are, in essence, responding in real time to the patient's needs. The new drug approval process does not allow for this kind of real-time changes in personalized treatment. As a result, the only way for most patients in need of hormone therapy to obtain the appropriate medication to fit their needs is through compounding.

(iii) *FDA-Approved BHRT Drug Products Cannot Treat All Patients And Patient Conditions*

Finally, there are not enough FDA-approved BHRT drug products on the market today to address the myriad patient populations and disease states that would benefit from hormone therapy. First, we note that FDA-approved hormone therapies are designed for, and approved to, treat certain disease states and are not, in fact, manufactured for hormone replacement therapy. Thus, the nature of compounded BHRT medications are fundamentally different than those of FDA-approved drug products and the hormone treatment protocol they achieve serves a fundamentally different medical purpose.

Thus, not only do compounded BHRT preparations allow for more choice with respect to the nature, dosage form and strength of the drug product, but compounded BHRT preparations are vital to treat conditions that are not addressed by the FDA-approved BHRT products on the market today. For example:

- **Testosterone** – There is no commercially available bioidentical testosterone approved for women. Women with low bone density, weight gain, loss of energy, hot flashes, night sweats, depression, and sleep issues benefit from testosterone treatment. Many women must resort to self-treatment with their husband's testosterone, which is not appropriately dosed for female patients. As a result, physicians regularly prescribe compounded bio-identical testosterone to resolve low libido, sleep issues, and bone mass deficiency in female patients. The compounded bio-identical formula is safer for female patients than using the commercially available testosterone for men.[27]
- **Combination Testosterone + Progesterone + Estrogen** – There is no FDA-approved combination testosterone, progesterone, and estrogen product, therefore, the only way a patient may be treated with this combination is via a compounded form of the

[27] Statement from Dr. Dorr, Exhibit 1-E ("In my professional medical experience, I have witnessed many female patients that require testosterone treatment and, as a result, are relegated to self-treating with their husbands' testosterone, which is dosed as male ranges and is unsafe for self-treatment by women."); *see also* Statement from Dr. Jacobs and Statement from Dr. Strobel, Exhibits 1-H and 1-O respectively, discussing the issues prevalent with no commercially available bioidentical testosterone approved for treatment in women.

medication. Physicians prescribe this combination of bioidentical hormones to treat menopausal symptoms, depression, anxiety, bone health issues, urinary problems, and andropause (in men only).[28]

- **Combination Progesterone + Testosterone** – There is no FDA-approved combination testosterone and progesterone product. Therefore, the only way to obtain this combination is via a compounding facility. Physicians prescribe combination testosterone and progesterone in creams or gels depending on how their patients absorb the therapy. Such compounded combinations are prescribed to treat menopause, depression, anxiety, bone health issues, and brain dysfunction.[29]

In fact, there are entire patient populations that can only be treated with compounded BHRT preparations. These include (1) patients with allergies; (2) patients who cannot use specific dosage forms (*i.e.* cannot swallow, pediatric, skin conditions, gut issues, etc.) and (3) patients who cannot tolerate side effects of commercially available hormone therapies.[30] Without the availability of compounded BHRT preparations, thousands of patients will needlessly suffer simply because they cannot be effectively treated by the commercially available BHRT drug products available today.

II. Compounded BHRT Preparations Are Safe, Effective And Do Not Present Demonstrable Difficulties For Compounding Consistently.

The Coalition understands that one of the primary concerns the Committee must consider is not simply that compounded BHRT preparations are necessary for treatment, but also that they are safe and effective. The Coalition wishes to assure the Committee that compounded BHRT preparations are indeed safe and effective, and do not present demonstrable difficulties to compound consistently.

(a) Compounded BHRT Preparations Are Known To Be Safe and Effective.

As is evident from the physicians' and nurse practitioner's statements accompanying this submission, and contrary to the narrative put forth by certain presenters to the Committee, compounded BHRT preparations have been shown to be consistently safe and effective for patients in a wide variety of circumstances that require hormone therapy. There is, in fact, no evidence of a pattern of "adverse events" associated with compounded BHRT preparations, nor is there a basis to assert that they are unsafe or an ineffective treatment for a variety of conditions.

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[28] Statement from Dr. Brownstein, Exhibit 1-C (describing the forms in which he prescribes compounded combinations of bioidentical testosterone, progesterone, and estrogen and for which conditions in his female patients because there is no commercially available bioidentical combination of these hormones).

[29] *Id.* (describing the forms in which he prescribes compounded combinations of bioidentical testosterone and progesterone and for which conditions in his female patients because there is no commercially available bioidentical combination of these hormones).

[30] *See* Statements from Dr. Grant, Dr. Jacobs, Dr. Peet, Dr. Warshowsky, Exhibits 1-G, 1-H, 1-K, and 1-P respectively, which discuss how commercially available bioidentical progesterone is contraindicated in patient populations that suffer from a peanut allergy, and how many side effects of commercially available bioidentical hormone therapies cannot be tolerated by patients.

As a threshold matter, Section 310.305(b) defines a "serious adverse drug experience" to mean:

> Any adverse drug experience occurring at any dose that results in any of the following outcomes:
>
> - Death;
> - A life-threatening adverse drug experience;
> - Inpatient hospitalization or prolongation of existing hospitalization;
> - A persistent or significant disability/incapacity, or
> - A congenital anomaly/birth defect.
>
> Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include
>
> - allergic bronchospasm requiring intensive treatment in an emergency room or at home;
> - blood dyscrasias or convulsions that do not result in inpatient hospitalization; or
> - the development of drug dependency or drug abuse.

21 U.S.C. § 310.305(b). The Coalition is not aware of serious adverse drug experiences associated with compounded BHRT preparations that would fall within the definition above.[31] Many purported risks associated with compounded BHRT preparations, moreover, are misleading or completely false.[32]

Nevertheless, to the extent there is ever an event that falls within "serious adverse drug experience," it will be reported to FDA. Section 503B outsourcing facilities must, pursuant to statute, submit adverse event reports to FDA. 21 U.S.C. § 353b(b)(5). Failure to report such events is a violation of the FDCA. Likewise, although Section 503A of the FDCA does not expressly require traditional compounders to report serious adverse drug experiences to FDA, FDA is required to have enhanced communications with the States and state regulatory bodies about concerns raised, or actions taken, against compounding pharmacies. 21 U.S.C. § 105. One of the ways FDA intends to pursue this communication is through the *Memorandum of Understanding Addressing Certain Distributions of Compounded Drug*

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[31] We note that recently FDA reported that during a routine inspection in 2018 of BioTE Medical, FDA investigators uncovered information about 4,202 alleged adverse events that had ***never*** been reported to the Agency. *See* Sept. 9, 2019 FDA Statement *On Improving Adverse Event Reporting of Compounded Drugs to Protect Patients*, https://www.fda.gov/news-events/press-announcements/statement-improving-adverse-event-reporting-compounded-drugs-protect-patients. These "adverse events" were not events that fell within the definition of "serious, life threatening or unexpected adverse drug experience" that would have required reporting to FDA. Rather, these "adverse events" were physicians' feedback to BioTE- which is a training organization. The overwhelming majority of this feedback described predictable and expected outcomes such as extrusions, cellulitis and hematomas and should not be construed as an indication that there is a public health risk associated with compounded BHRT.

[32] Statement from Dr. Pierce, Exhibit 1-L (discussing certain example of treatment with hormone therapy and how the treatment's alleged links to health risks are patently false).

Products Between the States and the Food and Drug Administration wherein States will agree to notify FDA of any complaint relating to a compounded preparation distributed outside the State involving a serious adverse drug experience or serious product quality issue and provide information about those events and issues. In addition, many States have similar adverse event reporting requirements, and both consumers and physicians are able to file MedWatch reports with FDA at any time with respect to a complaint about a compounded BHRT preparation. Thus, there are ample ways in which FDA will remain apprised of adverse events associated with compounded BHRT preparations.

Finally, even beyond the general lack of evidence to suggest that compounded BHRT preparations are unsafe or ineffective, both physician and patient experiences demonstrate that compounded BHRT preparations are safe and improve peoples' lives:

- **Allan B. Warshowsky, M.D., FACOG, ABIHM**[33] – Dr. Warshowsky is a board certified OBGYN who treats his patients with compounded BHRT instead of commercially available BHRT because compounded BHRT has proven to be a more effective treatment option for his patients. Many of Dr. Warshowsky's female patients come to him already being treated with commercially available BHRT that does not work for them – that is, they are not being fully treated, they are not able to tolerate the side effects, and they do not feel like they are getting better. In Dr. Warshowsky's experience, when he switches his patients from commercially available BHRT to compounded BHRT, these patients' health improves, their symptoms resolve, and they suffer far less negative side effects;
- **Gennell DeAn Strobel, M.D., FACOG**[34] – Dr. Strobel is a board certified OBGYN who treats many of her patients safely and successfully with compounded BHRT in ways that she is not able to do with commercially available BHRT. In Dr. Strobel's medical opinion, "one-size-fits-all" commercially available BHRT cannot relieve many of her patients' symptoms in the way that compounded BHRT can and does.

  Dr. Strobel has witnessed huge improvements in patient conditions when using compounded BHRT—for example, one patient told her that, "she had not been able to have intercourse or even wear panties or slacks for over 9 years and was able to resume these activities happily after 6 months of therapy!"[35] Once Dr. Strobel began treating the many breast cancer survivor patients with compounded BHRT, Dr. Strobel "quickly realized the impact of this treatment when women (and their spouses) literally cried tears of joy when they 'felt like a woman again' because they were able to enjoy intimacy again. Women would also tell [her] that their sleep, energy, hot flashes, moods, and many other aspects of life were improved as well."[36]

  Dr. Strobel has treated thousands of menopausal and perimenopausal patients and, in her medical experience, very few women have complete resolution of their menopausal and perimenopausal symptoms with commercially available hormone therapy. This data is drastically different with compounded BHRT which, in Dr. Strobel's

[33] *See* Statement from Dr. Warshowsky, Exhibit 1-P.
[34] *See* Statement from Dr. Strobel, Exhibit 1-O.
[35] *Id.*
[36] *Id.*

experience, resolves over 80% of these symptoms, and over 90% if sterile subcutaneous compounded pellets are used;

- **David Watson, M.D., FACOG**[37] – Dr. Watson is a board certified OBGYN who treats many of his patients with compounded BHRT because he witnesses "near immediate improvement in these patients' overall health"—a degree of treatment effectiveness he did not see with conventional, commercially available hormone therapies.[38] For example, Dr. Watson routinely witnesses severe osteopenia and osteoporosis completely reversed in patients after appropriate treatment with compounded BHRT. Dr. Watson also routinely sees his patients using less and less additional medication after being treated with compounded BHRT. That is, once taking compounding BHRT, these patients no longer need to rely on mood stabilizers, erectile dysfunction medication, or diabetes medication.

  Moreover, in Dr. Watson's medical experience, compounded BHRT reduces the risks associated with commercially available BHRT and, therefore, is a safer alternative. Specifically, when treating a patient with compounded BHRT testosterone pellets, in Dr. Watson's experience, the hormone is absorbed into the bloodstream and bypasses the liver, which results in a 70% reduction in breast cancer risk in patients where pellet therapy was the right dosage form. It is Dr. Waston's medical opinion that "compounded BHRT is real, it is effective, and it should be here to stay;"[39]

- **John Joseph Peet, M.D., FACOG**[40] – Dr. Peet is a board certified OBGYN who treats over 5,000 patients effectively with compounded BHRT. In Dr. Peet's medical experience, compounded BHRT is an effective hormone treatment option and "[a]pproximately 90-95% of [his] male and female patients treated with some form or combination of compounded BHRT have their symptoms completely resolved."[41]

  Further, compounded BHRT is a safe, and often safer, alternative to commercially available BHRT. In Dr. Peet's medical experience, compounded transdermal estradiol and compounded estradiol in subcutaneous pellets actually reduce the risk of heart attack and stroke when compared to the commercially available form. Similarly, compounded progesterone sublingual troches and oral capsules can be tolerated by 99% of his patients with absolutely no side effects—a sharp contrast, in his medical experience, to the side effects suffered by his patients when being treated with the commercially available form;

- **Laura Grant, M.D., NCMP**[42] – Dr. Grant is a board certified OBGYN who has specialized in menopausal hormone therapy for the past 12 years. In Dr. Grant's medical experience, her patients treated with compounded BHRT describe the therapy

[37] *See* Statement from Dr. Watson, Exhibit 1-Q.
[38] *Id.*
[39] *Id.*
[40] *See* Statement from Dr. Peet, Exhibit 1-K.
[41] *Id.*
[42] *See* Statement from Dr. Grant, Exhibit 1-G.

as "life saving," because "their quality of life would be so poor that it would not be worth living" if they were not treated with compounded BHRT.[43]

It is Dr. Grant's medical opinion that commercially available BHRT does not adequately treat her patients due to "ineffectiveness, non-toleration of side effects, insufficient dosages options to relieve symptoms, lack of variety in dosage and routes of administration, and complete non availability of testosterone."[44] Dr. Grant states, "my medical practice will be significantly hindered without the compounded hormone option, and female patients will be very poorly served to see this option removed. When the patient . . . returns to her ob/gyn or PCP for a better solution than the commercial product given, and the doctor responds, 'That's your only choice, take it or leave it.' I believe that we, as professionals entrusted with the care of midlife women experiencing life altering menopausal symptoms, can do a better of job, and we must not be hobbled in trying to do so;"[45]

- **Bruce Dorr, M.D., FPMRS**[46] – Dr. Dorr is a board certified OBGYN who treats his patients with compounded BHRT because it is an effective hormone therapy treatment option for his patients. Dr. Dorr finds that "it is effectively impossible to treat patients with a one-size-fits-all hormone therapy treatment."[47] Compounded BHRT is also a safer alternative to commercially available BHRT—for example, compounded BHRT in pellet form is much safer for patients with a history of blood clotting, such as deep vein thrombosis or pulmonary embolus;
- **Steven A. Komadina, M.D.**[48] – Dr. Komadina is a board certified OBGYN and New Mexico State Senator who switched to treating his patients with compounded BHRT because he witnessed the health of his patients significantly and quickly improve at rates that he had not previously seen with commercially available BHRT. In Dr. Komadina's experience, his patients better tolerate compounded BHRT and demonstrate more consistent results from treatment with compounded BHRT. In Dr. Komadina's medical judgement, if he had to return to treating patients with only commercially available BHRT, "I know that I would witness a decline in my patients' health and wellbeing;"[49]
- **Arlene Jacobs, M.D.**[50] – Dr. Jacobs is a board certified OBGYN whose patients simply feel better on compounded BHRT. In Dr. Jacobs' medical opinion, compounded BHRT "is a safer treatment as there is no risk of clotting and compounded BHRT carries far less side effects."[51] Further, compounded bioidentical hormone therapies

[43] *Id.*
[44] *Id.*
[45] *Id.*
[46] *See* Statement from Dr. Dorr, Exhibit 1-E.
[47] *Id.*
[48] *See* Statement from Dr. Komadina, Exhibit 1-I.
[49] *Id.*
[50] *See* Statement from Dr. Jacobs, Exhibit 1-H.
[51] *Id.*

bypass the liver and are safer for patients who have suffered a stroke or some form of blood clot; and

- **Christine Farrell MS.N, F.NP.-C**[52] – Ms. Farrell is a credentialed nurse practitioner who successfully treats approximately 90-95% of her patients with compounded BHRT. It is Ms. Farrell's professional opinion that compounded BHRT "is safer and more effective for patients requiring hormone therapy" than the commercially available BHRT options.[53]

As is evident from the above, and the other physicians' statements attached hereto, compounded BHRT preparations are safe and effective, and patients experience better health outcomes when using compounded BHRT preparations than they do when taking commercial BHRT drug products.

(b) Compounded BHRT Preparations Do Not Present Demonstrable Difficulties For Compounding.

The Coalition understands that Jane Axelrad of Axelrad Solutions, LLC has suggested that the Committee consider whether compounded BHRT preparations are demonstrably difficult to compound in order to inform its assessment of whether compounded BHRT preparations are safe and effective. As a threshold matter, the purpose and scope of this Study does not contemplate an analysis of whether compounded BHRT preparations are demonstrably difficult to compound. That is for FDA to determine in accordance with the parameters set forth in the FDCA. Accordingly, the Committee ***should not consider this issue*** for purposes of its Report.

Nevertheless, to the extent the Committee wishes to tackle the demonstrably difficult analysis, the Coalition maintains that compounded BHRT preparations ***do not*** present demonstrable difficulties for compounding such that the difficulties are reasonably likely to lead to an adverse effect on the safety or effectiveness of that drug product. The Coalition has a wealth of data to demonstrate that compounded BHRT is not demonstrably difficult to compound—and will provide it upon request. To the extent that the Committee does believe this analysis is integral to whether compounded BHRT is safe and effective, it should examine this data before coming to any conclusion. Without this data, the Report would be incomplete. The Coalition further notes that if the Committee is truly considering a detailed analysis on this subject, then a separate meeting is necessary to fully address this issue.

By way of background, both Section 503A and Section 503B of the FDCA require compounded drugs to satisfy several conditions in order to be entitled to certain statutory exemptions under the FDCA. Section 503A prohibits traditional compounders from compounding a drug product if it "presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product." 21 U.S.C. § 353a(b)(3)(A). Similarly, one of the conditions for compounding under Section 503B is that the drug cannot be on a list published by the Secretary of drugs or categories of drugs "that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into account the risks and benefits to patients," and that the drugs are compounded in accordance with "conditions that are necessary to prevent the drug or category of drugs from presenting [such]

[52] *See* Statement from Ms. Farrell, Exhibit 1-F.
[53] *Id.*

demonstrable difficulties." 21 U.S.C. § 353b(a)(6). Both Section 503A and 503B require FDA to develop a list of difficult to compound drugs through regulations, which means notice and comment rulemaking.

FDA has solicited nominations for the difficult to compound list(s), and several nominations submitted so far include hormone products, namely: estradiol (oral and topical); progesterone (oral and topical); progesterone with estradiol (oral and topical); testosterone pellets; and estriol (dosage form not specified).[54] FDA intends to consider a set of six criteria when considering whether a drug product is demonstrably difficult to compound. As set forth below, the six criteria do not support the conclusion that compounded BHRT preparations, including those already nominated, are demonstrably difficult to compound.

(i) *Complexity of the Formulation.*

One of the first considerations in determining whether a compound presents demonstrable difficulties is whether the formulation of the compound is complex. FDA has stated that a complex formulation refers to formulations in which the ingredients (both active and inactive) "are required to have certain physicochemical characteristics or properties that are necessary to achieve or maintain the proper performance of the drug product."[55] In addition, "the compatibility and/or stability (physical and chemical) of the API(s) and/or excipients in the final dosage unit may be evaluated to determine if the compounded drug product has a complex formulation." FDA has particularly focused on particle size and the concern that, if particle size distribution is not maintained, there will be changes in absorption both topically and orally.

First, with respect to compounded BHRT preparations, both Section 503A and Section 503B facilities that compound BHRT preparations have a wealth of stability and potency data demonstrating that compounded BHRT preparations are consistently stable over time. Compounders understand the importance of BHRT formulations that enable proper performance of the drug product, which must include optimal absorption within patients.[56]

Second, compounders understand that particle size in the context of hormone therapy is critical. There will always be variability in the particle size of a drug product. However, compounders have many tools available to them to deal with particle size distribution. For example, compounders can use a mortar and pestle to grind bulk ingredients into more uniform distributions. This is a traditional method that effectively reduces the particle size. Compounders also have mixers, blenders, and milling devices that can increase particle distribution while ensuring consistency of particle size. For example, an Unguator is a mixer that can be used for various preparations based upon time and RPM settings. An Unguator prepares uniform particle distribution consistently and repeatedly, ensuring uniform particle distribution that can aid in performance of the compound. A Ram or Resodyn Acoustic mixer delivers formulations within the FDA RSA value, actual results 3%. Compounders also use SpeedMixers and Mazerustar®

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[54] Please note that Abraham Morgentaler, M.D., who originally nominated testosterone pellets for the difficult to compound list, has expressed his intention to withdraw the nomination. His statement regarding his decision to withdraw compounded testosterone pellets from the difficult to compound nomination process is attached hereto as Exhibit 2.

[55] *See* PDF of Presentation by Jane Axelrad to NASEM: Understanding the List of Difficult to Compound Drug Products, June 27, 2019.

[56] The Coalition has access to a wealth of data demonstrating stability and can provide the same to the extent the Committee wishes to review the data.

planetary mixers, which provide fast and thorough mixing and deaeration simultaneously. Finally, an ointment mill can reduce particle size of a compounded preparation to under 20 microns using sheer force to reduce particle size. This equipment can be calibrated to ensure consistency over time. Overall, pharmacists can rely on equipment to aid in the particle distribution, prohibit agglomerate formation and employ particle size reduction with equipment at their disposal.[57]

As a result, the complexity of the formulation for compounded BHRT does not render them too difficult to compound.

(ii) *Complexity of the Drug Delivery Mechanism.*

FDA has stated that the complex drug delivery mechanism "refers to the way in which the drug is released from the dosage form or targeted for delivery in the body to achieve the desired therapeutic effect, such as passing through the stomach without dissolution and absorption or achieving permeation through the skin at a specific rate." Arguments suggesting that compounded BHRT preparations have a complex drug delivery mechanism include that estradiol, progesterone and testosterone must be administered using specific dosage forms to enable complex drug delivery and absorption mechanisms for GI transport, or for transdermal or vaginal transport. In addition, it is purported that since reproductive hormone API is highly lipophilic, formulations employing hard and soft gelatin capsules, which contain water, need to be carefully characterized to ensure water migration into fill material does not result in API precipitation, from conversion or particle size growth to the extent it changes the product performance, and safety and efficacy, over the shelf-life of the product.

These characterizations are inaccurate. Hormone pellets, for example, are compounded in a mechanism that has been around since the 1950s. Compressed pellets have been clinically shown to absorb at a rate consistent with clinical data being presented to the Committee. In addition, there is an approved drug with this mechanism in a singular strength that does not meet all patient needs. Likewise, with respect to micronized powder capsules, De Lignières found in 1999 that administration of oral progesterone micronized powder capsules as part of an HRT regimen in post-menopausal women is effective at preventing estrogen dependent endometrial stimulation.[58] Several pharmacokinetic studies have shown relatively consistent AUC, Cmax, and Tmax values.

In addition, proponents of placing compounded BHRT preparations on a difficult to compound list argue that many of the same concerns also apply to the oral and vaginal dosage forms which require sophisticated knowledge of the various delivery and absorption mechanisms and their designs, including the thickness, surface area, and water content of the dosage form, and the chemical structure of the mechanism of release from hard-gelatin capsules, tablets and soft gel capsules, or other lipid and crystalline based vehicles, such as pellets or suppositories. In a study carried out in 1999 by Ken Burry, "[s]ignificant increases in serum concentrations of progesterone were observed in all of the women studied."[59] Furthermore, in a study at the University of Sao Paulo, researchers found that compounded

[57] The Coalition can provide the Committee with supportive data if so desired.
[58] De Lignières B. Oral micronized progesterone. Clin Ther. 1999;21(1):41-60. doi:10.1016/S0149-2918(00)88267-3; Maxson WS, Hargrove JT. Bioavailability or oral micronized progesterone. Fertil Steril. 1985;44(5):622-626. doi:10.1016/S0015-0282(16)48977-6.
[59] Am J Obstet Gynecol 1999;180:1504-11.

vaginal progesterone prophylactically reduced the frequency of uterine contractions and the rate of preterm delivery in women at high risk for prematurity.[60]

Accordingly, the Coalition maintains that the complex delivery systems (e.g., oral capsules compounded without allergenic oils or pelleted hormones) affirmatively do not present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product.

(iii) *Complexity of the Dosage Form.*

The third factor FDA intends to consider is whether the physical dosage units of the compounded BHRT preparations present characteristics that are difficult to consistently achieve and maintain. In doing so, it intends to consider the "container closure systems that may interact with the compounded drug and affect its intended use, either through physical (inconsistent dose administration) or chemical interactions between the compounded drug and the container closure system."

As set forth in the chart provided in Section I(c)(i) above, compounded BHRT preparations can be prepared in a wider range of dosage forms than the commercially available alternatives. Nevertheless, while compounding allows for bioidentical hormones to be available to patients in a variety of physical dosage units, the characteristics of these dosage units are not too difficult to consistently achieve or maintain when performed in an appropriate environment and with equipment that can ensure consistency and safety.

Arguments that compounded BHRT preparations have complex dosage forms appear to lean towards water absorption from capsules causing degradation. First, the Coalition is not aware of any compounders that use water progesterone capsules dosed orally. Second, while this can be an issue for manufacturers where the drug products have expiration dates, but not for compounded products which employ beyond use dates. Compounding pharmacies employ lab services to test preparations to ensure stability and potency. Hormone pellets, for example, are made with dry active pharmaceutical ingredients (no water) compressed with only two ingredients. Full stability indicating stability studies ensure analytical testing identifies degradants and other parameters consistent with GMP level stability methods.

Accordingly, the variety of dosage forms available for compounded BHRT preparations does not make compounded BHRT too difficult to compound

(iv) *Complexity of Achieving Bioavailability.*

It is possible to ensure bioavailability of compounded BHRT preparations. FDA states that bioavailability refers to "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action." The Coalition understands that compounded preparations may be considered too difficult to compound if bioavailability is too challenging to achieve because of certain characteristics of the API or of the compounded formulation, such as low permeability and/or low solubility. However, that is not the case with compounded BHRT

[60] If the Committee wishes to see the underlying data, the Coalition will make that data available for review.

preparations. Numerous studies show that progesterone micronized powder capsules show appropriate bioavailability.[61] Hormone pellets show bioavailability from actual patient results achieved in well over a million pellet insertions and can be verified through the thoughts of physicians utilizing the therapy and from clinical studies. In addition, please see the enclosed synopses of studies with regard to absorption and bioavailability for compounded BHRT preparations.[62]

Moreover, sometimes systemic absorption bioavailability is not something that is desired in treatment. Estriol vaginal cream preparations can take care of vaginal dryness and atrophy without endometrial lining build up or systemic elevation by dosing at 0.5mg daily and then reducing to 0.5mg twice weekly. A review of data form 1950 to 1994 Voojis determined that single daily intravaginal estriol treatment dosages clearly and consistently demonstrate that endometrial proliferation does not occur. They further concluded that single-day estriol treatment binding to the endometrial estrogen receptor is too short to induce proliferative effect.

Finally, there is recent data to support that hormone pellets have achieved bioavailability.[63]

Accordingly, as the data shows, it is possible to ensure bioavailability of compounded BHRT preparations.

(v) *Complexity of the Compounding Process.*

As described by FDA, "[c]ompounding process complexity refers to whether compounding the drug requires multiple, complicated, or interrelated steps and/or specialized facilities and/or equipment to achieve the appropriate drug product."

Compounding performed by the members of the Coalition, which is performed according to the conditions set out in Section 503A and Section 503B of the FDCA, is done within specialized facilities using specialized equipment. For example, Section 503A compounders use SpeedMixers and Section 503B outsourcing facilities use Mazerustar® planetary mixers, which provide fast and thorough mixing and deaeration simultaneously. Achieved through continually revolving and rotating the container concurrently, the unique dual rotation action eliminates the need for mixing rods, blades or media, or an evacuation device and can dramatically reduce processing times.[64] Likewise, compounders can use a mortar and pestle, mill, blender, and/or automated sieving device to grind bulk ingredients into more

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[61] Maxson WS, Hargrove JT. Bioavailability or oral micronized progesterone. Fertil Steril. 1985;44(5):622-626. doi:10.1016/S0015-0282(16)48977-6; Handelsman D, Machey MA, Howe C, Turner L, Conway AJ. An analysis of testosterone implants for androgen replacement therapy. Cinical Endocrinology. 1997; 47, 311-315; Handelsman D, Conway AJ, Boylan L. Pharmacokinetcs and Pharmacodynamics of Testosterone Pellets in Man. Journal of Clinical Endocrinology and Metabolism. 1990; 70, 216-221; De Lignières B. Oral micronized progesterone. Clin Ther. 1999;21(1):41-60. doi:10.1016/S0149-2918(00)88267-3.

[62] Synopses of studies regarding absorption and bioavailability for compounded BHRT preparations, enclosed herein as Exhibit 3.

[63] F. Jockenhovel, E. Vogel, M. Kretzer, W. Reinhardt, S. Lederbogen and D. Reinwein, Pharmacokinetics and pharmacodynamics of subcutaneous testosterone implants in hypogonadal men, Clinical Endocrinology (1996) 45, 61-71.

[64] Dual Action Revolution & Rotation Mixers, Technic, https://www.technic.com/equipment/parts-supplies-accessories/mazerustar-planetary-mixers (last visited November 7, 2019).

uniform distributions. Compounder also has mixers, such as Unguator, Ram or Resodyn Acoustic mixers, and ointment mills.

Overall, there is nothing about the compounding process for BHRT that is too complex such that it is reasonably likely to lead to an adverse effect on the safety or effectiveness of the preparation.

(vi) *Complexity of the Physicochemical or Analytical Testing.*

Finally, there is sufficient release testing conducted that proves that compounded BHRT preparations are what they purport to be. FDA has stated that the physicochemical or analytical testing complexity "refers to the challenges presented with confirming the drug product will perform as expected with regard to certain characteristics." It is possible to test compounded BHRT preparations to ensure that they will perform as they are expected to perform, and many compounding facilities have the testing and data to support this.

USP and FDA set guidelines for testing compounded preparations. For Section 503A compounding pharmacies, these guidelines are set forth in USP quality assurance Chapter <1163> and Chapters <795> and <797>. FDA, in turn, has established cGMP requirements for 503B outsourcing facilities. According to analytical labs testing hormones, there is simplicity in testing due to hormones being small molecules with a good chromophore that allow for easy HPLC-UV detection. HPLC-UV is the most commonly used instrument in lab testing for small molecule drugs. No specialized instruments such as nuclear magnetic resonance, mass spectrometry, or x-ray powder diffraction are required in the testing of hormone substances. Compounders, whether they are Section 503A or 503B facilities, have access to independent lab services for microbial identification, potency/purity, sterility, particulate matter, and bioburden testing, including ARL Laboratories, DynaLabs, Eagle Labs, James River Labs, and Avomeen Laboratory.

In addition, with respect to Section 503A compounding pharmacies, underlying testing data supports the conclusion that compounded BHRT preparations are stable over time and are not too difficult to compound. Topical hormone studies, for example, show stability. Studies demonstrate that the compounding preparations are stable at the outset, and that the stability is maintained over time even in combination with multiple BHRT active ingredients. Compounded BHRT preparations prepared by Section 503B outsourcing facilities, in turn, are not too difficult to compound under cGMP. As shown by Product Annual Reviews (a requirement to comply with cGMP), important characteristics of stability, container closure, and related data demonstrates the safety and efficacy of compounded BHRT preparations. Studies show that compounded BHRT can be prepared safely and effectively, again and again over time.[65]

In sum, although the Committee ***should not*** consider this issue for purposes of its Report, the Coalition maintains that compounded BHRT preparations do not present demonstrable difficulties for compounding such that the difficulties are reasonably likely to lead to an adverse effect on the safety or effectiveness of that drug product.

[65] If the Committee wishes to see the underlying data, the Coalition will make that data available for review.

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III. Conclusion

The Coalition appreciates the attention of the Committee and hopes that this submission has contributed to the discussion regarding the clinical utility of compounded BHRT preparations. As set forth herein, the evidence supports finding that:

(1) compounded BHRT preparations are clinically necessary to treat the patient population; and

(2) compounded BHRT preparations are safe, effective and do not present demonstrable difficulties to compound.

As stated, although we understand that the Committee will be conducting a hearing on the Study on November 12, 2019, we respectfully request that the Coalition be granted a separate meeting with the Committee to present key experts and answer any questions the Committee may have. We look forward to hearing from you soon.

Very truly yours,

/s/ Rachael G. Pontikes

Rachael G. Pontikes

RGP:rl

Enclosures

Group Exhibit 1

Exhibit 1-A

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Statement from Jeffrey R. Baker M.D. M.S.

Qualifications

My name is Jeffrey R. Baker, M.D., M.S. My professional background is as follows. I received my Bachelor of Arts in Chemistry and Biology from Point Loma College in San Diego, California in 1978. I received my Masters of Science in physiology and immunology in 1980 and my Doctor of Medicine from Oral Roberts University School of Medicine in 1984. I completed my residency in Family Practice at the University of California Irvine Memorial Medical Center from 1984 to 1987, where I also served as Chief Resident of Family Practice in 1987. During residency, I practiced at Kaiser-Harbor City, California Urgent Care and Promptcare Urgent Care in Huntington Beach, California. My up to date CV is enclosed for reference.

I received certifications from the National Board of Medical Examiners and the American Board of Family Practice. I received the ABFP-Certificate of Added Qualification in Sports Medicine from 1993-2003. I have been licensed to practice medicine in Arkansas since 1997.

I have held numerous organization leadership positions. I was the Resident Physician Member of the American Academy of Family Physicians National Board of Directors from 1986-1987, the Delegate to the AAFP National Congress of Delegates from 1985-1987, the California AFP Board of Directors in 1987, the San Diego AFP Board of Directors from 1989-1994, the President of the San Diego County AFP from 1992-1993, the Executive Committee Graybill Medical Group from 1989-1995, the Executive Committee Palomar Medical Center from 1991-1994, the Chairman-Steering Committee for the Formation of the Department of Family Practice at Palomar Medical Center from 1991-1993, and the Board of Directors Palomar-Pomerado Medical Associates (IPA) from 1993-1994.

I have been in continuous private practice from 1987-present. During that time, I worked at Graybill Medical Group in Escondido, California in family practice, specifically inpatient care including ICU and surgery, and I worked in outpatient primary care and sports medicine from 1987-1997. I have also practiced Emergency Medicine and in-patient hospitalist duties at the V.A. Medical Center in Fayetteville, Arkansas from 1998 to present.

Presently, I work in outpatient primary care and integrative medicine at the Immanuel Clinic in Springdale, Arkansas, a position I have held since 1997.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

I treat approximately 900 patients annually in settings where compounded Bio-Identical Hormone Therapy ("*BHRT*") for male and female patients is a part of therapy, and the large majority of these patients are successfully prescribed and treated with BHRT using a compounded therapy solution.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I prescribe compounded BHRT to treat male and female patients of all ages depending on their individual symptoms. I prescribe compounded BHRT to treat andropause in male patients, and I prescribe compounded BHRT to treat various conditions and symptoms in teen through adult female patients. Specifically, I prescribe compounded topical creams, oral troches, oral capsules, vaginal creams, injectable testosterone and implantable pellets to treat the following conditions:

- Phase-related estrogen dominance and progesterone deficiency
- Perimenopausal hormone deficits
- Menopausal and post-menopausal hormone support therapy
- Disease-specific therapy for PCOS, fibrocystic breast disorder, endometriosis, ovarian cysts, fibroids, and cervical dysplasia

I prescribe compounded bioidentical hormone therapy to treat the above conditions in female patients because routinely available pharmaceutical options either lack necessary ingredients, or more commonly, do not have the manufactured dosage ranges required to individualize therapy.

Additionally, I prescribe individualized compounded progesterone in topical or oral forms for the management of post total abdominal hysterectomy with bilateral salpingo-oophorectomy ("*TAH/BSO*") patients with estrogen dominant side effects.

When applicable, compounded BHRT is prescribed to achieve normal peri and post-menopausal ranges of progesterone and androgen levels and can add to the comprehensive management strategy when fibromyalgia, chronic pain, and/or musculoskeletal issues are present.

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, the primary reason I choose to treat my patients with compounded BHRT instead of commercially available BHRT is the ability to individualize treatment, which is critical in hormone therapy. It is my professional medical opinion that the treatment needs of the patient population I see are too diverse to be treated by the current dosing forms of commercially available hormone therapies. Even if FDA were to approve more BHRT dosing forms in the future, these treatments would still not be tailored enough to meet the variety of hormone treatment needs of the majority of my patients. Safe and effective use of hormone therapy is idiosyncratic and requires ongoing reassessment of patient health, readjustment of hormone combinations, and readjustment of dosage strengths to effectively treat the patients that

need this therapy. Commercially available BHRT simply cannot be individualized to the extent it would need to be in order to treat these patients.

Additionally, non-enteral forms of delivery can be especially important for hormone therapy. Hormone metabolites are a common etiology for side effects and complications of oral therapy. Compounded progesterone in topical creams or oral troches are able to bypass many of these side effects. The use of compounded estriol can moderate the side effects of estradiol only therapy and can significantly reduced the estrogen dominant side effects that contribute to patient non-compliance with prescribed hormone therapy as well as some of the immediate to long term therapy complications, which can include fibrocystic breast disorder, fibroids, endometriosis and also the exaggeration of the 16 (OH) estrone/2 (OH) estrone ratios which have been proposed to promote pro-proliferative effects related and possibly predisposing to female reproductive cancers.

Finally, compounded BHRT allows me to properly address and resolve androgen deficiencies in female patients. The only available testosterone for treatment in women is found in one of two fixed estradiol/methyltestosterone formulations, which I avoid because: (1) oral forms of testosterone delivery promote adverse liver metabolites and (2) having only two dosing formats essentially negates appropriate individualized therapy for the majority of patients, making compounded testosterone the only reasonable option for treating androgen deficiencies in female patients.

Thank you for the opportunity to represent the medical concerns regarding continued availability of individually compounded BHRT for the many thousands of patients nationwide for whom these forms of therapy has been life changing.

Sincerely,

/s/ Jeffrey R. Baker, M.D., M.S.

Jeffrey R. Baker M.D. M.S.

Born: December 24, 1955

Married: Penne Baker Five children: 21-30 years of age

Undergraduate degree:

Point Loma College San Diego, CA

Double major Chemistry and Biology B.A 1974-78

Postgraduate Degrees:

Oral Roberts University-School of Medicine Tulsa OK

M.S. Physiology and Immunology 1978-80

M.D. Doctor of Medicine 1980-84

Residency Training

University of California Irvine Memorial Medical Center

Family Practice Residency 1984-87 Chief Resident-Family Practice 1987

Certifications:

National Board of Medical Examiners 1984

American Board of Family Practice 1987, 1993 and 2000

ABFP-Certificate of Added Qualification in Sports Medicine 1993-2003

Licensed in California 1985-1997

Licensed in Arkansas 1997-present

Organizational Medicine

American Academy of Family Physicians (AAFP) 1984-2007

Fellow of the AAFP 1991

California Chapter AFP 1984-1997

Arkansas AFP 1998-2000

California Medical Association 1987-1997

Arkansas Medical Society 1998-2000

San Diego County Medical Association 1987-1997

Washington County. AR Medical Society 1998-2000

American College of Sports Medicine 1990-2003

American College for the Advancement of Medicine 1990-present

Organizational Leadership:

-Resident Physician Member of the American Academy of Family Physicians National Board of Directors 1986-87

-Delegate to the AAFP National Congress of Delegates 1985-87

-California AFP Board of Directors 1987

-San Diego AFP Board of Directors 1989-94

-President San Diego County AFP 1992-93

-Executive Committee Graybill Medical Group 1989-1995

-Executive Committee Palomar Medical Center 1991-94

-Chairman-Steering Committee for the formation of the Department of Family Practice at Palomar Medical Center 1991-93

-Board of Directors Palomar-Pomerado Medical Associates (IPA) 1993-94

Occupational Experience

During residency:

-Kaiser-Harbor City, CA Urgent Care 1985-87

-Promptcare Urgent Care Huntington Beach, CA 1985-87

During private practice years 1987-2017:

-Graybill Medical Group Escondido, CA

-Family Practice, inpatient care including ICU and surgery 1987-1995

-Family Practice, outpatient primary care and sports medicine 1995-1997

-Immanuel Clinic Springdale, AR Outpatient primary care and Integrative Medicine 1997-present

-V.A. Medical Center Fayetteville, AR

-ER physician and in-patient hospitalist 1998-2015

-ER physician 2016-present

Contact:

900 Dorman Street Ste E

Springdale, AR 72762

479-756-3251 O

479-236-9047 C

baker900@gmail.com

Exhibit 1-B

texasgynecology

Statement From Dr. George Benson Branning, M.D.

Qualifications

My name is Dr. George Benson Branning, M.D. My professional background is as follows. I received my Bachelor of Arts in biology and microbiology from the University of Texas at Austin in 1983. I received my Doctor of Medicine at the University of Texas Southwestern Medical Center of Dallas in 1989. I completed my residency in obstetrics and gynecology at Baylor University Medical Center Dallas from 1989 to 1993, and I was Chief Resident from 1992 to 1993.

After residency, I worked as an attending physician at Baylor University Medical Center, Dallas from 1993 to 2008. In 2009 I moved my practice to Baylor Medical Center at Frisco (now Baylor, Scott and White Medical Center of Frisco), where I worked as the Chief of Staff from 2011 to 2012, and I worked as the Medical Director of Obstetrics from 2016 to 2017. Currently, I am a board-certified OBGYN in my solo practice, Texas Gynecology. I predominantly practice at Baylor, Scott and White Medical Center of Frisco. I no longer practice obstetrics and have dedicated my practice of medicine to gynecology, minimally invasive surgery, hormone balancing and aging, nutrition, sexuality, and overall human wellness.

I have numerous professional memberships. I am a fellow of the American College of Obstetrics and Gynecology and a Diplomate of the American Board of Obstetrics and Gynecology. I am a member of the Texas Medical Association, the Society of Laparoendoscopic Surgeons, the American Association of Gynecologic Laparoscopy, the Collin County Medical Association, the Dallas Ft. Worth Obstetrics and Gynecology Society, the Southwestern Gynecologic Assembly, and the Institute of Functional Medicine. For further information on my clinical interests and practice, please see my enclosed CV.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

As stated above, I have dedicated my practice in part to hormone therapy, which includes treating my patients with compounded bioidentical hormone replacement therapy ("*BHRT*"). I treat approximately 100 patients per month and all of them are being treated with some form of compounded BHRT. Approximately 90-95% of my patients being treated with compounded BHRT experience symptoms resolution, and patient compliance is near 100% with compounded BHRT options.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I prescribe compounded BHRT to treat a variety of medical conditions and symptoms in my male and female patients. Specifically, I prescribe compounded BHRT to treat the following:

Male Patients

- ADD-like symptoms
- Cognition fog
- Gain of fat mass
- Hypogonadism
- Loss of muscle mass
- Low libido
- Profound lack of energy
- Suboptimal testosterone levels

Female Patients

- ADD-like symptoms
- Cognition fog
- Loss of muscle mass
- Low libido
- Menopause symptoms (e.g., profound and abrupt drop of hormone levels, hot flashes, vaginal dryness, sexual dysfunction, and increase weight, among others)
- Problems with lipids
- Profound lack of energy
- Suboptimal testosterone levels (prior to menopause)
- Weight gain

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, I choose to treat my patients with compounded BHRT, where appropriate, instead of the commercially available BHRT, because compounded BHRT allows me to tailor critical hormone therapy to the individual needs of my patients. Compounded BHRT is important therapy because it mimics the way the ovary or the testicle makes the hormone. In my professional opinion, the biggest issue with FDA-approved BHRT is the inadequate nature of the dosing, and the unacceptable variance allowed in generics. In addition, some patients have issues with the adhesives with patches and as a result experience contact dermatitis, or will show significant absorption variability from one patient to the next with creams. These dosage forms may be the only option commercially available. Compounding allows me to treat the patient with both the dosage ***strength*** and dosage ***form*** that is best tolerated and best absorbed by the individual patient. In other words, I can trust the modern compounding pharmacy with dose, purity, and quality control that most optimally treats my patients for the conditions from which they suffer.

- **Testosterone**

I prescribe compounded bioidentical testosterone, typically in pellet form, for my male and female patients. Again, pelleted delivery mimics the gonad's delivery of testosterone. The commercially available bioidentical testosterone that is available as a cream is an issue for patients because each patient absorbs a cream differently, and the biochemistry is difficult to gauge. Additionally, patients must be careful with cross-contamination of testosterone creams, as touching or hugging partners, children, or pets, can unintentionally spread the medication to them. In my professional medical opinion, FDA-approved commercially manufactured testosterone is provided in too small a dose for optimization.

Creams also do not correspond with the same consistent serum absorption levels that are achieved with compounded pellet therapy. Compounded pellet therapy avoids the daily or weekly

rollercoaster of absorption that comes with testosterone creams, gels, patches, or injections. However, I want to note that depending on the specific patient needs (for example, in pre-menopausal women), compounded testosterone in cream form may be most appropriate and effective for that patient. I have found that pelleted delivery of the appropriate dose of compounded testosterone is preferred by the majority of my patients because of the success rate in treatment of the patient's symptoms and medical conditions.

Compounded testosterone is absolutely necessary to treat my female patients because there is no commercially available bioidentical testosterone approved for treatment in women. When I treat my female patients, I use a compounding pharmacy to compound bioidentical testosterone and bioidentical estradiol into a single dose consisting of their custom amount of compounded bioidentical testosterone in pellet form, and there is no commercially available option for this treatment for women.

- **Estradiol**

I prescribe compounded bioidentical estradiol in pellet form because of the sustained absorption levels that can be achieved that are not available in FDA-approved bioidentical estradiol options. Because of the sustained estradiol level, I am able to reduce patients' FSH levels to below menopausal levels, thus protecting them from, and often reversing, osteopenia or osteoporosis. This reduces the significant amount of fracture injuries found in osteoporosis patients. Only compounded estradiol pellets give the patients sustained levels of estradiol for months at a time, which is preferred by the body.

- **Progesterone**

I prescribe compounded bioidentical progesterone to female patients who still have a uterus and who are receiving estrogen in some form. In my professional medical opinion, female patients are most successfully treated with progesterone in a compounded oral pill. In my professional medical opinion, the increased risk of DVT and breast cancers with synthetic oral progestins (to be distinguished from the molecule progesterone) is unacceptable. Commercially available bioidentical generic progesterone creates too great of a variance in my patients. Generics are allowed 20% variance in the active ingredient by the FDA. In my professional medical experience, I saw too much vaginal bleeding when using generic micronized progesterone to offset the estradiol in patients with a uterus. However, when I prescribe the same dose of compounded bioidentical progesterone, these patients experience far less bleeding in the same situation.

Sincerely,

/s/ Dr. George Benson Branning, M.D.

George Benson Branning, M.D.

Texas Gynecology
Texas Hormone and Sexual Wellness

5575 Warren Parkway
Professional Building 1 Suite 314
Frisco TX 75034

T 214-824-2547
F 214-618-8038

george.branning@mac.com
www.texasobgyn.com

Profile

Born in Miami, Florida February 12, 1960
Dr. Branning has three children: Caroline, Addison and Benson

Practice Experience

Baylor Medical Center at Frisco **2005-Present**

Baylor Medical Center at Frisco **2016-2017**
Medical Director, Obstetrics

Baylor Medical Center at Frisco
Chief of Staff **2011-2012**

Baylor University Medical Center, Dallas **1993-2008**
Attending Physician

Managing Partner of Texas Obstetrics and Gynecology Associates, PLLC

Residency

Baylor University Medical Center Dallas 1989-1993
Department of Obstetrics and Gynecology
Chief Resident 1992-1993

Medical Education

Medical Doctor 1985-1989
University of Texas Southwestern Medical Center of Dallas

Undergraduate Education

The University of Texas at Austin 1980-1984
Bachelor of Arts in Biology and Microbiology

Memberships

Fellow of the American College of Obstetrics and Gynecology
Diplomate of the American Board of Obstetrics and Gynecology
Texas Medical Association
Society of Laparoendoscopic Surgeons
American Association of Gynecologic Laparoscopy
Collin County Medical Association
Dallas Ft. Worth Obstetrics and Gynecology Society/Past President
Southwestern Gynecologic Assembly
Institute of Functional Medicine

Clinical Interests

Advanced Endoscopic Surgical Techniques
Minimally Invasive Surgery
Advancements in Contraception and Sterilization
daVinci Robotic Surgical Systems
Hormone Balancing and Aging
Human Sexuality as it pertains to Wellness

Dr. Branning no longer practices Obstetrics. He has dedicated his practice of medicine to gynecology, minimally invasive surgery, hormone balancing and aging, nutrition, sexuality, and overall human wellness.

Exhibit 1-C

Center for Holistic Medicine
6089 W. Maple Rd. Ste. 200
West Bloomfield, MI 48323

Statement From David A. Brownstein, M.D.

Qualifications

My name is David A. Brownstein, M.D. My professional background is as follows. I received my Bachelor of Science in Psychology from the University of Michigan in 1989 and received my Doctorate of Medicine degree from Wayne State University School of Medicine in 1989. I conducted my residency at Providence Hospital Family Practice Residency in Southfield, Michigan from 1989 to 1992, during which time I also received a diploma from the National Board of Medical Examiners. Following my residency, I became a Diplomate of the American Board of Family Practice in 1992, 1998, 2006, and 2016. In 2006, I graduated from the Desert Institute School of Classical Homeopathy in Phoenix, Arizona. I am currently a Board-Certified family physician at the Center for Holistic Medicine in West Bloomfield, Michigan.

I have served as the Medical Director of the Center for Holistic Medicine since 1999. Prior to that, I served as a staff physician at the Detroit Medical Center from 1993-1999 and the staff physician for the Specialists in Family Practice from 1992-1993. I worked in the Emergency Room at Providence Hospital from 1991-1994. I have had numerous other affiliations, such as with the Center for Holistic Medicine, the American Academy of Preventive Medicine, the Omni Care Physician Ad Hoc Committee for Preventative Medicine, the American Academy of Medical Acupuncture, the American Academy of Family Physicians, and the Journal of Comprehensive Integrative Medicine, among many others. For a full list of all affiliations, please see my enclosed CV. I received the 2005 American College for the Advancement in Medicine Norman E. Clarke Sr. Award for Science and Practice and the 2005 ARC Excellence Award for Distinguished Clinician for his "Advancement in the Diagnosis and Treatment of Chronic Diseases" from the American Academy of Integrative Medicine.

Presently, I am a Clinical Assistant Professor of Medicine at the Wayne State University School of Medicine. I have been appointed to that position since 2016 and will remain in that role until 2021. Previously, I was appointed as a Clinical Assistant Professor of Internal Medicine at Wayne State University School of Medicine from 1999 to 2004.

Throughout the years, I have lectured internationally to physicians and other industry members about my success in using natural hormones and nutritional therapies in my practice. For example, I have served as a lecturer for the NAET Annual Symposium, PCCA Functional Endocrinology Symposium, Women's International Pharmacy, International College of Integrative Medicine, the American Holistic Medical Association, Thyroid Support Group, and Innovative Therapy Services. I am the author of 15 books including *The Miracle of Natural Hormones*, *Overcoming Arthritis*, *Overcoming Thyroid Disorders*, and *Iodine: Why You Need It, Why You Can't Live Without It*. For a full recitation of all presentations given and publications authored, please see my enclosed CV.

Experience with Treatment Of Compounded Bio-Identical Hormone Therapy

I am one of the foremost practitioners of holistic medicine. I have over 25 years of experience treating my patients with compounded Bio-Identical Hormone Therapy ("*BHRT*"). Of

all the patients I treat, approximately 80% of them are being treated with compounded BHRT because, in my professional medical judgment, commercially available BHRT is not an effective treatment option for these patients. My medical experience has proven that when compounded BHRT is prescribed appropriately and when patients comply with the treatment plan, not only is the treatment effective, but it also has an excellent safety record.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I treat a variety of medical conditions in my male and female patients with compounded BHRT. Of the 80% of my patients that I treat with compounded BHRT, approximately 70% are female patients and approximately 30% are male patients. The table below represents some of the medical conditions that my patients present with and that are effectively treated by compounded BHRT.

Male Patients

- Adrenal dysfunction
- Adrenopause
- Anxiety
- Cardiovascular Disease / Coronary Heart Disease
- Decline in brain dysfunction and complaints of being "unable to think"
- Depression
- Heart disease/failure
- Insomnia

Female Patients

- Adrenal dysfunction
- Anxiety
- Cardiovascular Disease / Coronary Heart Disease
- Decline in brain dysfunction and complaints of being "unable to think"
- Depression
- Heart disease/failure
- Insomnia
- Menopause symptoms (e.g., hot flashes, low libido)

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, I prefer to treat my patients with compounded BHRT instead of the commercially available BHRT because hormone therapy requires individualized treatment and a constant reassessment and adjustment of the hormone dose and the medication—it is effectively impossible to treat patients with a one-size-fits-all hormone therapy treatment.

First and foremost, the commercially available BHRTs do not contain all the bioidentical hormones and in enough of a variety of dosage strengths and forms necessary to optimize treatment for patients. Specifically, as set out below, I utilize compounding pharmacies to compound certain bioidentical hormones and certain combinations thereof because there is no commercially available bioidentical option to treat my patients.

- **Progesterone**

FDA-approved progesterone only comes in two dosage strengths and is only available in an oral pill or vaginal gel, whereas compounded progesterone can be prescribed in any strength and in any form needed to best treat the patient. I prescribe progesterone compounded in a gel,

cream or troche, depending on what works best for my patients. Some patients absorb better from a cream while others do best with a gel. I prescribe compounded progesterone to treat menopausal symptoms, bone health issues, brain disorders including depression and anxiety, fatigue, chronic fatigue syndrome, and fibromyalgia. My patients often require slight adjustments in strength of hormone therapy in order to receive the optimal benefits of therapy—the two commercially available progesterone products do not allow me to make these precise adjustments to the dosage strengths that are required in order to optimize treatment.

- **Estrogens**

There are a limited number of FDA-approved bioidentical hormones therapies and they are only approved in a few dosage strengths. Women need estrogen doses adjusted constantly depending on life events and health changes. I am not able to optimize my patient's estrogen status without the availability of compounded bioidentical estrogen. I prefer to treat my patients with estrogen compounded into a cream, gel, drops, troche, or a vaginal suppository, depending on what the individual patient can best absorb. Often, in my professional experience, I have patients switch from a cream to a gel or a suppository, as their health and medical conditions change—the FDA-approved estrogens do not allow me to treat patients in this way. I prescribe compounded estrogens to treat menopause, vaginal dryness, urinary tract problems, depression, anxiety, and bone health.

- **Testosterone**

There are only a limited number of FDA-approved testosterone dosage strengths, and there is no FDA-approved testosterone for treatment in both men and women. Compounded testosterone allows me to not only effectively treat my male and female patients, but allows me to adjust the dosage strength or combination of hormones slightly depending on the health status of my patients. I typically prescribe compounded testosterone in creams, gels, or injectables depending on how my patient best absorbs the therapy. I prescribe compounded testosterone to treat menopausal symptoms, muscle disorders, depression, anxiety, bone health, fibromyalgia, chronic fatigue syndrome, and andropause (in men only).

- **Combination Testosterone + Progesterone + Estrogen**

There is no FDA-approved combination testosterone, progesterone, and estrogen product, therefore, the only way I can get this product to treat my patients is from a compounding facility. I prescribe compounded testosterone, progesterone, and estrogen in creams, gels, and oral troches depending on what my individual patient best absorbs. I prescribe this combination of bioidentical hormones to treat menopausal symptoms, depression, anxiety, bone health issues, urinary problems, and andropause (in men only).

- **Combination Progesterone + Testosterone**

There is no FDA-approved combination testosterone and progesterone product. Therefore, the only way I can get this product to treat my patients is from a compounding facility. I prescribe combination testosterone and progesterone in creams or gels depending on how my patients absorbs the therapy. I prescribe this combination of hormones to treat menopause, depression, anxiety, bone health issues, and brain dysfunction.

Finally, it has been my experience that patients prefer the individualized treatment they receive from compounded BHRT treatment. Patients cannot obtain a personalized treatment plan using commercially available BHRT. As stated above, hormone therapy requires a constant reassessment of a patient's hormone levels, which requires patients to frequently have their blood tested so that the prescriber can evaluate how effective the medication is on each individual patient. This may then require me to write a new prescription for a different dose or a different combination of therapies to be compounded by a compounding pharmacy. My medical opinion is clear: the readjustment of the dose and therapies cannot be done with commercially available BHRT, and therefore without compounded BHRT, thousands of patients will be forced to go without the medication that best treats their individual medical conditions and they will suffer.

Sincerely,

CURRICULUM VITAE

David A. Brownstein, M.D.
6890 W. Maple Rd. Suite 200
West Bloomfield, MI 48322
(248) 851-1600 (P)
(248) 851-0421 (F)

EDUCATION:

Graduate: Desert Institute of Classical Homeopathy. 1.16. 06. Phoenix, Az.
Diplomate, American Board of Family Practice –July, 1992, July 1998, July, 2006
Providence Hospital Family Practice Residency - July, 1989 - June, 1992
Diplomate, National board of Medical Examiners - July, 1990
Wayne State University School of Medicine - M.D., June, 1989
University of Michigan - B.S., psychology, May, 1985. Graduated with distinction.
Graduate, Desert Institute School of Classical Homeopathy. Phoenix, Arizona. 2005-2006.
Diplomate. American Board of Family Practice. July, 2006
Diplomate American Board of Family Practice July, 2016

PUBLICATIONS:

Author: ***The Miracle of Natural Hormones***, 1998. 152pp. Medical Alternatives Press.
Author: ***The Miracle of Natural Hormones* 2nd Edition**, 1999. 204pp. Medical Alternatives Press.
Author, The Physician's Page Newsletter for the Road Back Foundation, Vol. 4, No. 3, Hormones and Chronic Disease, August, 1999
Principal Investigator in Research study: The Effect of a Gamma Oryzanol Formulation on insulin-like Growth Factor-1 in Volunteers, by David Brownstein et al. To be published.
Principal Investigator in Research study: The Effects of Flax Seed Oil and Glucobalance on Lowering Triglyceride Levels, by David Brownstein et al. To be published.
Principal Investigator in research study: NAET, A Novel Treatment for Allergies, By David Brownstein, et al. Submitted for publication.
Author: ***Overcoming Arthritis,*** 2000. 252 pp. Medical Alternatives Press.
Author: ***Overcoming Thyroid Disorders,*** 2002. 276pp. Medical Alternatives Press.
Author: ***The Miracle of Natural Hormones 3rd Edtiion***, 2003. 282 pp. Medical Alternatives Press
Article for Thyroid News, December, 2003.
Author: ***Iodine, Why You Need It, Why You Can't Live Without It.*** 2004. Medical Alternatives Press.
Author: ***Salt Your Way To Health.*** 2005. Medical Alternatives Press.
Article: Smart Life Forum Newsletter. November, 2005.
Article: http://www.bellaonline.com/site/thyroidhealth. Salt: Dietary Villain or Foundation of Health?

Author: The Saliva/Serum Iodide Ratio as an Index of Sodium Iodide Symporter Efficiency. The Original Internist. Vol. 12., No. 4. Winter 2005.
Author: Validation of the Orthoiodosupplementation Program: A Rebuttal of Dr. Gaby's Editorial on Iodine. The Original Internist. Vol. 12., No. 4. Winter 2005.
Quoted in article "Sorting Out Salt". Better Nutrition. June 2007.

Author: ***Iodine, Why You Need It, Why You Can't Live Without It, 2nd Edition.*** 2006. Medical Alternatives Press.
Author: ***Guide to Healthy Eating.*** Medical Alternatives Press. 2006.
Author: The Saliva/serum iodide ratio as an index of sodium iodide symporter efficiency. The Original Internist. Vol. 12, No. 4 . Winter, 2005.
Author: Celtic Sea Salt: Shattering the Myths of One of Nature's Most Helpful Nutrients. VRP Newsletter. Feb, 2006. Vol. 20, No. 2. VRP.com
Author: Iodine; The Final Story. VRP News. Vol. 20, No.4. April, 2006.
Interviewed for Newsletter article in Health Letter, Japan. May 2006.
Interviewed for article "Shake It Up" in Alternative Medicine. September. 2006.
Author: Health Letter, Japan. October, 2006
Author: ***Drugs That Don't Work and Natural Therapies That Do***. Medical Alternatives Press. 2007
Author: Refined vs. Unrefined Salt. Well Being Journal. Vol. 16, No. 3. May/June 2007
Author: Iodine Why You Need It Why You Can't Live Without It, 3rd Edition. Medical Alternatives Press. 2007
Overcoming Thyroid Disorders, 3rd Edition. Medical Alt. Press. 2008
Editor: Dr. Brownstein's Natural Way to Health Newsletter. First Edition May, 2008
Interviewed for Crusader Magazine Issue 45 Nov/Dec 2008. Iodine Article
Interview for Crusader Magazine Issue 46 Jan/Feb 2009 Salt Article
Author: Iodine Why You Need It, Why You Can't Live Without It, 4th Edition, 2009
Author: Iodine Deficiency. VRP News. March, 2009.
Author: Whole Blood Concentrations of Elemental Silver. The Original Internist. Vol. 16, No.1. March 2009.
Co-Author, Op-Ed in Wall Street Journal, "The Truth about Hormone Therapy". 3.16.09
Author: ***The Guide to a Dairy-Free Diet.*** Medical Alternatives Press. 2009
Author: Drugs That Don't Work and Natural Therapies That Do, 2nd Edition. Medical Alternatives Press. 2009.
Article for Newsmax Magazine, March 2010. "No To Low-Salt Diets."
Author of Monthly Newsletter, ***Dr. Brownstein's Natural Way to Health***. 2008-present
Author: Are you salt deficient? Caduceus. Issue 79. 2010
Author: **The Soy Deception,** 2011
Author: **Vitamin B12 for Health**, 2012
Author: **The Skinny on Fats,** 2014
Author: **The Statin Disaster** 2015
Author: **Ozone: The Miracle Therapy.** 2016
Author: **Heal Your Leaky Gut.** 2017

FACULTY APPOINTMENT:

Clinical Assistant Professor of Internal Medicine, Wayne State University School of Medicine, 1999-2004
Clinical Assistant Professor of Medicine, Wayne State University School of Medicine, 2016-2017, 2018-2021

AFFILIATIONS:

Medical Director, Center for Holistic Medicine, 1999
Research Committee, Nambudripods Allergy Relief Foundation, 1998
Nambudripods Allergy Relief Foundation, member 1996- present
Member Board of Examiners for American Academy of Preventive Medicine - 1996
American Academy of Preventive Medicine member - 1996-present
Physician Reviewer for Physician's Review Organization of Michigan- 1995-present
American Academy of Medical Acupuncture associate member, 1993 - present
Member Joint Family Practice Advisory Committee for credentialling family physicians Detroit Medical Center 1995-present
Member expert panel for Omni Care Physician Ad Hoc Committee for preventative medicine - 1996
Acupuncture Society of Michigan member 1995 - present. **Board of Trustees** 1995. **Vice President** 1996, **President**, 1997.
American Academy of Medical Acupuncture member, 1995-present
American Academy of Family Physicians member, 1985 – present
Peer Review of Michigan (PROM) reviewer: 2001-present
Editorial Board: Journal of Comprehensive Integrative Medicine. 2014-present

AWARDS:

2005 American College for the Advancement in Medicine Fall 2005 Norman E. Clarke Sr. Award for Science and Practice. Long Beach, California. December, 2005
2005 ARC Excellence Award for Distinguished Clinician for his "Advancement in the Diagnosis and Treatment of Chronic Diseases." From American Academy of Integrative Medicine. West Palm Beach, FL. December, 2005

PRESENTATIONS:

Guest lecture for NAET Symposium for Doctors, Buena Park, CA. 1997
Guest lecture for NAET Symposium for Doctors, Buena Park, CA. 1998
Guest lecture, American Holistic Medical Association, Sterling Heights, MI, April, 1998
Guest lecture for Fairview Hospital Women's Health Day. Cleveland, Ohio, September, 1998
Featured guest on Adrienne Selko radio show, Cleveland, OH, October, 1998
Guest lecture for Broda O. Barnes, M.D. Research Foundation, Stamford, CT, October 1998.
Guest lecture for Selko Communications Holistic Medicine for the 21st Century, Cleveland, OH, February, 1999
Lecture to Wayne State University School of Medicine, April, 1999
Guest lecture for Carrot Country GNC, Brandon, FL, May 1999
Guest lecture for American Association of Podiatric Physicians and Surgeons Annual Seminar, May, 1999
Guest lecture, Holistic Medicine for the 21st Century, West Bloomfield, MI, June 1999

Guest lecture for NAET Symposium for Doctors, Buena Park, CA, July 1999
Guest lecture for Thyroid Support Group, Plymouth, MI, September 1999
Guest lecture for Temple Beth El Health and Fitness Wellness 2000, November 1999
Guest lecture for Michigan Holistic Nurses' Association, January, 2000
Guest lecture for Wellness Seminar, Maumee, Ohio, February, 2000
Guest lecture for Michigan Chiropractic Society annual Meeting, Lansing, Michigan, February, 2000
Guest lecture for Innovative Therapy Services, Indianapolis, IN, March, 2000
Guest Lecture for The Road Back Foundation, Los Angeles, CA, March, 2000
Guest Lecture for Hadassah, West Bloomfield, MI April, 2000
Lecture to Wayne State University School of Medicine 4th Year Medical Students, April 7, 2000
Radio Interview for AM WKHB 600 AM Impact on Health, Pittsburgh, PA, May 24, 2000
Guest Lecture Gilda's Club, Royal Oak, MI, May 25, 2000
Guest Lecture Pituitary Disorder and Endocrine Support Group, West Bloomfield, MI , Nov, 2001
Lecture Broda O. Barnes, M.D. Research Foundation, Stamford, CT February, 2002
Lecture Wayne State University School of Medicine 4th Year Medical Students, April, 2002
Lecture Michigan Society of Infection Control Spring Conference, Lansing MI, April, 2002
Interview Mary Shomon, About.Com Web site, July, 2002
Lecture for Women's International Pharmacy, Madison, Wisconsin. Sept, 2002
Lecture Broda Barnes M.D. Research Foundation, Stamford, CT, Sept, 2002
Lecture Scleroderma Foundation, Troy, Michigan, Sept., 2002
Lecture: International College of Integrative Medicine, Dallas, Tx. April, 2003
Lecture: NAET Annual Symposium, Kauai, Hawaii, July 2003
Lecture: Broda Barnes, M.D. Research Foundation. Stamford, CT. September, 2003.
Lecture Nutramedicine Group, San Francisco, CA. April 2004
Lecture: Medical Alternatives Press, Novi, MI April, 2004
Lecture: Henry Ford Community College, Dearborn, MI April, 2004
Lecture: Orlando, Fl. National Advanced Practice Conference. April 15, 2004
Testimony to Human Rights and Wellness Subcommittee, Wash. D.C. July 22, 2004
Broda O. Barnes, M.D. Research Foundation, Sept, 2004. Stamford, CT.
Lecture to NFWL, Sarasota, Fl. Nov, 2004
Lecture to ProServ. Orlando, FL, Jan. 2005
Institute for Health Resources, Marquette, Michigan. April, 2005. Marquette, MI
Lecture: PCCA Functional Endocrinology Symposium. August, 2005. Houston, TX.
Lecture: Genesis Health Systems. October, 2005, Grand Blanc, MI.
Lecture: Novi Sheraton Hotel. Natural Therapies That Work. October, 2005. Novi, MI.
Lecture: Greensborough, NC. October 15, 2005. Biotics Research.
Lecture: Broda O. Barnes, M.D. Research Foundation. October 21-22, 2005. Stamford, CT.

Lecture: ACAM. November 11, 2005. Anaheim, CA.
Lecture: American Academy of Anti-Aging Medicine. December 10, 2005. Las Vegas, NV.
Lecture: Smart Life Forum. January 19. 2006. San Francisco, CA.
Lecture: Wayne State University School of Medicine 4th Year Medical Students Elective. April, 2006
Lecture: PCCA Funcitonal Endocrinology Symposium. April, 2006. Houston, TX.
Radio Interview: Dr. Stephen Hotze. May 5, 2006
Radio Interview: Healthy Talk Radio with Debra Ray. May 12, 2006.
Lecture: NAET Annual Symposium. Buena Park, CA. July, 2006
Lecture: PANLA Annual Lecture. Indiana, PA. August, 2006
Lecture: Genesys Learning Institute. September, 13, 2006. Flint, MI.
Lecture: Growing Connections 2006 Conference. Davisburg, MI. Oct. 2006
Lecture: North Carolina Chiropractic Association. November, 2006. Greensborough, N.C.
Lecture: PCCA Functional Endocrinology Symposium. November, 2006. St. Louis, MO.
Lecture: Age Management Medicine Group. November, 2006. Las Vegas, NV.
Lecture: PCCA Canada Functional Endocrinology Symposium. November 2006. Vancouver, Canada.
Interview: Healthmyths.net. December, 2006
Lecture: American Academy of Orthopedic Medicine. Boulder, CO. January, 2007
Lecture: Recent Advances of the Use of Iodine in Medicine. Scottsdale, AR. February, 2007
Lecture: Yoga Shelter. West Bloomfield, MI. February, 2007
Guest on Ron Hoffman's Healthy Talk Radio. www.wor710.com. 2.28.07
Guest on Debra Ray's Healthy Talk Radio. 3.4.07
Guest on The Power Hour with Joyce and Dave. 3.16.07
Guest on Temple of Health Radio Show. 4.20.07. www.templeofhealth.ws
Lecture Viotron International. Novi, MI. 3.17.07
Lecture Healthy Eating, Healthy Choices. 5.4.07. Novi, MI
Lecture NOHA, Inc. Morton Grove, IL. 5.3.07
Lecture to Institute for Functional Medicine: 5.25.07, Tuscon, AZ.
Lecture ZRT Conference on Bioidentical Hormones, Portland, OR. 7.29.07
Lecture: PCCA BHRT Conference. Denver, CO. 08/2007
Lecture: Cancer Control Society, Los Angelos, CA. 9.1.07
Lecture: PCCA Nutritonal Seminar. Houston, TX. 9.6.07
Lecture: Broda Barnes M.D. Research Foundation, Stamford, CT. 9.7-9.9.07
Radio Interview. Power Hour. 9.21.07
Lecture Iodine Conference. San Diego, CA. 10.5.07
Lecture. Viotron International. Indianapolis, IN. 10.13.07
Lecture ZRT Labs. Orlando, FL. 10.26.07
Lecture Viotron International. Cleveland, OH. 11.3.07
Dr. David Biles Radio Show. 12.16.07. California
Lecture: ZRT BHRT Symposium. 1.18.08 San Diego, CA

Lecture: Growing Connections. Troy Michigan. 2.2.08
Lecture: Biotics Research. Baltimore, MD. 2.23.08
Lecture: BHRT International Symposium. Las Vegas, NV. 2.29.08-3.1.08
Lecture: Colorado Functional Medicine Forum. Boulder, CO. May 8, 2008
Lecture: PCCA BHRT. Detroit, MI 5.16.08
Lecture: ZRT Annual BHRT Update: Portland, OR, July 11, 2008
Lecture: Genesys Regional Medical Center. August 13, 2008
Lecture: NAET Annual Symposium. Buena Park, CA. August 29, 2008
Lecture: Biotics Research. Atlanta, GA. September 6, 2008
Lecture Biotics Research, Tampa, Fl. October 4, 2008
Lecture ZRT Laboratory, Tuscon, AZ. October 24, 2008
Lecture: International Academy of Compounding Pharmacists. January, 2009
Lecture National Chiropractic College, Chicago, IL. 3.20.09
Lecture: Biotics Research. Chicago, IL 3.21.09
Lecure: Biotics Research: Massachusetts, 3.28.09
Lecture: Biotics Research: Houston, TX. 4.4.09
Lecture Biotics Research. Albuquerque, NM. 7.9.09
Lecture: Florida Chiropractic Association, Orlando, Fl. 8.29.09
Lecture: American Academy of Anti-Aging Medicine. San Jose, CA. 9.11.09
Lecture: Biotics Research: Los Angelos, CA. 9.26.09
Lecture: Amarillo Health Initiative. Amarillio, TX. 10.10/09
Lecture: Biotics Research, N.Y., N.Y. 11.13.09
Lecture: Providence Hospital Dept. of Cardiology. Southfield, MI 12.4.09
Lecture: National Institute for the Clinical Application of Behavioral Medicine. Hilton Head, S.C., 12.11.09
Lecture: Royal College of Medicine, London, England. January 20, 2010
Lecture Newsmax Cruise, March, 2010
Lecture: University of Miami Integrative Medicine Symposium, 2010. Miami, FL. 4.23-4.24.10
Lecture: Orthomolecular Medicine Annual International Conference April 30, 2010. Vancouver, Cananda.
Webinar to Agribus on Salt Your Way to Health. July 16, 2010
Lecture: Florida Chiropractic Association. August 27-28 2010. Orlando, Fl.
Lecture: Biotics Research. Los Angeles, CA. 9.25.10
Lecture: Florida Chiropractic Association. Naples, Fl. 11.19-20, 2010.
Lecture to NICABM, Hilton Head, SC. 12.8.10
Lecture to Fordham Page Nutritional Study Group March 4-5, 2011 Herndon, VA
Lecture Rebekah's Pure Living, Lapeer, MI March 26, 2011
Lecture Fellowship for American Academy of Anti-Aging Medicine, Orlando, Fl April 7, 2011
Guest on Dennis Courtney Radio Show April 15, 2011
Lecture to American Chiropractic Association Council on Nutrition. April 29, 2011 Orlando, FL
Lecture American Nutrition Association. May 6, 2011. Skokie, IL

Lecture to Metabolic Management Group, Schaumberg, IL May 7, 2011
Guest on Dennis Courtney Radio Show, May 13, 2011
Lecture to Biotics Research, N.W., Seattle, WA. May 21, 2011
Lecture to Florida Chiropractic Association, Boca Raton, FL. June 17-18, 2011
Radio Interview John Wycoff Radio, East Lansing, MI. 6.25.11
Radio Interview Dennis Courtney, Pittsburg, PA. 7.8.11
Lecture NAET Annual Symposium. Buena Park, CA. 7.29.11.
Lecture Fordham-Page Nutrition Study Group. Roanoke, VA. 8.26-8.27.11
Radio Interview Dennis Courtney Radio. Pittsburg, PA. 9.16.11
Radio Interview Power Hour. 9.30.11
Lecture Biotics Research. NY, NY. 10.22.11
Radio Interview Dennis Courtney Radio. Pittsburg, PA. 10.28.11
Lecture Big Lick Study Club. Roanoke, VA. 11.4.11
Lecture Biotics Research. Colorado. 11.12.11
Lecture Synergy Group. Calgary, CA. 11.18.11
Lecture NICABM. Hilton Head, SC. 12.8.11
Lecture Biotics Research, Houston, TX. 12.10.11
Lecture Webinar, Biotics Research, Houston, TX. January 9, 2012
Radio Interview Natural News Talk Hour, February 2, 2012
Lecture Kansas Pharmacy Association, Kansas City, MO. March 3, 2012
Lecture DSD International, Phoenix, AZ March 31, 2012
Lecture Biotics Research, San Francisco, CA. April 14, 2012
Lecture Halleluiah Acres, Shelby, NC. April 20, 2012
Lecture Biotics Research, Bedford, MA. May 12, 2012
Lecture Biotics Research, Falls Church, VA. May 19, 2012
Lecture Medical Alternatives Press, Novi, MI June 16, 2012
Lecture A4M Fellowship Program, Las Vegas, NV. September 7, 2012
Lecture IAOMT. September 21, 2012
Lecture Biotics Research. Virginia Beach, VA. September 29. 2012
Lecture A4M Fellowship. Tampa, FL. October 12, 2012
Lecture Age Management. Las Vegas, NV. November 2, 2012
Radio Interview Power Hour. November 30, 2012
Guest On Your Health TV Show, Dallas, TX. February 21, 2013
Lecture American Academy of Antiaging Medicine. Las Vegas, NV. March 1, 2013
Webinar. Biotics Research. March 12, 2013
Lecture International Academy of Oral Medical Toxicology. March 15, 2013
Lecture Westin A. Price Foundation. Romulus, MI March 24, 2013
Lecture Biotics Research. Orlando, FL. April 13, 2013
Lecture Biotics Research. Chicago, Il. May 11, 2013
Host of Thyroid Summit. June, 2013
Lecture Viotron Intl. Nashville, TN. September 28, 2013
Lecture Viotron Intl. Novi, MI. October 26, 2013
Lecture American Academy of Restorative Medicine, San Diego, CA. Oct.3-6, 2013
Lecture Westin A Price International Meeting. Atlanta, GA. November 10, 2013

Lecture PCCA. Las Vegas, NV. Feb. 21, 2014
Lecture Total Heath. Toronto, Ontario. April 4-5, 2014
Lecture Holistic Dental Assoc. Chicago, IL. April 11, 2014
Lecture Restore Health. Indianapolis, IN May 3, 2014
Lecture Biotics Research. Harrisburg, PA. May 17, 2014
Documentary Interview – Cure for Cancer. Aug. 29, 2014
Lecture IAOMT. Las Vegas, NV. Sept. 12, 2014
Lecture ICIM, Dearborn, MI. Sept. 26, 2014
Lecture Biotics Research. San Antonio, TX. Nov. 8, 2014
Lecture Biotics Research, New York, NY Nov. 15, 2015
Lecture Biotics Research. Charlotte, NC March 7, 2015
Lecture Biotics Research. Bethesda, MD March 21, 2015
Radio Interview Sal DiBella Radio Show, April 17, 2015
Lecture Orthomolecular Society. Toronto, Ontario April 24, 2015
Lecture AARM. Blaine, WA. Oct 1, 2015
Lecture Chicago Dental Society. Chicago, IL. Oct. 9, 2015
Lecture A4M Fellowship Program. Chicago, IL. Oct. 10, 2015
Lecture Biotics Research. Cleveland, OH. Nov. 14, 2015
Lecture: ICIM. Grand Rapid, MI. Octoberb5, 2017, Workshop on Intravenous IV Therapy.
Lecture: ICIM. Minneapolis, MN October 27, 2018
Lecture: Holistic Medicine for the 21st Century. Livonia, MI. February 2, 2019

EMPLOYMENT EXPERIENCE:

Medical Director, The Center for Holistic Medicine May, 1999-present
Staff Physician - Detroit Medical Center, November 1993 – April, 1999
Staff Physician - Specialists in Family Practice, Novi, Mi. July 1992- October, 1993
Emergency Room - Providence Hospital, Novi, Mi. 1991- 1994

Exhibit 1-D

October 20, 2019

To: National Academies of Sciences, Engineering, and Medicine (NASEM)
Ad Hoc committee to assess the clinical utility of treating patient with compounded "bio-identical hormone replacement therapy" (BHRT) drug products

From: Angela DeRosa, DO, MBA, CPE

Re: Importance of compounded hormones

Dear Committee Members,

As a female physician and menopausal woman, I felt it important to express the grave concern I have regarding the attempts to limit patient's rights and physician's ability to not only prescribe hormone therapies, particularly compounded bio-identical hormone replacement therapy (BHRT), but in a manner that individualizes their medical care.

In today's medical environment, we are becoming more and more restricted in the name of "protecting patients"; but the only way to truly do so is to not allow patients any exposures to any medicines, compounds etc. Every day, physicians are faced with the challenges of choosing the right treatment plans for each of our patients, but now sadly insurance companies, regulatory bodies and those with financial interests are directing care decisions and taking the provider and patient out of the equation. This time- honored relationship demands the ability to have informed choice, individualization and an unencumbered decision- making process that isn't influenced by untoward outside parties who have conflicts of interest. This relationship is being threatened on many levels and we must take a stand to protect it.

I have been a practicing internal medicine physician with over 20 years of specialty training and expertise in women's health. I have dedicated my career to the understanding and knowledge surrounding women's unique medical needs, particularly focused on the role that hormones played in them. (See attached curriculum vitae for full professional history and practice descriptions)

My career interests did not happen by accident. They were driven by my own personal struggles as a patient who went through premature menopause at the age of 35; experiencing the signs and symptoms all the while I was in medical school and residency training.

At the young age of 30, I found myself on multiple FDA approved medication to treat the symptoms of premature menopause (sleeping pills, antidepressants, beta blockers) and had thousands of dollars of medical work ups; all which could have been prevented if the medical profession had a better understanding of hormones and the vital role of hormone replacement. Once I found customized compounded hormones, my life changed for the better and the "band-aid" medications were stopped.

It was through this personal experience, that fueled my fire to understand how I could change the paradigm of women's health and the fears that were created by much misinformation and skewed media exposures to datasets that even the most novice statisticians could poke holes through.

I saw first- hand, while working as the west coast senior medical director at Procter & Gamble (P&G) pharmaceuticals, the inner workings of drug development, product marketing, and the FDA drug approval processes. I also saw the gender biases that were at play in female hormonal health. (I was responsible for their female hormonal health/sexual health and bone health product lines.) P&G spent years and millions of dollars in an attempt to bring to market the first female FDA approved testosterone product (Intrinsa matrix delivery patch) only to be shut down by the FDA due to unfounded fears about cardiovascular risk and breast health even when all the data to the contrary was evident. To make matters worse, there have been many forces at play that have not allowed female patients the same health choices as men and this is very apparent in the area of hormonal health.

Even, the majority of "key opinion" consensus statement/recommendations/guidelines from organizations are heavily funded by the pharmaceutical industry making them both financially and intellectually biased. This obvious conflict of interest propagates the bias against compounding hormones even when there is much research to supports its utilization and the benefits of personalized medicine.

The sad truth is that this failure to approve was over two decades ago and we still do not have any FDA approved testosterone products for women. This failure shouldn't not only be alarming but embarrassing to the medical profession as a whole in our inability to provide equal access to essential hormones that have been made available for men, but not to women. The good news, is that as in nature, when there is a void, something will attempt to fill it.

In the hormonal space, compounding pharmacies created BHRT products to fill the gap of not only the lack of availability of testosterone for women, but the ability to customize a dose or hormone combinations that cannot be accomplished with standard FDA approved products.

Although I agree with measures to ensure that patients receive quality compounded bioidentical hormones, we should not limit what doctors can prescribe or what patients need, when there is no medical data to suggest that harm is being done from these products, specifically when dosed correctly for each individual patient. Historically, negative hormonal outcomes usually occur due to first pass liver effect clotting from oral medications or from synthetic derivatives that the body doesn't quite know how to process as in progestins.

It's not to suggest we shouldn't use FDA approved products when appropriate; but we need more "tools in the toolbox". The current FDA approved product tool boxes have many broken tools, ones that don't work properly or most notably are missing some tools to do the job. Compounds can fill that void. (exhibit A)

I can personally attest to the fact that the compounded BHRT space saved my life and the lives of the thousands of patients I have had the privilege to treat over the last twenty years.

Through my exploration, learnings and trials experience over these twenty plus years, I have tried the multitude of FDA approved products, over the counter products, and then finally compounded hormones (creams, troches, pellets) in my practice. I have seen first -hand how patients are able to gain back their lives and health with many coming off multitudes of medications, losing weight and improving their metabolic risk factors, enjoying satisfying intimacy with their partners and building health, wellness and joy back into their family units.

My career has been very rewarding watching these life changing events versus having to continue to prescribe medication after medication to put band aids on symptoms which could all be resolved while getting to the root cause of many underlying chronic illness...hormone imbalances or deficiencies.

As patient advocates, it is important to remember the unique needs of our patients and we must fight protect our abilities to treat as such. This is reminiscent of Galileo's fight against orthodoxy, to make the sun the center of the solar system, the heliocentric view, rather than an immobile earth.

I welcome your questions and opportunity to speak in person with the committee if desired. Thank you for your consideration.

Best Regards,

Angela DeRosa, DO, MBA, CPE

480-316-5220

drderosa@drhotflash.com

Exhibit A

Most common conditions I treated with compounded drugs

1. Menopause/Peri-Menopause
2. Premature ovarian failure
3. Andropause
4. Hormone deficiencies
5. Pelvic Pain Syndromes
6. Fibromyalgia
7. Vaginismus
8. Yeast Infection
9. Vaginosis
10. Dermatitis
11. Mood disorders
12. Muscle wasting syndromes
13. Deconditioning
14. Spinal cord injuries
15. Fibroids
16. Fibrocystic breast disease
17. Interstitial cystitis
18. PCOS
19. Ovarian Cysts
20. Vitamin deficiencies
21. Sexual health
22. PMS
23. Hypothyroidism
24. Androgen resistance
25. Thyroid resistance
26. Sub-clinical hypothyroidism
27. Adrenal dysfunction
28. Autoimmune disorders
29. Bone health
30. Cognitive decline
31. Cardiometabolic disease
32. Insulin resistance/diabetes
33. Incontinence
34. Neurogenerative diseases
35. Obesity
36. Vulvodynia/Vestibulodynia
37. Vulvar vestibulitis
38. Lichen sclerosis
39. Dyspareunia
40. Atrophic vaginitis

Angela DeRosa DO, MBA, CPE
Email: angeladerosa@cox.net
Phone: 480-316-5220
Scottsdale, Arizona www.linkedinn.com/in/angeladerosa

EXECUTIVE SUMMARY

Highly accomplished Visionary, Entrepreneur, Senior Executive, C-Suite Officer, Consultant, Educator, Public Speaker and Board Member with extensive experience and successes in medicine, pharmaceuticals, hospital, clinic and long-term care medicine, managed care and government sectors. Leveraging extensive experience in leadership, operations and branding; valuable asset for similar sector companies looking for acumen in mergers and acquisitions, (M&A) due diligence and integrations, drug/productive development and launch, medical affairs and R&D. Broad expertise includes strategic planning, corporate development and growth, operations management, brand position and management, relationship building and management, physician sales and marketing strategy, regulatory affairs, policy and legislation, clinical practice and trials, internal medicine, women's health care and public speaking.

PROFFESIONAL COMPETENICES

*CEO/Business and Operations Leaders	*Board Communications/Collaboration	*Sale and Marketing
*Strategic Planning/Business Development	*Revenue Growth/Profit Delivery	*Internal Medicine/Women's Health
*M&A/Due Diligence/Integrations	*Brand Equity and Marketing Strategy	*Relationship Building/Management
*Innovation/Complex Problem-Solving	*Media Relations/Public Speaking	*Drug/Product Development/R&D

SELECTED ACCOMPLISHMENTS

- Created business plan and strategy, competitive/SWOT analysis and marketing/brand equity vision for DeRosa Medical, PC startup business in 3 months. Executed, operationalized and lead the business plan strategy for a total women's healthcare clinic, creating a culture of women caring for women with 3 locations across the Phoenix metropolitan area with 50 + employees over a 7-year period.
- Developed and executed strategy to convert DeRosa Medical, PC into a $7M platform company for partner acquisition to further leverage business legacy and met target in 9/2017 with acquisition by Nobilis HealthCare.
- Created business plan and strategy, competitive/SWOT analysis and marketing/brand equity vision for MiraVita, LLC a supplement and wellness program start up business in 2014. Operationalized and lead deployment of products into market (brick and mortar and on-line sales) with over $200K in sales in 3 years.
- Wrote and published "How Your Doctor is Slowly Killing You: A Women's Health Survival Guide" with full marketing and sales plan and launch in March 2014 with over 25K in sales/royalties.
- Won the 2016 Phoenix Business Journal "Healthcare Hero's Innovator of the Year" award for an innovative approach to delivering comprehensive women's' health care and approach to training and mentorship of women in the medical workforce in Arizona.
- Won the 2013 Arizona Osteopathic Medical Association, "Mentor of the Year" award for excellence in teaching osteopathic medical students.
- Created, developed and implemented the 1st On-line Second Year Medical School Women's Health and Human Development curriculum in 2007 for ATSU, College of Osteopathic Medicine. This coursework has become the platform for their on-going training of medical students remotely throughout the United States.
- Responsible for the development, expansion and coordination of the United States 19th women's health fast track curriculum and program of the department of Internal Medicine at Lutheran Medical Hospital/Advocate Medical Group in 1998 with subsequent development and leadership of the hospitals multi-disciplinary comprehensive women's health clinic.

EXPERIENCE

Founder and President: Hormonal Health Institute **08/2018-Present**

Created and Launch a hormonal health consultancy, for physicians seeking medical and practice development training on bio-identical hormone replacement therapy, with an emphasis on pellet therapy.

- *Strategic Development includes a variety of training formats and programs including live concierge level one-on-one training in physician's office, live and recorded webinars, self-paced digital classes, and peer support.*
- *Launched a digital education platform www.drhotflash.com, with two channels; one for physicans and one for consumers seeing easy to understand and comprehensive hormonal health content.*

Founder, President and Chief Medical Officer, DRM, Integrative, LLC **04/2019- Present**

Created business plan and strategy, competitive/SWOT analysis and marketing/brand equity vision for DRM Integrative, LLC. Executed, operationalized and lead the business plan strategy for a multi-location concierge hormonal health clinic.

President: Women's Health Division, Nobilis Health Corporation **10/2017-Present**

Reporting to Chief Strategy Officer responsible for leading strategic marketing and innovative growth/revenue plans for DeRosa Medical and Women's Health Service lines within Nobilis Health Medical Practices in Arizona and Texas.

- *Strategic Development and Growth of Primary Care Acquisitions and Interplay within companies brands as well as total women's care and hormonal health service line expansions within acquired organizations*

Founder, President and Chief Medical Officer, DeRosa Medical, PC **1/10-9/2017**

Created business plan and strategy, competitive/SWOT analysis and marketing/brand equity vision for DeRosa Medical, PC startup business in 3 months. Executed, operationalized and lead the business plan strategy for a total women's healthcare clinic, creating a culture of women caring for women with 3 locations across the Phoenix metropolitan area with 50 + employees over a 7-year period.

- *Developed and executed strategy to convert DeRosa Medical, PC into a $7M platform company for partner acquisition to further leverage business legacy and met target in 9/2017 with acquisition by Nobilis HealthCare.*

Board Certified Internist, Women's Health Specialist **8/98-Present**

Special Training and Focus on Menopausal and Hormonal Medicine

- *Licensed in Arizona, California, Tennessee, Illinois, Ohio, New Mexico,*
- *Certified Physician Executive*
    - *Board certification in medical management given to physicians who have completed the American College of Physicians Executives degree course work& demonstrate they have reached a level of excellence within the medical management profession, to effectively lead an organization.*

Clinical Assistant Professor **8/01-Present**

Midwestern University, Chicago College of Osteopathic Medicine

- *Internal Medicine Preceptor and Research Elective Rotations*

Vice President of Medical Affairs & Chief Compliance Officer **02/08-2011**

Matrix Medical Network/Community Care Health Network, Inc.

Reporting to Chief Operations Officer and Chief Medical Officer provided national management, budgeting/financial objectives and oversight to physician groups and managed care provider practice s and medical affairs department.

- *Responsible for Development and Initiation of quality improvement, research/grants, coding and compliance programs*
- *Lead operational strategic and tactical resource allocation& utilization for Health Risk Assessment Programs nationally*

Medical Director, Sub Acute Care Division: **10/06-12/07**

American Physician Inc.

Reporting to the Chief Medical Officer responsible for leading/managing business development and strategies a team of 15-20 Sub Acute Care Physicians within 50+ facilities in the Phoenix Metro area.

Senior Medical Director: **8/00-10/06**

Procter and Gamble Pharmaceuticals

Reported to Global Medical Director. Responsible for the oversite and development of regional, national and international key opinion leaders, oversite of technical and scientific teams for curriculum &training needs of scientific and sales force nationally.

- *Medical and Technical Liaison between regional teams and Medical& Technical Affairs including scientific data evaluation, Non- Company Sponsored Trials &Grants, scientific strategic planning &life cycle management & Phase IIIB and IV studies.*
- *Managed a $250,000 regional budget for R&D development based on investor scientific merit*
- *Lead Scientific &Business Development Strategies for all brands including osteoporosis, IBD and Female Sexual Health.*
- *Assist in the execution of phase IIIB and IV Company sponsored trials. Attend investigator meetings, monitoring issues, provision of follow-up and execution of timelines.*

Director of Women's Health Services and Education **6/98-6/99**

Lutheran General Hospital, Advocate Medical Group

Reporting to Internal Medicine Department Chief lead the development of a muti-disciplinary, comprehensive women's health clinic.

- *Physician liaison between large multispecialty group and hospital administrator in implementing joint efforts in women's health programs and coordination of educational programs between the Department of Ob/Gyn and Internal Medicine.*

EDUCATION

University of Massachusetts, Amherst, The Isenberg School of Management
MBA in Medical Management

Lutheran General Hospital/Advocate Medical Group
Internship and Residence in Internal Medicine/Women's' Health

Chicago College of Osteopathic Medicine
Doctor of Osteopathic Medicine

Wayne State University
Bachler of Arts with Honors in Biological Sciences

PROFESSIONAL ACTIVITIES

Board of Directors: Arizona Osteopathic Medical Association **1/12- present**

- *Current President 2018-2019*
- *Board of Delegates District 5*
- *Chair: Public Relations Committee*
- *AOA/AOMA speaker's bureau*

Board of Directors: American Osteopathic Foundation **7/03-5/09**

- *AOF is the premier philanthropic organization within the osteopathic organization. The Mission is to support education, research and the promotion of the osteopathic profession.*
- *Development Committee Chair: Responsible for initiating, developing and creating fundraising events for the Foundation*
- *Secretary of Board of Directors 2006-2007.*

PROFESSIONAL ASSOCIATIONS

- American Osteopathic Association
- Arizona Osteopathic Medical Association and PAC
- American Academy of Anti-Aging Medicine
- International Society for the Study of Women's Sexual Health
- European Menopause and Andropause Society
- International Menopause Society
- American College of Physician Executives

PUBLICATIONS/POSTERS

Women's Health Curriculum and Syllabus-Department of Medicine, Lutheran General Hospital.

Oral Presentation: "Are Physicians Treating Osteoporosis after Hip Fracture? Susan Broy, Angela Bohren-DeRosa, Tim Harrington, Angelo Licatta, Shewman ASBMR Toronto Sept.2000

Poster and Media Presentation: "Are Physicians Treating Osteoporosis after Hip Fracture? Susan Broy, Angela Bohren, Tim Harrington, Angelo Licatta, Shewman, ACR, October 2000.

MRS. AMERICA PAGEANT, Guest Lecturer to the Delegates on Osteoporosis and Health and Fitness Judge, September 2001

Poster Presentation: "Sustained Effects of Risedronate on Vertebral and Non-Vertebral Fractures over 5 years", American Osteopathic Association Annual meeting, Las Vegas, NV. Oct. 2002

Original Article: Arthritis and Rheumatism "Hip Fracture Patients Are Not Treated for Osteoporosis: A Call to Action" Harrington, Broy, DeRosa, Licata, Shewmon. Vol. 47, No. 6. Dec 15, 2002 pp 651-654

"To BMD or not to BMD" Journal of Osteopathic Association: Women and Wellness. Volume 1, number 2, Sept 2004 Page16.

"Taking a New Twist in Practice Guidelines" AOA Health Watch. Volume 3 Number 2, June 2008

"Hypothyroidism causes false positive: The BT test. AOA National Convention, October 2012

Gray, DeRosa Subcutaneous Pellets Testosterone Replacement Therapy: The "First Steps" in treating men with spinal cord injuries" JAOA, December 2013 Volume113, 921-925

DeRosa A, Adams S, Fee EK. Progressively worsening cyclic rash: diagnosis and approach to care. J Am Osteopath Assoc. 2015; 115(12):738-744. doi:10.7556/jaoa.2015.150.

"How Your Doctor is Slowing Killing You: A Women Health Survival Guide" Dr. Angela DeRosa

References Available upon Request

Exhibit 1-E

Jeannie Key
Katherine Tiedt

Statement From Bruce Dorr, MD, FPMRS

Qualifications

My name is Dr. Bruce Dorr, MD, FPMRS. My professional background is as follows. I received my Bachelor of Arts, *Cum Laude*, in chemistry and biology, with minors in German and psychology, from Hope College in 1986. I received the Presidential Scholar Scholarship and the Vienna Summer School Scholarship while I attended Hope College. I received my Medical Doctorate from Wayne State University School of Medicine in 1990, where I received honors for Ob/Gyn, Gyn Oncology, Medicine, Pediatric ICU and ENT with recommendations for Surgery, Pediatrics, and Family Medicine. I completed my internship and residency at the University of Colorado Health Sciences Center in obstetrics and gynecology in 1994, where I also received the Golden Apple Teaching Award for Outstanding Teaching Resident in 1990. I completed a clerkship at Sloan-Kettering Memorial Hospital in New York, New York in 1993, where I was part of the Galloway Fellowship in Gynecologic Oncology. I also completed a clerkship in urogynecology at the Evanston Continence Center in Evanston Illinois in 1996, where I studied urodynamics and urogynecology with Peter Sand, MD, who is affiliated with the Northwestern School of Medicine.

My work experience is as follows. I was a Loum Tenens Physician at Jackson & Coker, CompHealth from 1994 to 1995, where I performed local physician work in Arizona, Oregon, Michigan, New York, and Virginia. I was an Assistant Clinical Professor at the Denver Health Medical Center from 1995 to 1997, where I was the principle instructor of UroGynecology. I was a physician reviewer for the Colorado State medical Board from 2000 to 2010. I have been a Proctor at Intuitive Surgical since 2010, where I proctor and train new physicians for robotic surgery on XI and SI platforms I have been the Chairman of the Centura Littleton Robotics Division since 2013, where I have developed and consulted for hospital advancements in robotics surgery. I have been a Medical Missionary for Centura Global Health Initiatives since 2018, where I am the Chief Gyn Surgeon for Peru and Nepal missions. I previously served as the Chairman of the Department of Women's Services at Littleton Adventist Hospital, a position I held since 2014, where I reviewed credentials, peer reviewed cases, and served on the Medical Executive Committee.

Additionally, I am currently a physician in urogynecology, general gynecology, and minimally invasive surgery at Littleton Gyn and Wellness/Right Balance Hormone Health, a single specialty practice. I am specialty board certified in female pelvic medicine. I have an active patient base of approximately 5,000 patients, and approximately 10,000 patients in EMR. I treat these patients for, among other things, thyroid optimization, surgery, pelvic support surgery, and hormone issues in male and female patients.

Experience in Prescribing and Treating with Compounded BHRT

Approximately 30-40% of my patients are being treated with some form of compounded BHRT. My practice treats over 400 patients with compounded BHRT pellets per month.

David J. Watson,
Bruce R. Dorr,
Jeannie Key,
Katherine Tiedt,

Medical Conditions and Patient Populations Treated with Compounded BHRT

I treat a variety of medical conditions in my male and female patients of all ages with compounded BHRT. Specifically, I treat the following symptoms and conditions with compounded BHRT:

- Hormone replacement therapy for women during menopause
- Hormone deficiencies experienced by women prior to menopause
- Hormone depletion in men and women ages 20-29
- Endometriosis
- Brest cancer
- Depression
- Sleep issues
- Collagen or vascular disorders
- Rheumatologic disorders
- Autoimmune disorders

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, I prefer to treat my patients with compounded BHRT instead of the commercially available BHRT because hormone therapy requires individualized treatment and a constant reassessment and adjustment of the hormone dose and the medication—it is effectively impossible to treat patients with a one-size-fits-all hormone therapy treatment.

I prefer to treat my female patients with compounded BHRT because there is no commercially available testosterone approved for treatment in women. In my professional experience, I have witnessed many female patients that require testosterone treatment and, as a result, are relegated to self-treating with their husbands' testosterone, which is dosed at male ranges and is unsafe for self-treatment by women. I am able to successfully treat these female patients with compounded bio-identical testosterone in pellet form to resolve low libido, sexual side effects of testosterone deficiency, sleep issues, and bone mass deficiencies. I prefer to treat with the hormone pellets instead of transdermal creams or oral troches because then the hormone is delivered the way the ovaries are used to delivering hormones. Further, patient compliance with the pellet therapy is, in my professional experience, much higher than when my patients are treated with patches, creams, or pills.

Compounded bio-identical testosterone is also a necessary option for women because women are contraindicated to treatment with estrogen and testosterone is often the only option. Without treatment with compounded bio-identical testosterone, women are at an increased risk for

P 303-730-3600 · F 303-730-1445
LITTLETON

heart disease, dementia, and bone health deficiencies, among many others. For so many of my patients, compounded bio-identical testosterone is lifesaving. When my female patients are treated appropriately (i.e., with the right dosage strength and the right dosage form for what the patient can tolerate), their bone density will normalize within a year, they will lose weight appropriately, they will gain back energy, and many patients find that they no longer need sleeping aids or antidepressants.

I prefer to treat my male patients with compounded bio-identical testosterone in pellet form because every other dosage form of testosterone (e.g., shots, gels, creams, or the commercially available Testopel) delivers inconsistent levels of the hormone. That is, when bio-identical testosterone is prescribed in other dosage forms besides pellet therapy, the patient will experience peaks and troughs of the effects, or the patient might not absorb it at a consistent rate, or the patient may not absorb it at all. The bio-identical testosterone pellet delivers the hormone the way the body is meant to receive it, but commercially available bio-identical testosterone cannot do this.

Finally, I prefer to treat my patients who have a history of blood clotting with compounded subcutaneous pellet therapy. Pellet therapy is the only hormone therapy available for patients with a history of clotting, such as deep vein thrombosis or pulmonary embolus. There is no commercially available hormone replacement therapy that can treat these patients.

Sincerely,

/s/ Bruce Dorr, MD, FPAIRS

P 303-730-6000 · F 303-730-1445

Bruce Dorr

MD, FPMRS

7750 S. Broadway, Suite 200, Littleton, Colorado 80122 . 303-730-6000 [redacted]

Education

High School 1979 - 1982
Redford Union High School

General studies during High School 1982 - 1982
Oakland Community College

Bachelor of Arts 1982 - 1986
Hope College
Majors: Chemistry, Biology
Minors: German, Psychology

Directed European Studies 1984 - 1984
Center for European Studies, Vienna, Austria
Directed Studies in Art History and European economics

Medical Doctorate 1986 - 1990
Wayne State University School of Medicine

Internship and Residency 1990 - 1994
University of Colorado Health Sciences Center
Obstetrics and Gynecology

Clerkship July 1993 - August 1993
Sloan-Kettering Memmorial Hospital, New York, New York
Galloway Fellowship in Gynecologic Oncology

Clerkship in Urogynecolgy January 1996 - February 1996
Evanston Continence Center, Evanston, Illinois
Course of study in Urodynamics and Urogynecology with Peter Sand, MD--affiliated with the Northwestern School of Medicine

Work experience

Chairman, Department of Women's Services 2014 - present
Littleton Adventist Hospital
Reviewed credentials, peer review of cases, service on Medical executive committee

Skills

Honors/Awards

Undergraduate

Cum Laude Graduate,

Presidential Scholar Scholarship

Vienna Summer School Scholarship

Mortar Board Honor Society President

Medical School

Honors for Ob/Gyn, Gyn Oncology, Medicine, Pediatric ICU and ENT with recommendations for Surgery, Pediatrics and Family Medicine

Residency

Golden Apple Teaching Award for Outstanding teaching resident 1990

Galloway Fellowship in Gyn Oncology

Littleton Gyn and Wellness/Right Balance Hormone Health

Physician in Urogynecology, general gynecology, minimally invasive surgery

Medical Missionary 2018 - current

Centura Global Health Inititiatives

Chief Gyn Surgeon for Peru and Nepal missions

Chairman 2013 - present

Centura Littleton Robotics Division

Develop and consult for hospital advancements in robotics surgery

Platinum Trainer and Mentor 2013 - present

BioTE Medical

train practitioners in bio-identical hormone replacement and optimization therapy

Physician Reviewer 2000 - 2010

Colorado State Medical Board

Reviewer for State Mecical board for requested cases

Proctor 2010 - present

Intuitive Surgical

Proctor/train new physicians for robotic surgery on XI and Si platforms

Assistant Clinical Professor 1995 - 1997

Denver Health Medical Center

Principle instructor of UroGynecology

Admissions Committee Representative 1995 - 1997

University of Colorado Health Sciences Center

Committee representative for medical stucent admissions

Locum Tenens Physician 1994 - 1995

Jackson & Coker, CompHealth

Local physician work in Arizona, Oregon, Michigan, New York anc Virginia

Skills

Research

[redacted]

Medical School

Dorr, B., V. Maiviya, G. Deppe, et al,

"Does Limited Lymphadenectomy Based on Frozen Section of Uterus Decrease Survival in Patients with Endometrial Cancer."

Dorr, B., J. Abbott, and W. Schlaff, "Vaginal Bleeding in the Emergency Room"

Exhibit 1-F

BIO-IDENTICAL WELLNESS

CHRISTINE FARRELL MSN, FNP-C

Statement From Christine Farrell M.S.N., F.N.P.-C

Qualifications

My name is Christine Farrell M.S.N., F.N.P.-C. My professional background is as follows. I received my Bachelor of Science, *cum laude*, from the University of California, Los Angeles in 1989. I received my Family Nurse Practitioner/Masters in Nursing from California State University, Long Beach in 1997, where I focused in FNP training and acute/emergent care. My up to date CV is enclosed for reference.

I worked as a Registered Nurse in the Medical ICU at Huntington Memorial Hospital, in Pasadena, California from 1989 to 1990. I was responsible for the care of medically ill patients in critical condition and included treatment of respiratory, neurological, infectious disease, and gastrointestinal issues. I worked as a critical care flight nurse from 1992 to 1994, where I was independently responsible for the care of critically ill patients during flight transport nationally and internationally. It included Swan-Ganz monitoring, intubated patients, and ACLS institution as needed. I worked as a Registered Nurse at Northridge Hospital in Northridge, California from 1990 to 1992, where my responsibilities included care of critically ill patients, including open-heart, Swan-Ganz monitoring, vasopressors, ventilators, and code blue response team. I also worked as a Registered Nurse at the Northridge Hospital Trauma Center in Northridge, California from 1991 to 1994. My responsibilities included care of emergency room/trauma patients, which included orthopedic, OBGYN, pediatric, urgent care, cardiac, trauma, near-drowning, burn, and general medicine care. I was also the clinical care coordinator and charge for the unit. I assisted part-time in the hyperbaric chamber/center in emergency and wound care of patients.

After working in various roles at Northridge Hospital, I worked as a transplant nurse coordinator at the University of California San Diego Medical Center. My responsibilities included patient education, work-up, follow-up, physical assessment, in-patient assessment, and nursing education. I gained specialized knowledge of immunosuppression, pharmacology, cardiac/pulmonary pathophysiology, laboratory values, and crisis intervention. I worked as a Registered Nurse in the emergency room of Columbia West Hills Medical Center from 1996 to 1997.

I worked as a Family Nurse Practitioner at Affiliates in Medical Specialties Medical Group from 1997 to 2005. My responsibilities included primary care, internal medicine, and urgent care. I managed all levels of care, both chronic and acute, including women's health, diabetes, obesity, hypertension, orthopedics, and pediatrics, among others. I was a Wellness Program Director and

Aesthetic Clinical Specialist at Aesthetic Surgical Partners from 2005 to 2006, where I provided bio-identical hormone consultation and treatment, nutritional/weight loss counseling, pre- and post-op evaluations, laser treatments (e.g., Titan, Genesis, hair removal, vascular, and IPL), and injectable cosmetic enhancements (e.g., Botox, Restylane, Sculptra, Radiesse, and Jevederm). I worked as a Family Nurse Practitioner at AFP Associates from 2008 to 2010. My responsibilities included primary care and family practice, specifically managing all levels of care, both chronic and acute, including women's health and hormone therapy, orthopedics, hypertension, and diabetes.

I have been an Associate Clinical Professor at the University of California, Los Angeles since 2001. I am a clinical instructor/preceptor for the Nurse Practitioner program. I have also been a legal nurse consultant for PJ West and Associates since 2004, where I have provided expert testimony and case review of billing and medical records.

I belong to the North American Menopause Society, the International Menopause Society, and the International Hormone Society. I am certified in Vitapel hormone implant therapy.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

I currently work as a nurse practitioner, owner, and president of Christine Farrell MSN, FNP-C, Inc./Bio-Identical Wellness. I specialize in the treatment of hormonal imbalances in men and women of all ages. I provide women's health care and general health care. I have been in the practice of treating hormone imbalances for over 17 years.

I treat all of my patients with hormone therapy. Approximately 90-95% of my patients are treated with compounded Bio-Identical Hormone Replacement Therapy ("*BHRT*"). Approximately 75% of my patients treated with compounded BHRT are female, and approximately 25% are male. In my professional medical experience, I have witnessed a near 100% effectiveness rate when patients are appropriately treated with compounded forms of BHRT.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I treat a variety of medical conditions in my male and female patients with compounded BHRT. The table below represents some of the medical conditions and symptoms with which my patients present and that are effectively treated by compounded BHRT:

Male Patients	**Female Patients**
● Andropause	● Dysmenorrhea
● Depression	● Hot flashes
● Hyperlipidemia	● Hyperlipidemia
● Hypothyroidism	● Hypothyroidism
● Insulin Resistance	● Insulin resistance
● Joint Pain	● Irregular menstrual cycles
● Libido	● Joint pain
● Loss Of Muscle Mass	● Libido
● Memory Issues	● Memory issues
● Sleep Issues	● Menopause

- Weight Management

- Mood issues (anxiety and depression)
- Perimenopausal symptoms
- Polycystic ovarian issues
- Sleep issues
- Vaginal atrophy
- Weight management

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, I prefer to treat my patients with compounded BHRT instead of the commercially available BHRT because hormone therapy requires individualized treatment and a constant reassessment and adjustment of the hormone dose and the medication—it is effectively impossible to treat patients with a one-size-fits-all hormone therapy treatment. I monitor my patients' hormone levels by drawing blood every 2-3 months in the beginning, and then at a minimum every six months thereafter. Compounding allows me to make slight adjustments based off what my patients' blood results indicate.

In my professional medical opinion, FDA-approved BHRT is not suitable to treat the entire patient population that requires hormone therapy. For example, Prometrium is an FDA-approved bio-identical progesterone oral capsule that is dosed in 100 mg and 200 mg dosages. If I treat five different women each with a 100 mg capsule of Prometrium, each woman's blood test results will indicate different hormone levels. Additionally, Estrogel is an FDA-approved bio-identical Estradiol topical gel that is typically prescribed to female patients in doses of one pump (1 gram) per day, however, most female patients require more than one pump to effectively treat their symptoms. Not only is two pumps significantly more expensive for patients, but most patients cannot absorb two pumps (2 grams) of Estrogel in a consistent manner because of the amount of surface area on the body that the topical cream needs to cover. In these instances, I prescribe compounded bio-identical Estradiol in a more concentrated dose. With double the strength in one pump, patients get a better treatment that is tailored to what they actually need and their compliance with the prescribed dose is higher than if patients had two use two pumps of Estrogel each day.

Just because an FDA-approved, standardized dose exists does not mean that that dose is right for all patients. Frequently, FDA-approved dosages are either not adequate for what a patient needs or is not approved in a dosage form that is consistently and easily absorbed by the patient. Individualized hormone care is safer and more effective for patients requiring hormone therapy.

Sincerely,

/s/ Christine Farrell M.S.N., F.N.P.-C

343 s. Moorpark Rd, Thousand Oaks, CA 91361

818-865-8500

Christine Farrell M.S.N., F.N.P.-C

438 Havenside Ave.
Newbury Park, CA 91320
805-208-4439 cell
818-865-8500 work
818-865-8022 fax

Professional experience

Sept 2006-Present *Christine Farrell MSN, FNP-C, Inc./ Bio-identical Wellness*
Private practice- owner / president
Responsibilities: *Specializing in the treatment of hormonal imbalances in men and women of all ages. Providing women's health care and general health care.*

Jan 2008-Dec 2010 *AFP Associates*
Family Nurse Practitioner
Responsibilities: *Primary Care / Family Practice – manages all levels of care, both chronic and acute, including: women's health/hormone therapy, orthopedics, hypertension, diabetes, etc.*

July 2005-Sept 2006 *Aesthetic Surgical Partners*
Wellness Program Director / Aesthetic Clinical Specialist
Responsibilities: *Bio-identical hormone consultation and treatment, Nutritional/Weight loss Counseling, Pre/Post-op evaluations, laser treatments (Titan, Genesis, hair removal, vascular, IPL), injectable cosmetic enhancements (Botox, Restylane, Sculptra, Radiesse, Juvederm)*

May 2004-Present *PJ West and Associates*
Legal Nurse Consultant.
Responsibilities: *Expert testimony. Case review (billing and medical record).*

Apr 2001-Present *Associate Clinical Professor, University of California Los Angeles*
Clinical instructor/preceptor for Nurse Practitioner program.

June 1997-Sept 2005 *Affiliates in Medical Specialties Medical Group.*
Family Nurse Practitioner
Responsibilities: *Primary care / Internal Medicine / Urgent Care- manages all levels of care, both chronic and acute, including: women's health, diabetes, obesity, hypertension, orthopedics, pediatrics, etc.*

Jun 1996-Jun 1997 *Columbia West Hills Medical Center*
Registered Nurse, Emergency Room
Responsibilities: *Care of emergent and acute patients of all age groups.*

Christine Farrell M.S.N., F.N.P.-C, L.N.C.

Oct 1995- *University of California, San Diego Medical Center*
Jun 1996 *Transplant Nurse Coordinator*
Heart/Lung Transplant Division- Adult / Pediatric
Responsibilities: *Patient education, work-up, follow-up, physical assessment, in-patient assessment and nursing education. Includes specialized knowledge of immunosuppression, pharmacology, cardiac/pulmonary pathophysiology, laboratory values, and crisis intervention. Assistant editor of "transplant talk", organ procurement runs, community marketing and education*

MARCH 1990-AUG 1994 Northridge Hospital Medical Center

Aug 1991- *Northridge Hospital Trauma Center, Northridge,CA.*
Aug 1994 *Registered Nurse, Emergency Room*
Clinical Care Coordinator
Responsibilities: *Care of emergency room/trauma patients, including: orthopedic, OBGYN, pediatrics, urgent care, cardiac, trauma, near-drowning, burns, general medicine. Clinical care coordinator/charge for unit. Part-time assistance in the hyperbaric chamber/center in emergency and wound care of patients.*

Mar 1990- *Northridge Hospital, Northridge, CA.*
Mar 1992 *Registered Nurse, CCU, ICU, Trauma ICU*
Responsibilities: *Care of critically ill patients including: open-heart, Swan-Ganz monitoring, vasopressors, ventilators, code blue response team*

Jul 1992 - *Air Ambulance Incorporated, Van Nuys, CA.*
Aug 1994 *Critical Care Flight Nurse, on call (while still full time at NHMC)*
Responsibilities: *Independent care of critically ill patients during flight transport nationally and internationally. Included: Swan-Ganz monitoring, intubated patients, ACLS institution as needed.*

Jun 1989 - *Huntington Memorial Hospital, Pasadena, CA.*
Mar 1990 *Registered Nurse, Medical ICU*
Responsibilities: *Care of medically ill patients in critical condition. Included: respiratory, neuro, infectious disease, GI.*

Christine Farrell M.S.N., F.N.P.-C, L.N.C.

Education

California State University, Long Beach

Family Nurse Practitioner/Masters in Nursing

FNP training acute/emergent care focused

May 1997

University of California, Los Angeles

Bachelors in Science

Graduated June 1989, ***cum laude***

Professional membership/Certifications-

DEA# MF0544646
NPI# 1215197033
National Board Certification Family Nurse Practitioner (FNP-C)
Associate Clinical Professor, ***UCLA***
Member International Menopause Society
Member American Academy of Nurse Practitioners
Member North American Menopause Society
Member American College for the Advancement of Medicine
Member American Academy of Anti-Aging Medicine
Member of California Coalition of Nurse Practitioners
Member of Association Legal Nurse Consultants (local and national)
Member, North American Transplant Coordinators Organization
Anti-Aging/Aesthetic/Bio-Identical Hormone Training Course/Certification 2005
Restylane Training/Certification 2005
Sculptra Training/Certification 2005
Cutera Laser Training/Certification 2005
Bio-IdenticalHormoneTraining/Preceptorship 2004
Botox Training/Certification 2003
Trauma Nursing Care Course (TNCC) 1994
Certified Critical Care Nurse (CCRN) 1991
Advanced Cardiac Life Support 1994
Pediatric Advanced Life Support 1997
Trauma Management Course 1991

Accreditations

Who's Who of Professional Women 2004
Pi Lambda Theta Honor Society, member
Mobile Intensive Care Nurse of the Year, 1993
Outstanding College Students of America, member
Golden Key National Honor Society, member

References available upon request

Exhibit 1-G

Women's Wellness Center
www.womenswellnessnow.com

Statement From Laura Grant, MD

Qualifications

My name is Dr. Laura Grant. My professional background is as follows. I received my Bachelor of Science in biology, *magna cum laude*, from Southwest Texas State University in 1986. I received my Medical Degree from the University of Texas Health Science Center, San Antonio in 1990. I completed my residency in obstetrics and gynecology at the University of Texas Health Science Center, San Antonio in 1994. I am board-certified by the American Board of Obstetrics and Gynecology, continuously since 1996. I have been a Certified Menopause Practitioner by the North American Menopause Society ("*NAMS*") since 2009.

I have been practicing obstetrics and gynecology since 1994 in Columbia, Missouri. I now focus exclusively on gynecology and women's health. Recognizing the value of a multidisciplinary approach to women's healthcare, I founded Women's Wellness Center in 2007. I now specialize in perimenopausal health, and as stated above, I earned and continue to maintain the credential of NAMS Certified Menopause Practitioner, awarded by NAMS, the preeminent scientific organization focused on menopausal health. Those who hold this certification have demonstrated and maintain special competency in the field of menopause.

Another focus of my practice is on non-invasive office-based treatment of pelvic floor dysfunction, which is the root cause of bladder and bowel control problems such as urinary incontinence, overactive bladder, urinary urgency/frequency, and fecal incontinence. Pelvic floor dysfunction is also the cause of many chronic pelvic pain conditions, such as chronic sexual or genital pain, chronic pelvic pain, and chronic bladder pain or interstitial cystitis.

Experience Treating with Compounded BHRT

Starting in 1994, for the first 13 years of practice I provided full OB/GYN services in private practice, including treating menopausal symptoms. For the past 12 years of private practice, I have specialized in menopausal hormone therapy, and focused on that as a major part of my practice. When I use the term "bioidentical hormone" it refers to a hormone formulation where the hormone molecule is identical to what the body produces. There are commercially available bioidentical hormones, and there are compounded bioidentical hormones. It is my professional medical opinion, based on my research of published data and my experience, that bioidentical hormones are the best hormone treatment option for patients, because they replace the same compounds the human body lacks after menopause. Synthetic products (such as Premarin, Provera) were the only options when hormone therapy first came into use, but since biochemical advances have made it possible to isolate and produce the identical match of the body's hormones, it is my professional medical opinion that that is the best and safest approach, and we should abandon hormone substitutes. For example, published studies have linked synthetic progestins, not bioidentical progesterone, to breast and cardiac risk.

I have treated thousands of patients in my career, and I would estimate that at least half of my patients are relying on compounded BHRT as their "life saving" therapy. (I put that in quotes because they would *live* without hormone replacement, but by their own descriptions, their quality of life would be so poor that it would not be worth living.) The fact is, there are many patients that absolutely cannot get relief of symptoms with commercially available products, therefore, other choices are needed in our armamentarium.

Hormone therapy does not offer a one-size-fits-all solution. Typically when I start a patient on hormone therapy, initially I prescribe commercially available bioidentical products as my first line therapy, such as the estradiol patch and oral micronized progesterone. However, for reasons discussed below, sometimes a commercial regimen is not sufficient for the needs of certain patients. Then, we try different options until the patient is satisfied and symptoms are controlled. This often leads me into the compounded products, and I am so glad to have these options for my patients.

Medical Conditions and Patient Populations Treated with Compounded BHRT

My goal is to treat my patients with the most effective, safest, and most convenient solution. The method chosen will vary significantly from patient to patient. Accordingly, I often prescribe the following compounded BHRT instead of the commercially available for the following reasons.

- **Estradiol**. I prescribe estradiol to treat symptoms of estrogen depletion, such as hot flashes, night sweats, brain fog, mood instability, decreased libido, vaginal atrophy (dryness and painful intercourse), sleep disturbance, and cyclic headaches (estrogen withdrawal headaches that occur when endogenous estradiol levels are low).

  Bioidentical estradiol is available commercially in patch, gel, or spray formulations, but these products are sometimes not absorbed or tolerated well by patients. Sometimes with the patch they develop a skin rash, or the patch will not adhere well to the skin, making it ineffective. Sometimes the patch or gels are not effective in controlling symptoms. Based on my professional medical knowledge and experience, in these cases I prescribe compounded estradiol in a cream.

  Although bioidentical estrogen is commercially available in oral tablets, I prefer not to prescribe oral estrogen to midlife women due to their increased risk for thrombosis. This and other first-pass metabolism effects of oral estrogen can be avoided if the hormone is compounded into a transdermal estradiol cream. If skin absorption is not effective, or the cream is not tolerated by the patient, I prescribe compounded estradiol troches, which, like transdermal, avoids the first-pass effect when used properly.

- **Progesterone**. I prescribe progesterone for premenopausal patients to regulate and/or reduce volume of menstrual flow, to treat PMS, mood disturbance, anxiety, or sleep disturbance. For postmenopausal women who have not had hysterectomy, I prescribe oral progesterone to accompany estradiol and thereby protect the endometrium, as unopposed estrogen would increase risk of endometrial cancer.

  There are several indications for compounded progesterone, as opposed to commercially available products. Micronized progesterone is commercially available only in 100 mg and 200 mg oral dosage. In cases where lower potency is needed, I can order progesterone as a compounded capsule of lower dose. Further, I can order a topical progesterone cream for even lower potency, and this is very effective for treating women in the menopause transition, or those who have anxiety, PMS, night sweats, or sleep disturbance. Oral micronized progesterone in doses potent enough to protect the uterine endometrium, can give many patients CNS side effects, such as dizziness and fatigue. For these women, I often prescribe a progesterone vaginal suppository, which avoids the first-pass liver effect that is responsible for the sleepiness and other CNS side effects. And finally, those with a peanut allergy cannot take the commercially available micronized progesterone because it contains

peanut oil. Compounded oral progesterone products typically contain olive oil or a progesterone powder, and are well tolerated.

- **Testosterone**. I prescribe compounded testosterone topical cream or troches for women with low libido, or postmenopausal mood disturbance. Currently, there are no bioidentical testosterone products available for women commercially. Therefore, custom compounded testosterone products are the only option available.

  In my professional medical experience, testosterone is often needed for optimal well-being and quality of life in female patients. According to their testimonies, compounded testosterone has saved so many of my patients and their intimate relationships. There really is no substitute for compounded testosterone.

- **Vaginal Hormone Creams/Suppositories (Estradiol, Testosterone, DHEA)**. I prescribe vaginal hormone creams or suppositories to treat vaginal atrophy after menopause, which is a cause of painful intercourse and loss of intimacy. The other important use of vaginal hormones in my practice is to improve the health of bladder and vaginal mucosa for those undergoing pelvic floor therapy.

  As mentioned above, a major part of my practice is providing office-based pelvic floor therapy for conditions related to pelvic floor dysfunction. Efficacy of this treatment necessitates a healthy vaginal mucosa, which is lacking in a hormonally depleted woman. Without the availability of compounded bioidentical hormone products, there are many patients who would not be able to receive vaginal tissue rejuvenation that allows them to receive pelvic floor therapy. One reason for this is that sometimes the commercially available products are simply not effective for some patients. Another issue is that the commercially available products sometimes cause skin or vaginal irritation, and in those cases we can prescribe a compounded vaginal gel or cream in a hypoallergenic base. Further, there are some patients who do not wish to use estrogen, or in whom estrogen is contraindicated. For these, I prescribe vaginal DHEA or testosterone, which are equally effective as estrogen in restoring vaginal health. There is no vaginal testosterone (or any bioidentical testosterone for females) available commercially. And finally, all of the commercially available FDA approved vaginal hormone products are often prohibitively expensive.

  Healing vaginal atrophy and pelvic floor dysfunction represents a major proportion of my practice, and truly it would be tragic to deny women access to tolerable and affordable vaginal hormonal creams and suppositories. In some cases, it literally can make or break a woman's success in pelvic floor therapy outcome, not to mention the ability to have comfortable and pleasurable intimacy with their partner. Again, choices are needed, it's not one size fits all.

Why is Compounded BHRT Sometimes Preferred Over Commercially Available BHRT?

Based on my professional medical judgment and clinical experience, there are many instances in which it is necessary to have the option of compounded BHRT to prescribe for our patients. As a specialist in menopausal hormone therapy, my medical practice exposes me to multitudes of women who have already been to their general ob/gyn or primary care physician looking for a solution to their symptoms related to the menopausal transition. Their doctor or doctors typically have prescribed one or more of the commercially available options, and the patient has found it to be insufficient.

As detailed above, reasons for insufficiency are many: ineffectiveness, non toleration of side effects, insufficient dosage options to relieve symptoms, lack of variety in dosage and routes of administration, and complete non-availability of testosterone.

My medical practice will be significantly hindered without the compounded hormone option, and female patients will be very poorly served to see this option removed. When the patient example above returns

to her ob/gyn or PCP for a better solution than commercial product given, the doctor responds, "That's your only choice, take it or leave it." I believe that we, as professionals entrusted with the care of midlife women experiencing life altering menopausal symptoms, can do a better job, and we must not be hobbled in trying to do so.

Sincerely,

Laura Grant, MD

1705 E. Broadway Ste 300 • Columbia, Missouri 65201 • 573-449-9355 • fax 573-441-9355

Exhibit 1-H

Plano Women's Healthcare, PA.
Obstetrics, Gynecology and Infertility

Statement From Arlene Jean Jacobs, M.D.

Qualifications

My name is Dr. Arlene Jean Jacobs. My professional background is as follows. I received my Bachelor of Science from Tulane University, Newcomb College in 1981. I received by Doctor of Medicine, *summa cum laude*, from Tulane University School of Medicine in 1985, where I graduated second in my class. I completed an OB/GYN internship from 1985 to 1986 at Southwestern University, Parkland Memorial Hospital. I completed an OB/GYN residency from 1986 to 1989 at Southwestern University, Parkland Memorial Hospital. I have been licensed to practice medicine in Texas since 1985. I have been board-certified in obstetrics and gynecology since 1992. I have been working as an OB/GYN in private practice at Plano Women's Healthcare, P.A. since 1989. My private practice focuses on women's health, obstetrics, gynecology, surgery, preventive health care, hormone therapy, bladder health, brain health, bone health, and mental health.

I have been honored as D Magazine's Best Doctor in 2003, 2004, 2014, 2015, 2016, 2017, 2018, and 2019. I was Plano Star Courier's Best Women's Healthcare Doctor in 1999, 2003, 2009, 2016, and 2017. I have been awarded Texas Monthly's Best Doctor numerous times since 2003 and have been awarded as a Texas Super Doctor in 2006 and 2007. I have been honored as one of America's Top Obstetricians & Gynecologists in 2015, 2016, and 2017. For a complete list of my honors and awards, please see my enclosed CV.

I have also served numerous roles within the Medical Center of Plano. I have served as Chief of OB/GYN and Chief of Medical Staff, and I have served various roles on the Board of Trustees. For a complete list of my additional committee participations, please see my enclosed CV. I am a member of the following professional societies: the American Medical Association, the Texas Medical Association, the Dallas County Medical Association, the American College of Obstetrics and Gynecology, and the Society of Laparoendoscopic Surgeons.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

My entire private practice treats our patients with compounded BHRT. In my professional medical opinion, there is no effective commercially available BHRT. Compounding allows for optimization to change dosage forms and dosage strengths throughout patient treatment.

I treat over 300 patients per month with BHRT, of which approximately 200 of those are in the form of compounded pellet therapy. I have been treating patients successfully with compounded BHRT for approximately seven years. Based on my professional medical experience and judgment, I have chosen not to treat patients with synthetic and/or conjugated hormones for at least the past eight to nine years because of their associated negative side effects and general ineffectiveness, and the lack of ability to optimize dosage forms and strengths to meet patient needs.

Medical Conditions and Patient Populations Treated with Compounded BHRT

Based on my professional medical judgment, I have set out below the compounded BHRT that I prescribe to treat certain medical conditions and symptoms in my patients.

- **Compounded Progesterone.** I treat patients with compounded progesterone in transdermal creams, oral capsules, vaginal suppositories, and troches to treat the following conditions and symptoms:
    - Premenstrual syndrome
    - Dysfunctional bleeding
    - Heavy menses
    - Menopausal symptoms
    - Postmenopausal symptoms
    - Sleep and hormonal imbalance in hysterectomy patients

The FDA-approved progesterone currently available on the market is a generic version of Prometrium, which is currently approved in 100 mg and 200 mg oral capsules. These capsules are not as well absorbed by patients and often cause negative side effects, such as abnormal bleeding and inadequate improvement of symptoms. Instead, many of my patients absorb the compounded progesterone better when taken vaginally or orally. Further, the generic version of Prometrium contains peanut oil, which is contraindicated in patients with peanut allergies. Compounding allows for the medication to be made without such an allergen.

- **Compounded Estradiol.** I treat patients with compounded estradiol to treat the following medical conditions and symptoms in my patients:
    - Menstrual migraines
    - Perimenopausal bleeding
    - Menopausal symptoms, such as hot flashes, night sweats, sleeping issues, vaginal dryness, pain with intercourse, and mood instability
    - Bone loss, such as osteopenia and osteoporosis
    - Patients with family histories of dementia and Alzheimer's
    - Cardiovascular issues
    - Cholesterol issues

Regarding bone loss specifically, there is no commercially approved hormone therapy that combines bioidentical testosterone and bioidentical estradiol. The combination of these two bioidentical hormones helps rebuild bones naturally, which I validate through bone density testing routinely conducted with my patients to monitor their responsiveness to the hormone therapies.

I prefer to treat my female patients with compounded bioidentical estradiol because the commercially available versions, i.e., Vagifem and Femring, do not resolve symptoms and are not

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absorbed in my patients as well as the compound. Specifically, Vagifem is a local medication only—it does not have any systemic benefits, it does not absorb as well through the vagina, and it does not help longevity in my patients. Vagifem is only available in a few dosage strengths, so tailoring the hormone to the needs of my individual patient is difficult, if not sometimes impossible. Additionally, commercially available Femring is absorbed within the body systemically, but patient compliance with this treatment regimen is an issue as patients often cannot tolerate the side effects, such as discomfort and irritation, and it is difficult to place in the vagina. And, like Vagifem, Femring is not as effective due to absorption issues in the vagina. Therefore, I prefer to treat my patients with compounded bioidentical estradiol in dosage forms that my patients can successfully absorb and in strengths tailored to what my patient needs.

- **Compounded Testosterone**. I treat patients with compounded testosterone to treat the following medical conditions and symptoms in my patients:
    - Hormone imbalances in breast cancer survivors
    - Premenopausal symptoms
    - Perimenopausal symptoms, such as low energy, low stamina, impatience, low sex drive, low sex desire, cognition issues, and sleep issues
    - Migraine prevention
    - Bone loss
    - Cardiovascular issues
    - Cholesterol issues
    - Alzheimer's
    - Dementia

Compounded bioidentical testosterone must be made available for female patients because there is no commercially available testosterone approved to treat female patients. Further, as stated above, regarding bone loss, there is no commercially approved hormone therapy that combines bioidentical testosterone and bioidentical estradiol. The combination of these two hormones helps rebuild bones naturally, which I validate through bone density tests routinely conducted with my patients to monitor their responsiveness to the hormone therapies.

Additionally, compounded bioidentical testosterone is successful in treating male patients for androgen deficiencies, low sex drive, weight management, cholesterol issues, cognitive issues, bone loss, and to treat patients with family histories of Alzheimer's and dementia. I prefer to treat my male patients with compounded bioidentical testosterone because commercially available testosterone approved for treatment in men is too structured in dosing and does not allow the flexibility in treatment that is required in hormone therapy. In my professional medical opinion, in order to best treat my patients, I need to be able to adjust their hormone therapy based on the patient's lifestyle changes, illnesses, activity level, etc., and the commercially available

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testosterone dosage strengths do not allow me this flexibility like the compounded bioidentical testosterone does.

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, I prefer to treat my patients with compounded BHRT instead of the commercially available BHRT because of the way the compounded BHRT is processed by the body. Synthetic hormones are processed through the liver, whereas compounded bioidentical hormones bypass the liver. This is critical for patients who have suffered a stroke or some form of blood clot and therefore require hormone therapies to bypass the liver.

Further, I prefer to treat my patients with compounded BHRT because they feel better on compounded BHRT. It is a safer treatment as there is no risk of clotting and compounded BHRT carries far less side effects. There are not enough dosage forms and strengths of commercially available BHRT to treat the idiosyncratic nature of hormones. With compounded BHRT, I have the ability to adjust and optimize the patient's medication dosages rather than relegating my patients to cookie cutter, commercially available medication that does not work for them. With compounds, I am able to perform blood tests on my patients every 5-6 weeks to evaluate and re-evaluate how the patients is responding to the hormone therapy.

Finally, having the ability to treat patients with pellet therapy allows the hormone treatment to go straight into the bloodstream in a consistent manner. I prefer this dosage form so as to avoid the peaks and troughs of absorption caused by treatment in transdermal creams and troches.

Sincerely,

Arlene Jean Jacobs, M.D.

1600 Coit Road, Suite 202, Plano, TX 75075 • Phone 972-596-2470 • Fax 972-985-9892 • www.planowomenshealthcare.com

Curriculum Vitae

Arlene Jean Jacobs, M.D.
Plano Women's Healthcare, P.A.
1600 Coit Road, Suite 202 Plano, TX 75075

Licensure: Texas, 1985
Board Certified, 1992, Obstetrics/Gynecology

Education: Tulane University, Newcomb College, B.S. 1979-1981
Tulane University School of Medicine, 1981-1985

Postgraduate Education:
Southwestern University, Parkland Memorial Hospital
Internship: 1985-1986 (OB/GYN)
Southwestern University, Parkland Memorial Hospital
Residency: 1986-1989 (OB/GYN)

Work History: Private Practice, 1989 to present, Plano Women's Healthcare, P.A.

Awards and Honors:
Summa Cum Laude, 1985
Phi Beta Kappa
Omicron Delta Kappa
Tulane Scholar
Alpha Omega Alpha
Graduated 2nd in medical school class
D Magazine Best Doctor 2003, 2004, 2014,2015,2016, 2017, 2018
Plano Star Courier Best Women's Healthcare Doctor 1999, 2003, 2009, 2016, 2017
Texas Monthly Best Doctor 2003, 2004, 2005, 2006, 2007, 2008, 2009,2010
Texas Super Doctors 2006, 2007
Top Ob/GYN 2006, 2007, 2008, 2009, 2010, 2016
Patients Choice Award – 2010
America's Top Obstetricians & Gynecologists – 2015, 2016, 2017

Medical Center Of Plano:
Board of Trustees, 2004-2008, 2010-2014, 2016-2020
Board of Trustees Vice-Chair, 2018
Board of Trustees, Chairman of the Board, 2019
Past Chief, Medical Staff, 2003
Chief, Medical Staff, 2002
Vice Chief, Medical Staff, 2001
Chief, OB/GYN, 1996-1997

Committees:
Executive Committee, 1996-1997, 2002-2003
Operating Room Committee, 1996-1997
Peer Review Committee, 1995-1996
Credential Committee 1993-1995
Infection Control Committee, 1990-1993
Sweet Success – Maternity Diabetes Program Director, 2004
Diabetes Committee, 2005-2015

IT Committee, 2005
Day Surgery of Plano – Governing Board Committee 2004-Present
Crimson Tide Project 2010, 2011
TMCP Advisory Board 2009-present
Graduate Medical Education Committee, 2011-present
Continuing Medical Education Committee, 2012-present
Robotics Committee, 2012-Present

Professional Societies:

American Medical Association
Texas Medical Association
Dallas County Medical Society
American College of Obstetrics and Gynecology
Society of Laparoendoscopic Surgeons
Past Speaker; Cord Blood Banking

Personal & Professional References: Furnished upon request

Exhibit 1-I

Steven A. Komadina, M.D.
4801 McMahon Blvd. NW #101
Albuquerque, New Mexico 87114
(505) 893-2840

November 1, 2019

Statement From Steven A. Komadina, M.D.

Qualifications

My name is Dr. Steven A. Komadina. My professional background is as follows. I went to but did not receive an undergraduate degree from the University of New Mexico, because of early admission to medical school after just 3 years of undergraduate study. I received my Doctor of Medicine, with honors, from the University of New Mexico School of Medicine in 1970. I completed a rotating internship at the Naval Medical Center in San Diego, California from 1970-1971, where I was chosen as the Outstanding Surgical Intern. I also completed an OB-GYN residency at the Naval Regional Medical Center in San Diego, California from 1971-1974. I became fully board certified by the American Board of Obstetrics and Gynecology in 1976. In 1977 I became a Fellow of the American College of Obstetrics and Gynecology.

In 1969-70, I served as a missionary doctor in Katmandu, Nepal. After eight years of active duty in the U.S. Navy, I returned to Albuquerque to practice as a full-time private practice OB-GYN from 1977-2001. Since 2001, I have practiced gynecology and preventive medicine, doing lifestyle medicine and office gynecology. I treat male and female patients with a specific focus on hypothyroidism, male and female hormone balance, cardiac function, infertility, healthy lifestyle, and nutrition counseling. Also, since 2001, I have become an internationally recognized lecturer on weight loss, health, and nutrition, and more specifically on preventative medicine and dietary prevention of disease. I have lectured to the public and to physicians on five continents. I am licensed to practice medicine in New Mexico.

I have served as Hospital Chief of Staff, President of the Greater Albuquerque Medical Association, and a Councilor of the New Mexico State Medical Society and President of the New Mexico Medical Society. I have served as a member of the clinical faculty in the Department of Ob-Gyn at the University of New Mexico School of Medicine, UCLA, UC San Diego and UC Irvine.

From 2008-2019, I have served on the New Mexico Board of Medicine, which licenses all doctors and physician assistants in New Mexico. Most recently I served as Secretary, until completing my term a few months ago.

I have professional memberships with the American Medical Association, American Fertility Society, New Mexico Medical Society (where I served as President from 2000-2001), Greater Albuquerque Medical Association, Southwest Ob-Gyn Society, and the International Society of Clinical Densitometry.

In addition to the practice of medicine, I also served 8 years from 2001-2008 as a New Mexico State Senator. For a full list of my public elected offices, please see my enclosed CV.

Experience With Treatment Using
Compounded Bio-Identical Hormone Therapy

I have been prescribing hormone therapy to my patients since 1970. In my medical experience and judgment, where it is best for the patient, I prefer to treat them today with compounded Bio-Identical Hormone Therapy ("BHRT"). In the last twenty years, I have treated over 40,000 patients with compounded BHRT. In the last 7 years, I have used compounded sterile hormone pellets, compounded hormone troches and compounded vaginal creams almost exclusively. My patients treated with compounded BHRT routinely thank me for saving their lives, as the compounded BHRT treatment allows these patients to stop taking cholesterol medication and SSRIs and benzodiazepines for mood disorders, among others. My patients treated with compounded BHRT report to me that they feel hormonally balanced and feel like they have gotten their lives back.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I use compounded BHRT to treat patients of all ages depending on their individual symptoms and laboratory tests. Specifically, I use compounded capsules of progesterone to successfully treat heavy vaginal bleeding in female patients of all ages and inadequate luteal phase in infertility patients. Depending upon the age and symptoms of the patient, it may be more appropriate and/or effective to treat with non-pellet therapy, such as prescribing compounded BHRT troches to treat menopause, andropause, perimenopause, and polycystic ovarian disease. Compounded hormone cream is also used for lichen sclerosis et atophica and senile vaginitis in elderly patients.

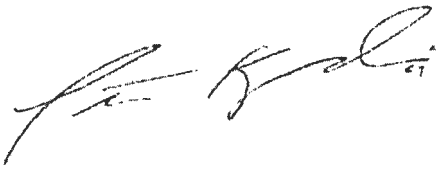
Based on my medical judgment, and when best for the patient, I choose to prescribe subcutaneous pellet therapy in both men and women with low hormone symptoms and to prevent diseases caused by low hormones, such as osteoporosis. I also successfully treat a large number of male and female patients with compounded BHRT for anxiety and depression. As a result, I am often able to get these patients off of their psychiatric medications they have been prescribed.

Why is Compounded BHRT Preferred Over Commercially Available BHRT ?

In my professional medical judgment, I choose to treat my patients with compounded BHRT instead of commercially available BHRT, because I can customize the dosage based on age, weight, symptoms and lab results in order to best treat my patients, I need to be able to customize the dose and the dosage form of the medication throughout treatment and only compounded BHRT allows me to do that. I have observed that my patients demonstrate a significantly better results and tolerance to compounded BHRT therapy than when these patients were treated with commercially available BHRT. My patients also experience more consistent results from treatment with compounded BHRT than when treated with commercially available BHRT.

Prior to becoming familiar with treating patients with compounded BHRT, I used to treat patients with commercially available hormone therapy such as Premarin and Provera. When I switched to treating patients with compounded BHRT, the health of these patients significantly and quickly improved at rates that I was not seeing when treating patients with commercially available hormone therapies. If I had to return to treating my patients with only commercially available BHRT, I know that I would witness a decline in my patients' health and wellbeing.

Respectfully,



Steven Komadina, M.D.

NEW MEXICO STATE SENATOR
STEVEN A. KOMADINA, M.D.
CURRICULUM VITAE

PUBLIC ELECTED OFFICE:

2001-2008 New Mexico State Senator, District 9
Senate Judiciary Committee 2001-2004
Senate Public Affairs Committee 2001-present
Senate Rules Committee 2005- present
Legislative Health and Human Services Committee
Revenue Stabilization and Tax Policy Committee
Tobacco Settlement Revenue Oversight Committee
Information Technology Oversight Committee
Water and Natural Resources Committee

2003-2005 National Conference of State Legislatures
Health Committee

2003-2004 Council of State Governments
National/Associates Advisory Council

2004-2008 ALEC Health and Human Services
Committee

WHO'S WHO LISTINGS:

Marquis Who's Who.....
In American Colleges and Universities
In America
In the West
In American Politics
In Science and Engineering
In Medicine and Healthcare
In Professionals and Executives
In Finance and Industry
America's Top Ob-GYNs 2004-2018

EDUCATION:

Undergraduate: 1963-1966 University of New Mexico

Medicine: 1966-1970 University of New Mexico School of Medicine, M.D.

1970-1971 Rotating -O- Intern
Naval Regional Medical Center, San Diego, Ca.

1971-1974 OB-GYN Residency,
Naval Regional Medical Center, San Diego, Ca.

Honors:

President of Freshman, Sophomore, Junior and Senior Men's Scholastic Honorary University of New Mexico
Three years in University of New Mexico Student Senate
G.E. College Bowl
Early admission to Medical School (age 19)
President of Medical School Class four years
Graduation from Medical School with honors
President of Intern Class
Chosen Outstanding Surgical Intern

NM Medical Society Community Service Award 2000
Outstanding Freshman Senator Designee 2001

LICENSURE / CERTIFICATION:

Medical License: New Mexico
California (not current)

Certification: Diplomat American Board of Obstetrics and Gynecology 1976

Member American College of Physician Executives 1989

Certified Clinical Densitometrist 1999

Professional Memberships:

American College of Physician Executives.
American Medical Association 1970-2010
American College of Obstetrics and Gynecology 1974-2013
American Fertility Society
New Mexico Medical Society
Greater Albuquerque Medical Association.
Southwest Ob-Gyn Society
International Society of Clinical Densitometry

Professional Activities:

September 1969-May 1970 Physician District Clinics United Mission to Nepal, Kathmandu
July 1974-June 1977 Deep selected as Commander and Captain in the US Navy Medical Corps, Long Beach Naval Regional Medical Center.
January 1976-June 1977 Chairman OB-GYN Dept. Long Beach Naval Regional Medical Center
July 1977-December 1988 Private Practice OB-GYN Albuquerque, NM
January 1989-December 1989 Vice President St. Joseph Healthcare System, Albq., N.M.
January 1987-September 1987 CEO Foundation Health Plan

January 1982-December 1986 Member of Congressional Issue Advisory Board for Congressman Manual Lujan, Jr.
January 1989-December 1989 Part time Gynecology practice
January 1995-2005 Associate Clinical Professor UNM School of Medicine, Department of OB-GYN
January 1996-97 President of The Greater Albuquerque Medical Association.
April 1997- Medical Director "Global Hilton" around the world balloon flight attempt
May 1998- Medical Director "Spirit of Peace" around the world balloon flight attempt

January 1990-2001 Full-time Private Practice OB-GYN, Albq, NM

March 2000-2001 President New Mexico State Medical Society

October 2001-present: Private practice of Lifestyle Medicine and Office Gynecology. Treating both men and women. Special focus on hypothyroidism, male and female hormone balance, cardiac function, infertility, healthy lifestyle and nutrition counseling.

2001-present: Internationally recognized lecturer on weight loss and health and nutrition. Frequently seen on television and lectures monthly around the world. Lectures on preventative medicine and health and nutrition with an emphasis on weight loss and dietary prevention of disease. He has lectured to the public and physicians on 5 continents.

2003 – 2010: Clinical associate with Dr. David Heber at UCLA Center for Human Nutrition
2003—2010: Educator on Nitric Oxide working under Nobel Prize Laureate for Medicine 1998, Dr. Louis Ignarro
2004-Present International Teacher of Neonatal Resuscitation to medical school faculty and public health workers worldwide

2009-2019 New Mexico Medical Board member. Elected Secretary of the Board 2018-2019.

HONORS:

Community: Selected by the Albuquerque Tribune as the "Rising Star" in Health for New Mexico, 1989.

Elected by State Medical Society to the Wyeth-Ayerst Award for outstanding community service outside of medicine 1999

AUTHOR:

***Born to be Healthy and Thin*: South Carolina: BookSurge (2005)**

CAREER GOALS: To teach my patients that health lies not in the treatment of disease, but in the proper nourishment of our bodies, lifestyle choices and prevention of disease.

To help patients understand that illness is based chiefly on lack of nutrition, malnutrition, and unhealthy lifestyles.

To empower patients to wisely make informed health care decisions.

Exhibit 1-J

MELVILLE MEDICINE

THE CHOICE FOR YOUR PRESENT & FUTURE WELLNESS

Statement From Dr. Daniel Elias Melville, M.D.

Qualifications

My name is Dr. Daniel Elias Melville, M.D. My professional background is as follows. I received my Bachelor of Science in biology and general engineering, with distinction, from the United States Air Force Academy, in Colorado in 1999. I received my Doctor of Medicine from the Louisiana State University College of Medicine in 2004. I completed a family medicine internship and family medicine residency at the Louisiana State University Health Sciences Center from 2004 to 2007. I was the Chief Resident of the Louisiana Department of Family Medicine – Rural Tract at the Louisiana State University Health Sciences Center from 2006 to 2007.

I was an independent physician contractor in emergency medicine at North Caddo Medical Center in Vivian, Louisiana from 2006 to 2007. I then worked as a physician contractor in emergency medicine at Bourbon Community Hospital in Paris, Kentucky from 2008 to 2010. During this time, I also worked as a staff family medicine physician at Paris Primary Care in Paris, Kentucky from 2007 to 2009. I also worked as an Assistant Professor and Medical Director of Inpatient and Outpatient Service Lines at the University of Kentucky Department of Family & Community Medicine in Lexington, Kentucky from 2009-2012. From 2012 to 2014, I worked as the Medical and Laboratory Director of Doctors Express in Southlake, Texas. Subsequently, from 2014 to 2018, I worked as the Medical Director and Lead Physician of Destination Health in Southlake, Texas. Currently, I am an emergency room physician at Texas Health Harris and I am the Owner and Medical Director of Melville Medicine, which is a comprehensive and integrated concierge family medicine practice striving to find the best and safest balances of increasing life expectancy with improving quality of life.

I have current clinical privileges at Texas Health Resources Southlake. I am a Diplomat of the American Board of Family Medicine. I am a member of the National Speaker Bureau for Bale Doneen Cardiovascular Prevention Method. I am certified with Reversing Cognitive Decline (ReCODE) Program through the Institutes of Functional Medicine. I am a member of the American Academy of Family Physicians, the Texas Medical Society, the North Tarrant County Medical Society, and the Beta Beta Beta National Biological Honor Society.

I am an author of numerous publications on borderline personality disorder as well as literature regarding abdominal trauma and meeting the health challenges of seniors. For a complete list of my publications as well as additional information as to my professional background, please see my enclosed CV.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

I have been prescribing compounded bio-identical hormone replacement therapy ("*BHRT*") for nearly 15 years in various forms. At the present time, I treat approximately 75 patients total and approximately 35 of my patients are being actively treated with compounded BHRT. I have witnessed great success with resolution of my patients' symptoms and improvement in medical conditions with the appropriate treatment of compounded BHRT.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I prescribe compounded BHRT as a component of a prevention strategy for heart attack, stroke, and dementia. With the prevalence of heart attacks/strokes/dementia increasing in postmenopausal women, I try to focus on the current statistics in balance with health risks, such as breast cancer. Regarding the cardiovascular system alone, hormone

optimization increases HDL, decreases LDL, smooths and dilates blood vessels so perfusion improves, and decreases free radicals, which ultimately can damage arteries and other healthy tissue (which is the primary cause of Alzheimer's dementia). Before prescribing a targeted therapy, the patients and I review benefits/risks, ensure that the patients are updated on all preventive screens, and educate the patients on the ever-evolving hormone and medical treatment strategies.

In my medical opinion, compounded BHRT is highly effective at treating hormone imbalance in general in male and female patients. That is, I prescribe compounded BHRT to treat low libido, fatigue, cognitive decline, andropause and menopause symptoms, insomnia, and metabolic syndrome (which is a triad of high cholesterol, glucose metabolic deficiencies, and hypertension). I also prescribe compounded BHRT to prevent the inflammatory cascades that increase risks of breast cancer, prostate cancer, heart attack, and stroke.

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, I choose to treat my patients with compounded BHRT instead of commercially available BHRT because the commercially available hormone therapies do not yield the same results in my patients. Compounding allows me to tailor important hormone therapy to the individual needs of my patients. Because of the critical nature of hormone therapy, I check in with my patients on compounded BHRT at frequent intervals—I then meticulously adjust the patient's hormone therapy based on the patient's inflammatory markers, clinical responses to the hormone therapy, and changes in cholesterol profile, among others. I am not able to make these important adjustments with the same accuracy with commercially available BHRT, hut I am able to do so with compounded BHRT.

- **Progesterone.**

I prescribe compounded, micronized bioidentical progesterone in an oral pill instead of the commercially available progesterone because although the commercially available version may be labeled as "micronized," it is often not fragmented as finely as the compounded, micronized bioidentical progesterone. The fragmentation/particle size is critical for the medication to cross the absorption barrier, and it is my professional medical opinion that symptoms in my patients are improved with better absorption of the compounded medication.

I also prefer to treat my patients with lower doses of compounded bioidentical progesterone than is offered by commercially available bioidentical progesterone. Compounding allows me to adjust the amount of progesterone in very small increments, which further allows me to better treat and tailor the medication to the individual needs of my patient.

- **Estrogens**

I typically prescribe compounded estrogens in transdermal form and in pellets because the ratio of estradiol to estrone in commercially available oral estrogen is, in my professional medical opinion, unfavorable to patients. Estradiol and estrone must be carefully balanced, as estradiol carries many of the therapeutic effects while estrone, in the wrong ratio, can carry more toxic effects (although our bodies do need some of it). Compounding allows me to better control the ratio of estradiol to estrone in the therapy I prescribe my patients, whereas commercially available estrogens tend to cause estrone levels in patients to spike to dangerously high levels.

I have anecdotally observed that compounded estrogens in pellet forms help resolve inflammatory markers in my patients, which are the body's internal metrics as to whether the body is responding well to certain treatments. The proper balancing of hormones lowers inflammation within the body, and I am able to control this outcome with compounded bioidentical estrogens in a way that I cannot do with commercially available bioidentical estrogens.

- **Testosterone**

I prescribe compounded bioidentical testosterone, typically in pellet form, for my female patients because there is no commercially available bioidentical testosterone approved for treatment in women. I prescribe compounded bioidentical testosterone, typically in pellet form, to treat my male patients because it produces consistent serum levels in the bloodstream as opposed to the inflammatory spikes that are caused by the commercially available gels and creams. Creams and gels, such as commercially available Androgel, are inflaming and do not absorb into the body as well as pellet therapy. Additionally, creams and gels also carry the risk of being transmitted to other parties aside from the patient, such as partners, children, or pets. Because of this, patient compliance with the commercially available options are low, whereas patient compliance on pellet therapy increases tenfold.

Bioidentical testosterone is also commercially available as an injectable for treatment in men. However, injectables that must be administered weekly or biweekly cause more inflammation than subcutaneous pellets that are administered every 5-7 months in male patients.

In conclusion, in my medical experience, I have seen more patients benefit from the balanced and judicious use of hormone therapies afforded by compounded BHRT. Individualization of hormone therapies is where I have found the most success, and compounded BHRT allows the most precision with this individualization.

Through these experiences, among many other anecdotal observations, I have adopted an approach to hormones that some presence of hormones is better than none, but that too little is just as detrimental as too high (cumulatively speaking). Therefore, individualized and precise hormone therapy treatment (via compounding) is the best way to optimize hormone levels in patients and resolve hormone deficiencies.

I sincerely hope that physicians and clinicians may maintain a certain degree of autonomy when prescribing therapies for our respective patients.

Sincerely,

Daniel Elias Melville, M.D.

Daniel Elias Melville, M.D.

1545 E Southlake Blvd, Ste 110 • Southlake, TX 76092

Doctor@MelvilleMedicine.com • (817) 676-2010

EDUCATION

July 2006-June 2007	**Louisiana State University Health Sciences Center,** Vivian and Shreveport, LA Department of Family Medicine – Rural Tract Chief Resident
July 2005- June 2007	**Louisiana State University Health Sciences Center,** Vivian and Shreveport, LA Department of Family Medicine – Rural Tract Family Medicine Residency
July 2004-June 2005	**Louisiana State University Health Sciences Center,** Shreveport, LA Department of Family Medicine Family Medicine Internship
August 2000- June 2004	**Louisiana State University College of Medicine,** Shreveport, LA Doctor of Medicine
July 1995- May 1999	**United States Air Force Academy,** USAFA, CO Bachelor of Science, Biology and General Engineering Distinguished Graduate

LICENSURE AND CERTIFICATIONS

- Texas Medical Board License #P4352 (active)
- Kentucky Medical Board License #41035 (inactive)
- Louisiana Medical Board License #MD.200658 (inactive)
- Diplomat of American Board of Family Medicine
- Member of National Speaker Bureau for Bale Doneen Cardiovascular Prevention Method
- Certified with Reversing Cognitive Decline (ReCODE) Program through IFM
- Certified Provider of BioTE Hormone Replacement Therapy
- Current Clinical Privileges at Texas Health Resources Southlake

EMPLOYMENT

June 2019-Present	**Melville Medicine,** Southlake TX Owner and Medical Director
April 2014-Present	**Texas Health Harris Southlake,** TX Emergency Room Physician

March 2014-June 2018	**Destination Health,** Southlake TX Medical Director and Lead Physician
September 2012-March 2014	**Doctors Express,** Southlake TX Medical and Laboratory Director
October 2009-September 2012	**University of Kentucky Dpt of Family & Community Medicine**, Lexington, KY Assistant Professor, Medical Director of Inpatient and Outpatient Service Lines
August 2007-July 2009	**Paris Primary Care**, Paris, KY Staff Family Medicine Physician
July 2008–April 2010	**Bourbon Community Hospital**, Paris, KY Physician Contractor-Team Health, Emergency Medicine Coverage
July 2006–June 2007	**North Caddo Medical Center**, Vivian, LA Independent Physician Contractor-Correct Care, Emergency Medicine Coverage
July 2001–June 2004	**Intelligent Fitness**, Shreveport, LA Personal Fitness Instructor and Nutritionist Counselor

PROFESSIONAL MEMBERSHIPS

- American Academy of Family Physicians
- Texas Medical Society
- North Tarrant County Medical Society
- Beta Beta Beta National Biological Honor Society

PUBLICATIONS

Melville DE, Elder W. "Borderline Personality Disorder." 5 Minute Clinical Consult. Lippincott Williams & Wilkins. 2015.

Melville DE, Elder W. "Borderline Personality Disorder." 5 Minute Clinical Consult. Lippincott Williams & Wilkins. 2014.

Melville DE, Elder W. "Borderline Personality Disorder." 5 Minute Clinical Consult. Lippincott Williams & Wilkins. 2013.

Melville DE, Elder W. "Borderline Personality Disorder." 5 Minute Clinical Consult. Lippincott Williams & Wilkins. 2012.

Melville DE, Melville SC. "Abdominal Trauma." Current Diagnosis and Treatments in Emergency Medicine, Seventh Edition. McGraw-Hill. 2011. Chapter 25.

Melville DE, Melville SC. "Central Venous Catheter Placement." The Essential Guide to Primary Care Procedures. Lippincott Williams & Wilkins. 2009. Ch 6: pgs. 33-42.

Melville DE. Meeting the health challenges of seniors. Healthpoint. 2009 May: 2.

Exhibit 1-K

Woodlands
Gynecology & Aesthetics

Statement from Dr. John Joseph Peet, MD, FACOG

Qualifications

My name is Dr. John Joseph Peet, M.D., FACOG. My professional background is as follows. I received my Bachelor of Arts in zoology from the University of Texas at Austin in 1992, and I received my Doctor of Medicine from Texas A&M University Health Science Center in 1996. I completed both internship and residency in obstetrics and gynecology at the Scott & White Memorial Hospital from 1996 to 2000. I received the Special Service Award from the Scott & White Abstinence Based Sex Education Program in 2000. I also received the Patricia J. Sulak Award for Excellence in Resident Research for best paper in 1999, the Organon, Inc. Resident Research Award for Outstanding Research in Women's Health in 1999, and the Texas A&M University Academic Excellence Award in 1993, 1994, and 1995. In addition to professional awards, I have also received numerous academic awards, which are further detailed in my enclosed CV.

After completing my residency, I practiced at the Sadler Clinic Health Center for Women in The Woodlands, Texas from 2000 to 2010. I then joined St. Luke's – Texas OBGYN Specialists, which is part of the Woodlands Doctor Group, in The Woodlands, Texas from 2010 to 2012. Presently, I am an owner of and practitioner at the Woodlands Medical Aesthetics Institute and owner of and practitioner at the Woodlands Gynecology & Aesthetics, PLLC. I have held these ownership positions since 2013. I have been licensed to practice medicine in Texas since 1997. I have been certified by the American Board of Obstetrics & Gynecology since 2002.

I have held practice affiliations as active staff physician with the Memorial Hermann Hospital The Woodlands and the Conroe Regional Medical Center. I was an active teacher in family medicine at the Lone Star Family Health Center. I am currently affiliated with St. Luke's Community Medical Center The Woodlands in The Woodlands, Texas and Memorial Hermann Conroe Surgery Center in Conroe, Texas as an active physician. I was also the Vice Chair OB/PEDI of Section 2002 at Conroe Regional Medical Center. I am a member of the Texas Medical Association, the Montgomery County Medical Society, the Texas Association of Obstetricians and Gynecologists, and the American Association of Anti-Aging Medicine, and I am a fellow of the American College of Obstetricians and Gynecologists.

For a full recitation of my prior and ongoing research activities and my professional activities, please see my enclosed CV.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

I have over 20 years of experiencing prescribing hormone therapy, and I have been prescribing compounded Bio-Identical Hormone Therapy ("*BHRT*") specifically for ten years. I have over 5,000 patients currently being effectively treated with compounded BHRT.

Woodlands
Gynecology & Aesthetics

Approximately 90-95% of my male and female patients treated with some form or combination of compounded BHRT have their symptoms completely resolved. Over 90% of these patients are still complying with their compounded BHRT plan years later, and the side effect profile is only 5-10% (and they are all easily managed, modifiable and not dangerous).

Medical Conditions and Patient Populations Treated with Compounded BHRT

I prescribe compounded BHRT to treat male and female patients of all ages depending on their individual symptoms. Specifically, I prescribe compounded BHRT in the following forms and combinations to treat the following medical conditions in **female patients**:

- **Compounded estradiol in transdermal creams, sublingual troches, subcutaneous pellets, and transvaginal creams**: Compounded estradiol treats menopausal symptoms, such as hot flashes, genitourinary syndrome, cognitive decline, skin changes, hair changes, insomnia, depression, and urinary incontinence. Systemically, estradiol helps to prevent bone loss, heart disease, colon cancer and Alzheimer's dementia.

- **Compounded testosterone in transdermal creams, sublingual troches, subcutaneous pellets, and transvaginal creams**: Compounded testosterone treats female androgen deficiency in pre- and post-menopausal female patients. Androgen deficiency symptoms include fatigue, muscle loss, insomnia, anxiety, depression, decreased libido, poor sexual response, concentration problems, and lack of motivation/drive. Testosterone helps to prevent bone loss, Alzheimer's dementia and likely also breast cancer.

- **Compounded progesterone in oral capsules and sublingual troches**: Compounded progesterone treats chronic insomnia and mood problems. It is also required to treat female patients with an intact uterus who are receiving estradiol to prevent uterine cancer. It also treats menstrual disorders in pre-menopausal women, such as heavy or irregular bleeding.

I prescribe compounded BHRT in the following forms to treat the following medical conditions in **male patients**:

- **Compounded testosterone in subcutaneous pellets**: Compounded testosterone in the form of subcutaneous pellets treats androgen deficiency from all causes (i.e., regardless of whether the androgen deficiency is caused by, for example, testicular issues, cancer and radiation issues, or brain issues). Symptoms associated with androgen deficiency that are treated by compounded testosterone subcutaneous pellets are fatigue, muscle loss, insomnia, anxiety, depression, decreased libido, joint pains, concentration problems, motivation problems, and erectile dysfunction. Testosterone also prevents bone loss, Alzheimer's dementia, and likely prostate cancer.

Woodlands
Gynecology & Aesthetics

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, I choose to treat my patients with compounded BHRT instead of commercially available HRT because the commercially available hormone therapy cannot treat my patients as well as the compounded hormone therapy. Specifically, the commercially available HRT carries too many side effects for patients and does not effectively treat their symptoms, which causes patients to forego their prescribed treatment plans and end up with worse health than when the patient first required hormone treatment. It is known that 50% of patients prescribed Premarin will quit in less than one year. Commercially available forms of HRT also contain allergens that cannot be prescribed to certain patient populations (peanut oil in progesterone). And, compounding the hormone therapies allow me to get better hormone serum levels which is simply not an option with commercially available bioidentical hormone therapies. We have very specific goals for serum levels and dose testosterone pellets with a computer algorithm that includes age, weight, starting hormone levels and renal function on labs. All patients are lab tested 4-6 weeks post treatment to insure adequate and balanced levels.

Below, I set out my reasoning, based on my medical experience and judgment, as to why I prefer to treat my patients with compounded estradiol, progesterone, and testosterone as opposed to the commercially available bioidentical hormones.

- **Estradiol**

Estradiol is commercially available as an oral pill. Oral estradiol increases the risk of blood clotting disorders such as deep vein thrombosis as well as risk of pulmonary embolism because they are metabolized by the liver prior to systemic delivery. Because of the increased clotting, they may not be protective against heart attack and stroke as desired. They also can cause liver and gallbladder problems because of first pass liver metabolism.

Compounded transdermal estradiol and compounded estradiol in subcutaneous pellets do not increase the risk of blood clotting disorders such as deep vein thrombosis and do not increase the risk of pulmonary embolism. Compounded transdermal estradiol and compounded estradiol in subcutaneous pellets actually ***reduce*** the risk of heart attack and stroke and they cause no issues with the liver or gallbladder. They bypass first pass liver metabolism and are absorbed directly into the bloodstream.

I do use synthetic transdermal commercially available estradiol some, but the doses are too low and rarely return the estradiol levels to the premenopausal range. They are better for symptom control than for disease prevention.

- **Progesterone**

Only approximately half of the patients treated with commercially available progestins can tolerate the hormone because the side effects are so severe that they cause patients to discontinue the treatment. The side effects of commercially available progestins include mood changes,

headaches, nausea, bloating, menstrual cramps, fluid retention, and irritability. Progestins, such as Provera have been shown to increase the risk of blood clots and breast cancer. This medicine should have been taken off of the market years ago in my opinion.

Prometrium is a commercially available bioidentical progesterone medication available as an oral capsule. I do use this medication often, but it has its problems. The capsule contains heat sensitive oils that can denature the progesterone during shipping and delivery of the medication. Additionally, the capsules contain peanut oil, so those patients with a peanut allergy cannot be treated with it. Finally, only approximately 80% of the patient population treated with Prometrium can tolerate the medication because of the progestin-type side effects. If left to only Prometrium, approximately 20% of patients needing progesterone treatment would be left untreated.

On the other hand, compounded progesterone sublingual troches and oral capsules that I treat my patients with are tolerated by 99% of my patients with absolutely no side effects.

- **Testosterone**

The only commercially available testosterone for women is Estrotest for the treatment of androgen deficiencies, which is a ***synthetic*** testosterone (not bioidentical) combined with an oral estrogen. Even if patients can tolerate the side effects of oral estrogen, Estratest rarely effectively treats the patient's androgen deficiency symptoms, and it does not treat the deficiencies to the extent that compounded bioidentical testosterone does. And as stated earlier, I do not use oral estrogens because of the risks. So, this leaves women (millions of them) with no commercial alternative to treat female androgen deficiency syndrome. There are no options except for bioidentical testosterone that is compounded.

I prescribe compounded testosterone for women in creams, sublingual troches, and subcutaneous pellets. I prefer to prescribe compounded testosterone as a subcutaneous pellet because pellets deliver more consistent serum levels with less peaks and troughs compared to the creams and troches. The more peaks in serum levels cause more side effects (acne, abnormal hair growth, oily skin, fluid retention); the more troughs in serum levels means the treatment is less effective. Approximately 90-95% of my female patients being treated with compounded testosterone pellets for androgen deficiency have all androgen deficiency symptoms resolve without any side effects. Any side effects that are caused by the compounded testosterone pellets are minor, temporary, and easy to treat and timely resolve. There are no dangerous or permanent side effects.

Woodlands
Gynecology & Aesthetics

Androgel, the commercially available testosterone cream for men, does not reliably absorb well in male patients---rather, the serum levels spike too high and cause side effects or drop too low and the result is poor efficacy. The serum level spikes and troughs both occur within 24 hours of application of the cream. Similar risks are associated with commercially available injectable testosterone for men—the serum level spikes (day 2) are too high and cause acne, hair loss, fluid retention, elevated estradiol levels and elevated red blood cell count. And the serum level troughs (days 5-7) are too low and result in less efficacy of the treatment.

I prescribe bioidentical compounded testosterone for men in creams and subcutaneous pellets. I prefer to prescribe compounded testosterone as a subcutaneous pellet to my male patients because pellets deliver more constant serum levels with less peaks and troughs compared to the commercially available creams and injections. The efficacy is far superior to the commercial creams and the side effects are much more rare. Any side effects that are caused by the compounded testosterone pellets in men are minor, temporary, and easy to treat. There are no dangerous or permanent side effects.

I sincerely appreciate you allowing me to share my experience and thoughts. Thank you for taking the time to fully evaluate compounded bioidentical hormones. Thousands of my patients and millions more would suffer if their availability were to disappear.

Sincerely,

John Joseph Peet, M.D., FACOG

17350 St. Luke's Way • Medical Arts Center 2 • Ste. 390 • The Woodlands, TX 77384 • 936-273-1600 • Fax: 936-273-1635
www.texasgynandaesthetics.com

JOHN JOSEPH PEET, M.D.

Curriculum Vitae

PRACTICE EXPERIENCE

Jan 1, 2013 to present	Owner, Woodlands Gynecology & Aesthetics, PLLC 17350 St. Luke's Way Medical Arts Center 2, Suite 390 The Woodlands, TX 77384
Oct 2013 to Present	Owner, Woodlands Medical Aesthetics Institute 17350 St. Luke's Way Medical Arts Center 2, Suite 380 The Woodlands, TX 77384
June 6, 2010 to Dec 31, 2012	St. Luke's - Texas OBGYN Specialists Woodlands Doctor Group 17198 St. Luke's Way, Medical Arts Center 1, Suite 440 The Woodlands, TX 77384
July 1, 2000 to June 5, 2010	Sadler Clinic Health Center for Women 17191 St. Luke's Way The Woodlands, TX 77384 Sadler Clinic Board of Directors 2/02 - 12/09

PRACTICE AFFILIATIONS

July 1, 2000 to 2018	Memorial Hermann Hospital the Woodlands 9250 Pinecroft Dr The Woodlands, TX 77380 Active Staff Physician
July 27, 2000 to 2017	Conroe Regional Medical Center 504 Medical Center Blvd Conroe, TX 77304 Active Staff Physician Vice Chair OB/PEDI Section 2002
September 11, 2003 to present	St. Luke's Community Medical Center the Woodlands 17200 St. Luke's Way The Woodlands, TX 77384 Active Staff Physician

August 11, 2000 to present	Memorial Hermann Conroe Surgery Center 1501 River Pointe Dr Conroe, TX 77304 Active Staff Surgeon - Owner Board of Managers 3/03 - 4/06 Block Time Committee 3/03 - 4/06
Nov 1, 2004 to Sept 30,2009	Lone Star Family Health Center Conroe Family Medicine Residency 704 Old Montgomery Road Conroe, TX 77301 American Academy of Family Physicians Active Teacher in Family Medicine

UNDERGRADUATE EDUCATION

June, 1988 to June 1992	Bachelor of Arts in Zoology University of Texas at Austin Office of the Registrar Austin, TX 78712

MEDICAL SCHOOL

July, 1992 to June, 1996	Doctor of Medicine Texas A & M University Health Science Center 159 Reynolds Medical Building College Station, TX 77843-1114

INTERNSHIP

July, 1996 to June, 1997	Obstetrics/Gynecology Scott & White Memorial Hospital 2401 S. 31st Street Temple, TX 76508 254-724-2111

RESIDENCY

July, 1996 to June, 2000	Obstetrics/Gynecology Scott & White Memorial Hospital 2401 S. 31st Street Temple, TX 76508 254-724-2111

HONORS AND AWARDS - PROFESSIONAL

Special Service Award - Scott & White Abstinence Based Sex Education Program, 2000
Patricia J. Sulak Award for Excellence in Resident Research - Best Paper - 12th Annual Resident Research Day, 1999
Organon, Inc. Resident Research Award for Outstanding Research in Women's Health, 1999
Texas A&M University Academic Excellence Award, 1993, 1994, 1995
BioTE Practitioner of the Year 2017

HONORS AND AWARDS

Order of Omega, 1991
Alpha Epsilon Delta, 1990
The University of Texas Athletic Director's Academic Honor Roll, 1989
Texas Banc Savings Academic and Citizenship Scholarship, 1988

PROFESSIONAL ACTIVITIES

Treasurer - Friends of Senator Brandon Creighton - Texas State Senate, District 4, 2002 to Present

Cellular Medicine Association(CMA)-
Faculty Trainer, 4/16 to present

First Financial Bank (FFIN) - Board of Directors, 12/2015 to present

Sciton Laser-Clinical Investigator/Physician Educator/Luminary, 5/15 to present

BTL Aesthetics-Luminary, 10/17 to present

Age Management Medical Group (AMMG)-Faculty Speaker, 6/17 to present

BioTE Medical - Practice Mentor/Consultant, 6/15 to present
Coordinator-Clinical Advisory Team, 1/18 to present
Coordinator-Mentor Program, 2/18 to present

Vice President, Texas A&M College of Medicine Class of 1996, 1992 – 1996

Volunteer, First Co-Chairman of the Board of Directors, Chairman of Supply Committee and Member of Founding Group of Texas A&M Medical Students for Martha's Health Clinic, a student-managed health care clinic for the homeless

LICENSURE/CERTIFICATION

Medical License – Texas, 1997 to Present
American Board of Obstetrics & Gynecology – 2002 to Present

RESEARCH

Johnny J Peet MD. The Safety and Tolerability of Ablative Fractional Er:YAG Laser Treatment for Vaginal Rejuvenation. 2015.

JJ Peet, KP Huddleston, MD Custer. "Isolated Fetal Cystic Lymphangioma of the Anterior Abdominal Wall and Groin: A Case Report with Sonographic Findings." Presented at Bunkley Research Day, Texas A&M-Scott & White, 1998.

JJ Peet, KM Maedo, KW Coates, TJ Kuehl. "Bacteriuria in an Ambulatory Urogynecologic Referral Population." Presented at Bunkley Research Day, Texas A&M-Scott & White, 1999.

ONGOING RESEARCH

Safety and Efficacy of Hybrid Fractional Laser (diVa) Treatment for Symptoms of Genitourinary Syndrome of Menopause

Safety and Efficacy of Hybrid Fractional Laser (diVa) Treatment for Treatment of Symptoms of Urinary Incontinence

PROFESSIONAL SOCIETIES

Texas Medical Association (TMA)
Montgomery County Medical Society (MCMS)
Fellow - American College of Obstetricians and Gynecologists (ACOG)
Texas Association of Obstetricians and Gynecologists (TAOG)
American Association of Anti-Aging Medicine (A4M)

INTERESTS AND ACTIVITIES

Family, Baseball Coach
Church Sunday School Teacher
Fishing, Hunting, Golf, Exercise, Travel

Exhibit 1-L

Ageless ...FOREVER

JOHN J. PIERCE, DO
MEDICAL DIRECTOR
www.AgelessForever.net

6020 S RAINBOW SUITE C
LAS VEGAS, NV 89118

PH. 702-838-1994
FAX 702-870-0068

To whom it may concern,

I am writing this letter in support of compounded bio identical hormone therapy (BHRT). I have been practicing medicine for over 16 years and have been using compounded BHRT for over 13 years. In my clinical experience I have found that compounded products are very safe, reliable and reproducible results on labs and patient outcomes. I have found the ability to tailor an individual's needs based off of their symptoms and labs is a much better approach to care than the "one size fits all" approach offered by commercial hormone products.
Compounded products allow me to offer my patients options for delivery that fit their personal needs better than commercial products. BHRT pellets are a prime example of this. Hormone therapy is most effective when there are steady state levels and this is best provided in a pellet delivery. This minimizes forgotten doses, untimely refill requests and other patient errors that can allow for side effects associated with vacillations in hormone levels.
I have read the report submitted by Catalent Applied Drug Delivery Institute, titled "Comments Supporting Nominations of Certain Reproductive Hormone Drug Products For Inclusion on the Demonstrably Difficult to Compound List" I have a few comments on this paper that should be brought to the attention of the readers so that they are not mislead by the writing. The author(s) are apparently trying to do deceive the reader using medical myth and dogma to support their position. The problem is some of this fear mongering has been proven to be false in the medical literature.

Example 1. "estradiol has been linked to increased risk of breast and endometrial cancer". This statement is false. While estradiol has been implicated in breast cancer, there is not a medical study to date that shows that receiving estradiol therapy increases the risk of breast cancer. In fact, the Women's Health Initiative showed the opposite. A nice summary of the many studies that show this to be true is found in an article by Allan Lieberman, MD titled 'In Defense of Progesterone: A Review of the Literature'. The endometrial cancer aspect of unopposed estrogen is true. This is prevented with progesterone and the above article will help sort out the differences between progesterone and progestins. Once one understands the differences and the harm of progestin use, one would be left to wonder why these carcinogenic patented synthetic hormones are still available.

Example 2. "Risks for overdosing of testosterone therapy can include exacerbation of BPH or prostate cancer and increased risk of blood clots." The most recent medical literature proves that testosterone replacement therapy (TRT) has no negative impact on prostate cancer. In fact, there are cases of prostate cancer patients being treated with testosterone to eliminate the disease. (Teply, Benjamin A, et al. "Extreme Response to High-Dose Testosterone in BRCA2- and ATM-Mutated Prostate Cancer." *European Urology)*

To say testosterone exacerbates BPH shows yet more ignorance to the medical literature as illustrated in the article by Rasrellli et al titled 'Testosterone and Benign Prostatic Hyperplasia",
which concluded "Testosterone is not detrimental for the prostate, and treating hypogonadism could even produce relief from LUTS and limit prostatic inflammation, which generates and maintains the process leading to BPH."

There are many studies that have tried to make the link to TRT and venous thromboembolism due to the secondary erythrocytosis caused by TRT. To date there has not been a single study that makes this link. The most that can be said is the link is inconclusive. ("Erythrocytosis and Polycythemia Secondary to Testosterone Replacement Therapy in the Aging Male." *Sexual Medicine Reviews*, Elsevier, 16 Dec. 2015)

Example 3 "However, recent evidence shows increases in endometrial cancers resulting from the use of compounded estradiol and progesterone." The author of this paper must not respect the intelligence of the reader as the article she cites does not make this statement at all. The author actually concluded, "This survey indicates substantial use of C-HT across the country and the possibility of higher rates of endometrial side effects with such products." Possibility is the key word. In science we all understand that correlation does not equal causation.

These three examples of how the author of the paper tries to use nonsense to scare the reader, in my humble opinion, invalidates any other point the author is feebly trying to make. I have found in my years of experience working with compounded hormones and the commercially available products there is relatively no difference in quality and consistency. I have found compounded products offer me many more options to fit the needs of individual patients. I can treat PMS issues with low dose progesterone orally. These doses do not exist in the commercial "one size fits all" world. Patients that have sensitivities to the fillers in commercial products are able to find treatment options in compounded products.

In my opinion, the push to try to remove hormones from the hands of competent compounding pharmacists is based not on patient safety concerns, as I have not seen any peer reviewed literature to suggest safety issues based off of evidence, but more on financial concerns of revenue lost to the bigger pharmaceutical companies to more personalized compounded pharmaceutical products. If safety was the concern, as it should be, the offenders should be under the scrutiny and jurisdiction of their state pharmacy boards. This should not be an FDA issue, but a state issue, in my opinion.

I thank you for your time and consideration in reading my position and I hope I have shed some light on the subject of how important and safe the use of compounded hormones are in medical practice.

Sincerely,

Dr. John J. Pierce, DO

Exhibit 1-M

MODERN MEDICINE

PERSONALIZED, PROGRESSIVE CARE

Statement From Cory Stephen Rice, D.O.

Qualifications

My name is Dr. Cory Rice. My professional background is as follows. I received my Bachelor of Science in forensic science and biochemistry from Baylor University in Waco, Texas in 2000. I completed my Doctor of Osteopathic Medicine at the Arizona College of Osteopathic Medicine Midwestern University in Glendale, Arizona in 2006. I completed my residency and chief residency in internal medicine at Methodist Dallas Medical Center in Dallas, Texas from 2006 to 2009. I became ABIM board certified in internal medicine in 2009.

After I completed my residency, I worked as a staff physician, hospitalist, and intensivist at Lake Pointe Medical Center in Rowlett, Texas in 2009. From 2011 to the present, I have been the owner and operator of Modern Medicine, PLLC in Addison, Texas and Forney, Texas. My practice treats patient with an emphasis in functional and lifestyle medicine. We employ nutritionists to help patients through chronic disease and disease burden. We also specialize in thyroid and hormone management.

I am a published author in the subject of thyroid disease. For a complete list of my publications and research endeavors, please see my enclosed CV.

Experience Treating with Compounded BHRT

Approximately 60% of my patients are female and approximately 40% are male. Approximately 85% of my total patient based is currently being treated with compounded BHRT. Of this percentage, approximately 65% of these patients are female and approximately 35% are male.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I treat the following medical conditions and symptoms with compounded BHRT in my male and female patients:

- Cardiometabolic disease
- Diabetes

MODERNMEDICINE

PERSONALIZED, PROGRESSIVE CARE

- Autoimmune diseases, such as thyroid disease and arthropathies
- Neurodegenerative diseases, such as Alzheimer's and Parkinson's
- Obesity
- Bone health
- Mood disorders, such as anxiety, depression, and sleeping issues
- Sexual health, such as erectile dysfunction, vaginal health, stress issues, and incontinence

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

Based on my professional medical judgment and clinical experience, I prefer to treat my patients with compounded BHRT instead of commercially available BHRT or synthetic hormone therapies because compounded BHRT allows me to treat patients as individuals. I was trained on synthetic hormone replacement therapy. When patients were treated with synthetic hormones, they suffered severe side effects such as weight gain, cognitive issues, and acne, which often led to patient noncompliance with the hormone therapy. Specifically, patients would return often having never refilled their prescription after the first prescription fill.

This experience with patient noncompliance caused me to research compounded BHRT, specifically in the forms of transdermal creams and subcutaneous pellets. When I treated patients with compounded subcutaneous pellets, I found that patient retention and compliance with the hormone therapy increased. I also saw fewer side effects than with the commercially available BHRT.

Moreover, my patients treated with compounded BHRT have been able to stop taking their other prescription medications for conditions such as depression and anxiety. Treatment with compounded BHRT has reduced the disease burden for my patients, as I have witnessed fewer heart attacks and stroke compared with patients treated with commercially available BHRT. In light of the above, it is my professional opinion that it would be medical negligence to withhold compounded BHRT from patients.

Sincerely,

Cory Stephen Rice, D.O.

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Cory Stephen Rice, DO
992 E US Highway 80, Suite C
Forney, TX 75126
Office: (972) 552-2920

EDUCATION AND TRAINING

August 2009	ABIM Board Certification in Internal Medicine
2006 – 2009	Chief Resident 2008-2009 Internal Medicine Residency Program Methodist Dallas Medical Center Dallas, Texas
2002 - 2006	Doctor of Osteopathic Medicine Arizona College of Osteopathic Medicine Midwestern University Glendale, Arizona
1996- 2000	Bachelor of Science in Forensic Science/Biochemistry Baylor University Waco, Texas

PROFESSIONAL EXPERIENCE

2011- Present	Owner/Operator Modern Medicine, PLLC (Locations in Addison, TX, Forney, TX)
2009	Staff Physician/Hospitalist/Intensivist Lake Pointe Medical Center Rowlett, TX
2000 – 2002	Instructor and Lab Director Department of Anthropology, Sociology and Forensic Science Baylor University Waco, Texas

PROFESSIONAL SOCIETIES

American Board of Internal Medicine (Diplomate)
American College of Physicians
American Medical Association
Institute for Functional Medicine

PUBLICATIONS

Thyroid Disease- A White Paper Monograph, July 2018
Gary S. Donovitz M.D., Cory Rice D.O., Mandy Cotten D.N.P.

Linder, Jeffrey D., **Rice, Cory S.**, Brown, De'Andre A., King, Philip W., Tarnasky, Paul R., "Is Deep Sedation with Propofol Safe During ERCP?", Digestive Disease Week, May 2007.

RESEARCH

Principal Investigator- IRB approved Clinical Case Observational Study involving Resolvins/Specialized Pro-Resolving Mediators (Fall 2015)

Principal Investigator- IRB approved Clinical Case Observational Study involving a medical food for digestive health (Spring 2016)

Exhibit 1-N

Meridian Health Center
For Functional Medicine
and Hormone Therapy

Statement From Ann Elizabeth Stanger, MD

Qualifications

My name is Dr. Ann Stanger. My professional background is as follows. I attended the Indiana University School of Medicine from 1985 to 1989. While there, I received the Faculty Women's Club Scholarship, the Dr. Margaret Hatfield Award, and the John B. Hemenway Scholarship. I completed my residency in obstetrics and gynecology from the University of Wisconsin Hospitals and Clinics from 1989 to 1990. I completed advanced practice modules in hormone, cardiometabolic, detoxification, immune, energy, and GI at the Institute for Functional Medicine between 2011 and 2016. I completed a professional course at the National Center for Homeopathy in 1990, and I completed a course in applying functional medicine in clinical medicine at the Institute for Functional Medicine in 2003. In 2008, I completed courses in clinical thermography and physician thermology from the American College of Clinical Thermography.

I worked as a physician volunteer at the Madison Community Health Center in 1993. I worked as a core physician at the VRG international Research Group from 1993 to 1994. While there, I worked as an associate physician at Walk-In Medical of Madison from 1991 to 1996. After that, I worked as an associate physician and a primary care physician at Midwest Health Systems, Inc. from 1996 to 2001. From 2001 to 2008, I worked in general outpatient medicine as the owner of Innovative Health Clinic.

I have been a certified thermology reader with the Electronic Medical Interpretation Group since 2010. I have been the medical director of Amanda Reed Medical Spa since 2013, and I have been the owner of Meridian Health Center since 2017. I have been the owner of Ann Stanger, MD, LLC, a practice in functional medicine, since 2008.

I am a member of the State Medical Society of Wisconsin, the Institute for Functional Medicine, and the American College of Clinical Thermography. Further details are set out in my enclosed CV.

Experience Treating with Compounded BHRT

My current practice focuses on functional medicine, which means we treat male and female patients with compounded BHRT. I have 20 years of experience treating patients with compounded BHRT.

I treat approximately 1,000 patients per year. Approximately half of these patients are successfully treated with compounded BHRT. Of this 50%, approximately 80% are female patients and approximately 20% are male patients. Compounded BHRT is an effective treatment in all of my patients who are treated appropriately with it.

Meridian Health Center
For Functional Medicine
and Hormone Therapy

Medical Conditions and Patient Populations Treated with Compounded BHRT

I treat the following medical conditions and symptoms with compounded BHRT in my male and female patient.

- I prescribe **compounded bioidentical estradiol with bioidentical estriol and bioidentical testosterone**, if indicated, in various dosage strengths based on laboratory testing of the patient in a cream or a gel dosage form, with a separate progesterone oral capsule, at a lower dose than is commercially available, to be taken at bedtime. I prescribe this formulation to menopause symptoms, including hot flashes, night sweats, vaginal dryness, and mood issues (e.g., anxiety and depression). I also prescribe this formulation to treat postmenopausal symptoms and bone density issues.

- I prescribe **compounded bioidentical estriol** in a cream or gel to treat vaginal dryness. Bioidentical estriol is not commercially available, but in my professional medical experience it is much more effective at treating vaginal dryness and has a lower risk of endometrial thickening compared to commercially available bioidentical estradiol (i.e., the commercially available form of estrogen approved to treat vaginal dryness). I also prescribe this formulation to treat postmenopausal symptoms and bone density issues.

- I prescribed **compounded bioidentical progesterone** in topical creams or oral capsules to treat PMS and PMDD because I am able to prescribe higher doses of the bioidentical progesterone than is available in FDA-approved bioidentical progesterones.

- I prescribe **compounded bioidentical estriol** to treat interstitial cystitis. Sometimes, I prescribe compounded bioidentical estriol with progesterone if the patient's individual lab results indicate the appropriate need.

- I prescribe **compounded bioidentical testosterone with estriol** to treat low libido and sexual dysfunction in women, and **compounded bioidentical testosterone with progesterone** to treat low libido and sexual dysfunction in men.

- I prescribe **compounded thyroid hormones (levothyroxine or liothyronine) or adrenal hormones (DHEA or hydrocortisone) and bioidentical testosterone** to treat fatigue in my male and female patients.

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

Based on my professional medical judgment and clinical experience, I prefer to treat my patients with compounded BHRT because the one-size-fits-all nature of FDA-approved BHRT does not come in enough dosage strength variety and in enough different dosage forms to treat all of my patients. The commercially available BHRT are only available in certain dosing—physicians and patients need more flexibility in dosage strengths and forms. Not all patients can

tolerate a patch or a thick, transdermal cream. Alternatively, many patients are sensitive to the fillers in commercially available oral capsules.

Further, compounding allows for greater ease in dosing the individual patient. With compounding, I am able to prescribe combinations of multiple bioidentical hormones in one transdermal cream or capsule, which makes the use of hormone therapy more tolerable for patients. The more tolerable the medication, the greater the patient compliance with the treatment regimen. I know which hormones and combinations thereof my patients require because I evaluate blood tests on my patients every three months to once a year. These blood test results allow me to consistently monitor hormone levels of my patients and adjust hormone treatment dosages accordingly. For example, many menopausal women cannot tolerate the side effects (e.g., dizziness, fatigue, and depression) of 100 mg of micronized progesterone, which is the lowest commercially available dose. Many women better tolerate lower doses of micronized progesterone, and progesterone is necessary treatment if these women are on an estrogen therapy and have a uterus. Thus, being able to compound lower doses of micronized progesterone is critical for these patients to avoid the side effects of the commercially available option. And, compounded bioidentical testosterone is very important for women, as there is currently no bioidentical testosterone FDA-approved for treatment in women.

Additionally, there is no treatment as successful at treating bone density issues as hormone therapy. I receive multiple referrals from the University of Wisconsin Bone Density specialists and endocrinologists for patients who are unable to tolerate the commercially available hormone therapy. I am able to prescribe compounded combinations of bioidentical hormones to successfully treat these patients.

Being appropriately treated with the right dosage and right form of compounded BHRT is often lifesaving for my patients. Many of my female patients initially present to me nearly suicidal because of menopause or premenstrual symptoms and feeling that they cannot function in day-to-day tasks. If these patients' hormone needs are not met, they cannot be functioning members of society. These patients cannot be effectively treated by the FDA-approved BHRT—they need individualized dosages and combinations that is an option only available through compounded BHRT.

Sincerely,

/s/ Ann Elizabeth Stanger, MD

ANN ELIZABETH STANGER, MD

2984 TRIVERTON PIKE DRIVE
FITCHBURG, WI 53711
Voice: 608-233-2378, Fax: 608-233-2375
drann@meridianhealthcenter.com

MEDICAL EXPERIENCE

Meridian Health Center Owner	May 2017-present
Ann Stanger, MD, LLC Functional Medicine	May 2008 to the present
Amanda Reed Medical Spa Medical Director	April 2013 to the present
Innovative Health Clinic, owner General outpatient medicine	June 2001-May 2008
Electronic Medical Interpretation Group Certified Thermology reader	April 2010-present
Midwest Health Systems, Inc Primary care physician-Lake Edge Clinic Associate physician-Dane County Jail	November 1996-June 2001
Walk-In Medical of Madison Associate physician	December 1991-November 1996
VRG International-Research Group Core physician	February 1993-September 1994
Madison Community Health Center Physician Volunteer	March 1993-October 1993

MEDICAL EDUCATION

American College of Clinical Thermography Clinical Thermography course Physician Thermologist course	April 2008
Institute for Functional Medicine Applying Functional Medicine in Clinical Medicine	March 2003

National Center for Homeopathy — June 1990
Professional course

Institute for Functional Medicine
Advanced Practice Modules
Hormone — July 2011
Cardiometabolic — March 2015
Detoxification — July 2015
Immune — February 2016
Energy — July 2016
GI — October 2016

University of Wisconsin Hospitals and Clinics — July 1989-December 1990
Obstetrics/Gynecology residency

Indiana University School of Medicine — August 1985-May 1989
Honors: Faculty Women's Club Scholarship
Dr. Margaret Hatfield Award,
John B. Hemenway Scholarship

PROFESSIONAL ORGANIZATIONS

State Medical Society of Wisconsin
Institute for Functional Medicine
American College of Clinical Thermography

Exhibit 1-O

G. DeAn Strobel, MD, PA

Hormonal Balance & Wellness

G. DeAn Strobel, MD
230 East Evergreen Street, Sherman, TX 75090
(903) 957-0275 Fax (903) 957-0279

Statement From Gennell DeAn Strobel, MD

Qualifications

My name is Dr. Gennell DeAn Strobel. My professional background is as follows. I received my Bachelor of Science in Mathematics and Spanish from the University of Louisiana in Monroe, Louisiana, in 1989. For a short time, I attended graduate school in engineering at Louisiana Tech University before deciding to pursue medicine as a career. I later received my Doctor of Medicine from Louisiana State University Medical Center in Shreveport, Louisiana, in 1995. I completed my residency in obstetrics and gynecology at Baylor University Medical Center in Dallas, Texas from 1995 to 1999. I am currently Board Certified and have completed annual recertifications since 2005. I completed my written board examination in 1999 and my American Board of Obstetrics and Gynecology Oral Board Exam in 2002.

I earned several awards throughout my undergraduate, graduate, and doctoral degrees. While at the Louisiana State University Medical Center, I received the Bernstein Memorial Scholarship, the Reginald and Ruby Slaughter Scholarship, the L.P. Whitehead Scholarship for Christians, the Louisiana Presbyterian Scholarship Foundation Award, and the Lewis Gottlieb Scholar Award, which goes to a "student that clearly demonstrates scholarship and devotion." During my residency at Baylor University Medical Center, I received the Five-Star Spirit Award, which is nominated by patients. I also received the Teaching Award, which is nominated by fellow residents.

Throughout my life and career, I have enjoyed teaching. While an undergraduate, I tutored students in mathematics and chemistry on behalf of the university as well as private tutoring. While completing my studies in biological sciences and chemistry prior to attending medical school, I worked as an instructor in the Department of Foreign Languages and taught introductory and intermediate level Spanish classes. I also worked as graduate student teacher in the Department of Chemistry. During my residency in Obstetrics & Gynecology, I presented countless lectures during grand rounds and resident learning periods as well as presenting a series on Fetal Heart Rate Monitoring in the Perinatology Conference Annual Meeting in Dallas, Texas, in 1998.

Following completion of my residency training, I continued my teaching while in private practice by participating as guest faculty with the family medicine residency program in Texoma Medical Center for lectures as well as an optional site rotation. I have given lectures and presented across the country and in Mexico on various topics including osteoporosis, laser technologies, and hormone replacement therapy. I am also certified through the International Society for Clinical Densitometry (ISCD) and have worked to teach many physicians and their offices in proper interpretation and techniques for DEXA scans.

My employment experience is as follows. I was an employed physician in obstetrics and gynecology at Hillcrest Healthcare Association, Inc. from 1999 to 2002. I have been the Medical Director and Owner of Allure Laser & Medical Spa since 2004, and I also own a private practice, G. DeAn Strobel, MD, PA, where I have practiced since 2002.

I have had several hospital appointments and committee participations. I was active staff at the Wilson N. Jones Medical Center in Sherman, Texas from 1999 to 2012. I served on the Surgical/Invasive Committee and the Medical Executive Committee, both in Sherman, Texas, from 2004 to 2006. I was the Department Chair of Obstetrics and Gynecology at the Wilson N. Jones Medical Center from 2004 to 2006. I have worked at the Texoma Medical Center Hospital, Heritage Park Surgical Hospital, and Baylor Scott & White Hospital in Sherman, Texas, from 2010 to the present. For a full list of my hospital appointments and committee participations, please see the enclosed CV.

I have also had many leadership and committee roles. I served on the Baylor Outpatient Clinic Continuity Committee and the Medical Education Committee while completing my residency at Baylor University Medical Center. While at the Wilson N. Jones Medical Center from 2001 to 2006, I served on the Women's & Children's Strategic Planning Committee, the Information Technology Committee, the Utilization Review Committee, the Surgical Invasive Committee, the Medical Executive Committee, and I was the Department Head of Obstetrics and Gynecology. I was on the Medical Executive Committee of Heritage Park Surgical Hospital from 2014 to 2017. For a complete list of my leadership roles, please see my enclosed CV.

I am currently part of the Grayson County Medical Society, the Texas Association of Obstetrics and Gynecology, the Texas Medical Association, the American College of Obstetrics and Gynecology, and the American Medical Association. I was part of the Dallas County Medical Society from 1995 to 1999, and the American Association of Gynecologic Laparoscopists from 1999 to 2001.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

I am an actively practicing, board-certified obstetrician gynecologist, and I treat many of my patients with compounded Bio-Identical Hormone Replacement Therapy ("*BHRT*"). My practice is in north Texas in an area of the country with a large geriatric patient population. The average household income in my city is approximately $32,000 per year. My practice is a traditional payor mix (commercial insurance, Medicare, and uninsured) with patients of all races, ages, and ethnicities. My practice treats approximately 60-80 patients per day. Once I stopped practicing obstetrics and started doing gynecology only in private practice, my menopausal patient population soared. As mentioned in the opening section, I am ISCD-certified. Because of the region of the country where I practice and live, I have a huge patient population with osteopenia and osteoporosis as well as many other medical comorbidities such as cancer, heart disease, and more.

I began studying options for BHRT after I quickly learned that commercially-available pharmaceutical products did not relieve most of my patients' symptoms. I came to understand that a "one size fits all" strategy using tradition HRT did not work to relieve many symptoms. Of course, HRT can often help with hot flashes or even vaginal dryness, but there were many other things of which my patients complained for which I had no answer or remedy. Some of these complaints

were things such as memory disturbances, night sweats, anxiety or depression, sleep disruption, fatigue, weight gain (or difficulty losing weight despite exercise and diet), joint pain, low libido, and orgasmic disorders. I, like many, was determined to implement the standard of care for many of these issues and firmly believed that other prescription medications and psychological evaluation (which is what we are taught to offer for anxiety, depression and sexual dysfunction) would help with many of these issues.

I tried to prescribe or recommend various antidepressants, sleep medications, etc. to try to alleviate some of those symptoms. Unfortunately, my attempts to use the standard therapies were proven unsuccessful when patient after patient did not see improvement but rather experienced side effects to some of the therapies. It was around this time that many of my patients started telling me that they went to other doctors to get "bioidentical" hormone replacement via either compounded creams or pellets and had fantastic results. Patient after patient begged me to learn more. I resisted as I had seen a position statement from ACOG regarding bioidentical hormones, but I didn't really understand what "bioidentical hormone replacement therapy" or BHRT meant. I decided to read and learn about BHRT and, specifically, about testosterone use in women.

I began to call some of the compounding pharmacies since there are no available testosterone products for women. I had many conversations with the pharmacists to confirm the exact method of compounding to assure the safety for my patients and began cautiously using compounded testosterone creams (of various strengths) for my female patients with or without the addition of a commercially-available product for estrogen (I have used them all – pills, patch, gels, & depot injections). I followed serum lab values as well as clinical response and side-effects. I learned that creams were variably absorbed by patients (but so were patches and gels) but that vaginal dosing was absorbed much better than topical. Slowly, my patients started telling me they were seeing improvements.

Gradually, I felt more comfortable with prescribing compounded testosterone cream and was able to learn better how to tailor dosing to each patient. But the issue I still found was that the half-life of many creams and gels required twice daily (BID) dosing in order to achieve satisfactory results. Patient compliance was an issue. Some patients also did not get any results, and other patients complained of a "mess" or vaginal irritation, so I had to consider learning about other options as well. I had heard about the use of subcutaneous implants or pellets by many of my patients. Several of my patients traveled to Dallas to get these implants. I had no idea how to dose them nor how to have a pharmacy safely manufacture them, so I decided not to pursue that avenue at that time.

A few years later, in 2009, became trained in dosing and in the use of pellets and began using pellets in my practice immediately. To date, I have performed over 18,000 insertions. Once I began to learn how to truly optimize patients' hormones, I began to receive countless letters and calls thanking me and my practice for "giving them their life back" or "saving their marriage". Never had I received such incredible satisfaction!

My experience treating thousands of menopausal and perimenopausal patients over the last several years is that very few women have complete resolution of their menopausal and perimenopausal symptoms with traditional HRT, but this data is drastically different with compounded BHRT. Compounded BHRT resolves over 80% of those symptoms—if sterile subcutaneous implants are used, over 90% of their symptoms are improved.

I strongly believe that hormone therapy must be individualized with respect to the type of hormone (s), the dose, and the delivery system according to the patient's symptoms, medical history and laboratory evaluation. Prescriptions of traditional HRT do not take into account any of these factors, and, in fact, most OB/GYNs across the country are taught that doing lab evaluation of hormones is "not necessary". I cannot disagree more.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I prescribe many forms of compounded BHRT in my practice to treat a variety of patient conditions and symptoms. Many of my patients have complex medical conditions and are referred to me by other physicians (including oncologists, cardiologists, neurologists, psychiatrists, and more) for hormone evaluation and treatment. Only compounded BHRT allows customization of therapy in so many ways and for so many patients and reasons.

Patients present to my office at all ages and with a myriad of complaints. I perform a complete medical and family history as well as physical examination and laboratory evaluation and have them return for discussion and formulation of a treatment plan. A healthy, young woman has many more options than an older woman or a woman with a complex medical history such as breast CA, stroke, heart attack, and hypercoagulability. Each treatment plan must consider these individuals and their needs.

While there are many forms of estrogen available on the market, estrogen is not the hormone that resolves most complaints from patients. Testosterone was initially used in the 1930s to relieve the symptoms of menopause in castrate women and was found to have good results, but when conjugated estrogens were isolated in the late 1930s and marketed widely in the 1940s, testosterone was "forgotten" by many as the pharmaceutical company era began.

The chief complaints from my female patients are that traditional hormone replacement therapy (i.e., FDA-approved hormone replacement therapy or synthetic hormones) do not adequately address their symptoms, which include night sweats, hot flashes, orgasmic dysfunction, fatigue, weight gain, low libido, and more. These conditions have improved and/or been resolved by treatment with compounded testosterone, which is a hormone treatment that is not currently considered standard therapy for women.

In my experience, I have found that testosterone use, in most of my female patients, has led to significant improvement and/or resolution of the following conditions or complaints: night sweats, sleep disruption, irritability, brain fog, difficulty concentrating, fatigue, weight gain (difficulty losing weight), joint pain, low libido, orgasmic dysfunction, vaginal dryness, and even osteoporosis. Prior to using testosterone in women, I would never have believed that improvement or even resolution and normalization of bone mineral density in women would be possible! I spent many years traveling as a lecturer for Eli Lilly on the drugs Evista (raloxifen) and Forteo (teriparatide). I also have spent considerable time using almost all of the currently-available osteoporosis drugs, but none seem to compare to the use of testosterone in improvement of bone

mineral density. Plus, the side "benefits" of testosterone use in these women are extraordinary as opposed to the many side-effects and long-term risks of bisphosphonates.

Lichen sclerosus is a chronic, debilitating skin condition which affects the genital and anal areas and is most commonly seen in prepubescent and postmenopausal women. It causes a patchy, white area which is usually widespread and bilateral and symptoms of severe pruritus and burning. Often it leads to genital deformities as well. The traditional therapy for this condition is topical steroids and topical testosterone. In my prior experience, this was one of the most frustrating conditions because most women saw only control of symptoms (if they were lucky) but no resolution. With the use of testosterone pellets, I have seen huge improvements and, in many cases, resolution of this condition as well. One patient told me that she had not been able to have intercourse or even wear panties or slacks for over 9 years and was able to resume these activities happily after 6 months of therapy!

Additionally, some of my other female patients with complex medical histories include women who are or would have been suffering needlessly without hormone therapy. These patients include patients with a history of hypercoagulable state, history of breast cancer, history of stroke and/or heart attack, and many more.

Commercially-available oral estrogen replacement therapies (such as Prempro, Premarin, Estrace, generic oral estradiol) as well as progestins (PremPro, Provera) are contraindicated in patients with history of hypercoagulable states, stroke, and heart attack. While non-oral options are now known NOT to increase risk of hypercoagulability, most clinicians are unaware of this fact and continue to tell patients with these conditions that they "can never use hormones". These patients could use one of the non-oral forms of estrogen, but oral micronized progesterone (which is absolutely critical to use in patients on estrogen with an intact uterus) until recently was only available in one product, Prometrium. Prometrium and its generic equivalent contain peanut oil and many patients with severe peanut allergy are unable to take this product. This makes the need for compounded micronized progesterone vital.

In addition to patients with hypercoagulable states, many other patients (and relationships with their partner/spouse) have suffered needlessly for too long. One of the best examples is the breast cancer survivor. Breast cancer survivors traditionally have been told that they CANNOT be treated with any type of hormone. After their diagnosis and treatment, they not only have to endure mutilation and fear of death, but they also suffer from quality of life issues and changes in their intimate relationship that they did not expect. Quality of life issues that these patients endure are poor sleep, chronic fatigue, temperature dysregulation, night sweats and hot flashes, severe joint pain, "brain fog", vaginal dryness, and dyspareunia. Many times, the dyspareunia is so severe that they are no longer able to have intercourse at all! There have been many studies over the last several decades using testosterone replacement in breast cancer survivors, but these studies are not widely known. Once I became more comfortable with the data regarding hormone replacement in these patients, I began to treat them and quickly realized the impact of this treatment when women (and their spouses) literally cried tears of joy when they "felt like a woman again" because they were able to enjoy intimacy again. Women also would tell me that their sleep, energy, hot flashes, moods and many other aspects of life were improved as well.

Another group of patients in which compounded testosterone is vital is the male patients. As a gynecologist, I previously only saw male patients for infertility consultations or treatment for sexually-transmitted infections when they were in a relationship with one of my female patients, but this drastically changed about 10 years ago when patient after patient literally begged me to see their husband, boyfriend, son, or relative. The patients knew that proper optimization of their hormones had made such an impact that they wanted the same thorough evaluation and individualized approach to help their male relatives. I began seeing males and have noted the same trend in improvement in their quality of life. The impact of testosterone replacement in men with testosterone deficiency is vital. Many studies show that patients with testosterone replacement have worsening dyslipidemia, weight gain, increased insulin resistance, increased incidence of heart disease, poor cognition, bone loss, and more. Over time, most of these patients have IMPROVEMENTS in these conditions. The patients will begin to lose weight, and they are often able to come off of many of the prescription medications such as anti-hypertensives, statins, NSAIDs for pain, and diabetes medications.

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

I have witnessed many patients who are now seeking compounded BHRT because the therapy can be monitored and tailored to the patient. Hormone replacement therapy simply does ***not*** work with a one-size-fits-all approach. Regardless of the therapy, each patient is an individual with a unique medical history genomic structure which is vital for metabolizing hormones and other medications — all of which must be taken into consideration when evaluating a patient.

In my professional medical judgment, I prefer to treat my patients with compounded BHRT instead of the commercially available BHRT because hormone therapy requires a constant reassessment and adjustment of the hormone dose and the medication. It is impossible to treat patients with a one-size-fits-all hormone therapy treatment. The commercially available options are limited in the dosages available.

As stated above, many of my patients are medically complex. For women, there are three separate components to BHRT: Estradiol, Testosterone, and Progesterone. For the postmenopausal patient who needs Estradiol, there are several options if the patient is under 60 years old and healthy—that is, these patients can be treated with oral pills, transdermal patches or gels, and vaginal rings, all of which are commercially available. There are many dosages available in oral form, but the oral forms are not advised in patients with gallbladder dysfunction, dyslipidemia, history of stroke or heart attack, or in patients with family history of hypercoagulable states. The oral form is contraindicated also in patients with personal history of deep venous thrombosis or pulmonary embolism. There are commercially available brand-name and generic estradiol options as well, but the dosages are much more limited (the patches come in several dosages, but the highest dose is not often adequate for many; the gels come in only 1 strength). In addition, only approximately ***half*** of patients are able to absorb the transdermal formulations which means that the available strengths often are not sufficient. If the patient desires to continue transdermal administration, often a compounded, stronger version of the BHRT is required in order to treat the patient in the way the patient needs. Transvaginal absorption will yield improved results in many, but the commercially available products are gel which is alcohol-based so cannot be applied or inserted to the vaginal area. Also, compounded subcutaneous pellets offer better absorption, improved results, and better patient satisfaction, but these are not at all commercially available.

The next component that often is needed in female patients is Progesterone. Until the last year, all commercially-available HRT combination products (one product with an estrogen AND a progesterone-like product) contained progestins. Because of the risks and side-effect profile of progestin therapy, I stopped prescribing these products and implemented the use of micronized oral progesterone instead of progestin therapy several years ago. Bioidentical or micronized oral progesterone is commercially available but only in two dosages – 100 and 200 mg. Also, as mentioned earlier, the commercially available products contain peanut oil and cause severe somnolence and dizziness in some women. I have many patients that require much smaller or much higher dosages than the 100 mg and 200 mg capsules that are commercially available.

The last component of female bioidentical hormone replacement – and the most critical and vital, in my opinion – is Testosterone. Why testosterone replacement is not commercially-available nor widely used is a mystery to me. I have spent countless hours over the last many years studying and implementing testosterone replacement in females, and strongly believe that inability to prescribe compounded testosterone would be disastrous to women across the country. I think fear and misinformation are the leading factors with this. Also, in the past, there has been no established "normal" levels for testosterone that are widely used. I believe that there are 2 vital papers related to testosterone use in women that summarize its use and safety well. One of the papers is a review paper written by Dr. Rebecca Glaser and Dr. Constantine Dimitrakakis entitled "Testosterone therapy in women: Myths and misconceptions". It was published in *Maturitas* in 2013. The other is the recently published "Testosterone Insufficiency and Treatment in Women: International Expert Consensus" by Dr. Gary Donovitz, et al.

Although there are various commercially-available testosterone products for males, many male patients cannot get adequate serum levels nor results from traditional formulations or strengths and require compounded testosterone. Current options include testosterone injections, patch, gels/creams, intranasal spray, sublingual rapidly-dissolving tablets, and pellets. Injectables are notorious for being dosed incorrectly at only 1 or 2 injections per month (half-life is 4-8 days). Transdermal application of these products in men has the same concerns over absorption with only ~half of men absorbing the products (achieving adequate serum levels to resolve symptoms).

Testopel is currently the only commercially-available testosterone pellet option, and it is only approved for use in males. The dosages are restricted to 75 mg pellets only, and a maximum of 6 pellets can be used for men. Many men do not achieve adequate serum levels nor results with this dose (this is mostly seen in men over 180 pounds since testosterone dosing is weight-dependent). The other compounded options (such as pellets) or higher strengths (in compounded creams) allow the patient to have adequate serum levels as well as improved results from the therapy.

I hope you find the information provided in my statement to be insightful and helpful. I appreciate your time in reading this letter.

Sincerely,

G. DeAn Strobel, MD, FACOG

Gennell DeAn Strobel, MD

230 East Evergreen, Sherman, TX 75090
Office: (903) 957-0275 Fax: (903) 957-0279
Email: gdstrobelmd@gmail.com

Personal Information

Marital Status	Happily married with twin sons
Board certification status	Board certified Written board examination, June 1999 American Board of Obstetrics & Gynecology Oral Board Exam, January 2002 Annual recertification, 2005 thru present
Birthdate	January 17, 1968
Birthplace	Vicksburg, Mississippi
Citizenship	United States of America
Medical licensure	Texas K3004 National Board of Medical Examiners, 1996
UPIN number	G95979

Education

Postgraduate	Residency, Obstetrics & Gynecology Baylor University Medical Center Dallas, Texas, July 1995- June 1999
Graduate	Doctor of Medicine Louisiana State University Medical Center Shreveport, Louisiana, June 1995 Studies in biological sciences, chemistry Northeast Louisiana University Monroe, Louisiana, 1989-91 Studies in engineering Louisiana Tech University Ruston, Louisiana, 1989
Undergraduate	Bachelor of Science, Mathematics and Spanish Northeast Louisiana University (now University of Louisiana – Monroe) Monroe, Louisiana, May 1989

Hospital Appointments & Committees

Heritage Park Surgical Hospital Sherman, TX	2010 to present
Texoma Medical Center Hospital Sherman, TX	2010 to present

Department Chair, Obstetrics/Gynecology	Wilson N. Jones Medical Center July 2004 to July 2006
Medical Executive Committee Sherman, TX	July 2004 to 2006
Surgical/Invasive Committee Sherman, TX	July 2004 to 2006, 2008
Wilson N. Jones Medical Center Sherman, Texas	Active staff, August 1999-2012
Utilization Review Committee Sherman, TX	July 2000 to 2006
Utilization Review Committee Chairperson	August 2005 to 2006
Community Medical Center	Courtesy staff, 1999-2001 (hospital bought out)
Center for Ambulatory Surgery	2003 to present
Heritage Park Surgery Center	2008 to present
WNJ Foundation board member	October 2005 to 2008

Committees and Leadership Roles

BioTE Medical	Director of Clinical Education, April 2018 to present Medical Advisory Board, 2013 to present Mentor, 2013 to present Teaching Faculty, 2017 to present
Heritage Park Surgical Hospital	Medical Executive Committee, 2014 – 2017
Wilson N. Jones Medical Center	Department Head, Obstetrics & Gynecology, 2004 – 2006
	Medical Executive Committee, 2004 – 2006
	Surgical Invasive Committee, 2004 – 2006
	Utilization Review committee, 2000 – 2006
	Information Technology committee, 2000 – 2006
	Women's & Children's Strategic Planning committee, 2001 – 2005
Baylor University Medical Center	Baylor Outpatient Clinic continuity committee, 1995-1999 Medical Education committee, 1998
Louisiana State University Medical Center	Class president, 1991 – 1995 Freshman, Sophomore, Junior and Senior years
	Honor Council, 1992

	Subcommittee for university self-evaluation, 1992-93
	Medical Student Research Forum, 1994
Northeast Louisiana University	Group leader for Women and Minorities in Science, 1987

Professional Organizations

American Medical Association, 1991-present

American College of Obstetrics and Gynecology, 1995-present

Texas Medical Association, 1995-present

Texas Association of Obstetrics and Gynecology, 1995-present

American Association of Gynecologic Laparoscopists, 1999-2001

Dallas County Medical Society, 1995-1999

Grayson County Medical Society, 2000-present

Research Experience

Syneron	FDA trial for VelaSmooth , 2004 – 2005 Research led to FDA-approval for cellulite reduction
	FDA trial for VelaSmooth, 2005 to 2007 Research in device's effects on stretch marks
Baylor University Medical Center	"Mitochondrial Defects in Fat Oxidation", 1999 - 2000
Louisiana State University Medical Center	"Clinical and Echocardiographic Findings in Heart Failure" Abstract published in *Journal of the Louisiana State Medical Society*, July 1994
Louisiana Tech University	Research assistant, civil and mechanical engineering, 1989
Applied Research Associates, Inc. Vicksburg, Mississippi	Engineering research assistant, Summer 1988 Research in conjunction with United States Department of Defense

Employment Experience

G. DeAn Strobel, MD, PA	Physician, Self-Employed Private Practice, October 2002 to present
Allure Laser & Medical Spa	Medical Director, Owner May 2004 to present
Hillcrest Healthcare Association, Inc.	Physician, Obstetrics & Gynecology, 1999-2002
Northeast Louisiana University	Instructor, Spanish Beginning and intermediate levels, 1989-91

Graduate Assistant
Spanish and chemistry, 1989

Tutor
Mathematics, 1986-89

Louisiana Tech University

Graduate Assistant
Engineering, 1989

Tutor
Physics and mathematics, 1989

Honors and Awards

Baylor University Medical Center

Teaching Award
Awarded by fellow residents, 1997

Five-Star Spirit Award
Nominated by patients, 1997

Louisiana State University Medical Center

Lewis Gottlieb Scholar Award
Award to "student that clearly demonstrates scholarship and devotion", 1995

Louisiana Presbyterian Scholarship Foundation
1991-92, 1993-94

L. P. Whitehead Scholarship for Christians, 1992-93

Reginald and Ruby Slaughter Scholarship, 1992-93

Bernstein Memorial Scholarship, 1991-92

Northeast Louisiana University

Alpha Epsilon Delta, 1990
Pre-Med Honor Society
Valedictorian, May 1989 Largest graduating class

Outstanding Senior Mathematics Award, 1989

Outstanding Graduating Senior Award, 1989
Alpha Lambda Delta

One of NLU's Outstanding Juniors and Seniors, 1988

Sigma Delta Pi, 1988
National Spanish Honor Society

Gabriela Mistral Award, 1988

Phi Kappa Phi, 1988
National Honor Society

Outstanding Initiate Award
Phi Kappa Phi

Omicron Delta Kappa, 1988
National Honor Society

Alpha Lambda Delta, 1985
Freshman Honor Society

Rho Lambda, 1988
Honor Society for Panhellenic women
Vice-president

Outstanding Freshman Mathematics Award, 1985

Presentations and Lectures

Texoma Medical Center Family Medicine Residency program	Guest faculty and clinical training site, 2015 – 2018
Medical Advisory Board	BioTE Medical, 2013 to present Clinical trainer
Guest Speaker	Age-Management Medicine Group, November 2017 "Estrogen" and "Abnormal Bleeding in the Peri- and Menopause Patient"
	Age-Management Medicine Group, November 2015 "Hormone Hold-Ups"
Speakers' Bureau	Syneron, 2003 to 2008 Educate medical staff on non-ablative laser technology
Speakers' Bureau	Eli Lilly Co., June 2004 to 2012 Osteoporosis (Evista & Forteo)
Preceptorship Program	Boston Scientific, October 2005 to 2007 Instructor for HTA (Hydrothermal Ablation)
Sherman, Texas	"Urinary Incontinence" Patient education seminar, 2002
Sherman, Texas	"HRT in the 21st Century – What You Need to Know" Educational meeting for family practitioners, 2001
Austin College Sherman, Texas	"HRT in the 21st Century" Community Educational series, 2001
	"Women's Health in 2004" Breast Cancer Awareness month, October 2004
	"Today's Woman: Her Health & Beauty Needs" Staff Development Day, January 2005
Wilson N. Jones Medical Center Sherman, Texas	"Pregnancy and Preexisting Diabetes" Women's & Children's Grand Rounds, 2000
	"Fetal Hydronephrosis" Women's & Children's Grand Rounds, 2000
Texas Medical Association Dallas, Texas	"Fetal Heart Rate Monitoring" Annual Meeting, 1999
Texas Association of Obstetricians & Gynecologists Dallas, Texas	"First Reported Case: Prenatal Diagnosis of Carnitine-Acylcarnitine Translocase Deficiency" Annual Meeting, 1999
Baylor University Medical Center	"Fetal Heart Rate Monitoring"

Dallas, Texas	Perinatology Conference, 1998
	"Mitochondrial Fatty Acid Oxidation Defects" Dallas Doctors' Club, 1998
	"Fetal Heart Rate Monitoring" Grand Rounds, OB/GYN, Sherman, TX, 1998
	"Carnitine-acylcarnitine Translocase Deficiency" Grand Rounds, Neonatology, 1998
	"Carnitine-acylcarnitine Translocase Deficiency" Perinatology Conference, 1998
	"Antibiotic Therapy in Gynecologic Infections" Continuing Medical Education, 1998
	"Hemorrhage in Pregnancy" Continuing Medical Education for nurses, 1996-98
	"Hypertensive Disorders of Pregnancy" Continuing Medical Education for nurses, 1998
	"Thrombosis and Vascular Complications of Surgery" Gynecology Morbidity and Mortality Conference, 1998
Northeast Louisiana University	Guest speaker for Women and Minorities in Science, 1990

Abstracts

1. "Clinical and echocardiographic findings in heart failure". GD Strobel, T Ratts
2. "First Prenatal Diagnosis of Carnitine-Acylcarnitine Translocase Deficiency using Tandem Mass Spectrometry". GD Strobel, D Roe, JM Graham, C Roe, M Brivet
3. "Identification of a novel mutation in patient with carnitine-acylcarnitine translocase (CACT) deficiency". JH Ding, BZ Yand, JM Mallory, DS Roe, GD Strobel, M Brivet, CR Roe

Special Skills

Bilingual	Spanish and English
Martial arts	Taekwondo, 1st degree black belt
Medical mission work	San Luis Potosi, Mexico, 1994

Interests

Family activities
Health & wellness
Foreign and domestic travel
Languages

Exhibit 1-P

ALLAN WARSHOWSKY MD, FACOG, ABIHM
150 PURCHASE ST; STE 7
RYE, NY 10580
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Statement From Allan B. Warshowsky M.D. FACOG, ABIHM

Qualifications

My name is Dr. Allan B. Warshowsky FACOG, ABIHM. My professional background is as follows. I received my Bachelor of Arts, *magna cum laude*, from Queens College of CUNY in Queens, New York in 1969. I received my Doctor of Medicine from Downstate Medical Center of SUNY in Brooklyn, New York in 1973. I completed my rotating internship, OB/GYN residency, and OB/GYN Chief Residency at Long Island Jewish Medical Center in Queens, New York from 1973 to 1977.

I am a board-certified OB-GYN. I am a founding Diplomat and Director Emeritus of the American Board of Integrative Holistic Medicine, a past member of the American Holistic Medical Association, a member of the American Board of Obstetrics and Gynecology, and a respected member of the Board of Xymogen Advisors. I was a founding physician and director of the Women's Program at Beth Israel's Continuum Center for Health and Healing in New York City from 2000 to 2003. I am the author of multiple articles on topics that include natural cures to fibroids and health risks to women. For a complete list of my publications, please see my enclosed CV.

I am at the forefront of integrative, holistic medicine. Despite being conventionally trained, I am a leader in the field of integrative, holistic medicine treating men and women of all ages. I have been in practice for over 35 years, and my practice combines the best of conventional medicine with the latest in integrative, holistic modalities.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

My practice covers many areas of medicine and healing, which specifically includes compounded bio-identical hormone replacement therapy ("*BHRT*") for men and women. Approximately half of my patients are currently being successfully treated with compounded BHRT.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I prescribe compounded BHRT in my practice to treat a variety of patient conditions and symptoms. Specifically, I treat the following conditions with some form of compounded BHRT:

- Aging optimally in women and men
- Autoimmune diseases – Hashimoto's, SLE (lupus)
- Bladder problems
- Breast disorders, including menopausal care after breast cancer
- Cancer risk reduction through an integrative holistic approach in women and men
- Cervical dysplasia and abnormal pap smears
- Chronic fatigue, fibromyalgia and chemical sensitivity in women and men
- Chronic pelvic pain
- Chronic yeast disorders
- Contraceptive counseling and management
- Detoxification disorders in women and men
- Endometriosis
- Fertility Problems –through an integrative, holistic approach
- Fibroid tumors of the uterus
- High cholesterol
- Hormone imbalance in women and men
- Heavy metal toxicity in women and men
- Intestinal problems including irritable bowel syndrome, constipation and IgG4
- Food allergies
- Migraine headaches
- Menstrual irregularities of all kinds
- Metabolic Syndrome
- Nutritional and wellness counseling
- Obstetrical counseling – to achieve an optimally healthy pregnancy
- Optimal aging and disease prevention
- Osteoporosis and bone health
- Ovarian Cysts
- Perimenopausal and Menopausal care
- Premenstrual Syndrome
- Preventive health care
- Polycystic ovary syndrome
- Sleep Disorders
- Thyroid and other endocrine disorders
- Uterine problems
- Vulvar pain syndromes

More specifically, I use the follow compounded bioidentical hormones or combinations thereof to treat the follow medical conditions and symptoms.

- **Compounded Progesterone**. I prescribe compounded progesterone in oral capsules to treat any patient that exhibits an estrogen dominance. Specifically, compounded progesterone treats my patients with the following medical conditions and symptoms:
  - Premenstrual Syndrome, especially in women who are already taking birth control and are not making enough progesterone on their own
  - Polycystic ovary syndrome
  - Perimenopausal and Menopausal care
  - Hormone imbalance in women and men
  - Endometriosis
  - Early pregnancy losses in young women who have frequent miscarriages when their bodies are not making enough progesterone
  - Preventive health care, specifically when treating menopausal symptoms to lower risk of cognitive decline, heart problems, and colon cancer
  - Cognitive decline in men and women

- **Compounded Estradiol + Estriol**. I prescribe compounded Estradiol and Estriol to treat symptoms of menopause, specifically hot flashes, night sweats, mood issues (depression, sadness, and anxiety, among others), and osteoporosis, and to treat patients with a family history of colon cancer, dementia, and/or Alzheimer's. Estriol is very weak and tends to be a balancing form of estrogen that reduces any negatives effects of the stronger hormone, Estradiol.

- **Compounded Pregnenolone + Dehydroepiandrosterone ("*DHEA*")**. I prescribe compounded Pregnenolone and DHEA in transdermal creams to treat adrenal fatigue in men, women, and children or in patients who are under severe stress. For male patients with low testosterone, compounded DHEA will convert into testosterone in the body and treats adrenal fatigue, exhaustion, poor stress management, weight management, sleep management, body temperature regulation, and frequent infections, among others.

- **Compounded Testosterone**. I prescribe compounded testosterone in a transdermal cream to treat fatigue, muscle weakness, loss of commitment and focus, and low libido in my male and female patients. I also prescribe it to treat the follow medical conditions in men specifically:
  - Unhealthy aging
  - Decrease in muscle tone
  - Sarcopenia
  - Erectile Dysfunction
  - Lack of interest in sex
  - Muscle strength loss

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

In my professional medical judgment, I prefer to treat my patients with compounded BHRT instead of the commercially available BHRT because compounded BHRT allows me to dose medication to the individual patient. Hormone therapy is inherently idiosyncratic and therefore the hormones or combinations thereof, dosage strengths, and dosage forms need to be tailored to the individual patient. Bioidentical hormone therapy is not a one-size-fits-all therapy.

Commercially available synthetic estrogens do not effectively treat female patients for the conditions and symptoms they experience as a result of hormone imbalances or deficiencies. Instead, women often end up taking too much of the commercially available synthetic estrogens without the balancing effects of Estriol. Being able to compound combinations of bioidentical hormones allows me to treat patients better with less risk and fewer side effects experienced by the patient.

Similarly, Premarin is an FDA-approved conjugated equine estrogen, which carries a dose of estrogen that is far too strong for most women. The primary hormone in Premarin is Estrone, which is an inflammatory estrogen that carries negative side effects for women. These may include weight gain, breast tenderness, abdominal bloating and irregular uterine bleeding.

Additionally, Prometrium is the only natural FDA-approved progesterone therapy. Prometrium is a commercially available combination medication available as an oral capsule and

contains heat sensitive oils that can denature the progesterone during shipping and delivery of the medication. The capsule also contains peanut oil, so those patients with a peanut allergy cannot be treated with it. Without compounded BHRT, there is no way for these patients with allergies to get appropriately treated with progesterone.

Further, if men are inflamed, their bodies turn testosterone into estrone, which causes male breasts and/or abdominal bloating. These men often need to be treated with a combination of therapies to reduce inflammation and conversion of testosterone to estrone.

In my professional medical experience, many of my female patients initially come to me already being treated with commercially available BHRT and it is not working for them—that is, they are not being fully treated, they are not able to tolerate the side effects, and they do not feel like they are getting better. When I switch these patients to individually tailored, compounded BHRT, their health improves, their symptoms resolve, and there are far less side effects.

Sincerely,

/s/ Allan B. Warshowsky M.D. FACOG, ABIHM

Allan B. Warshowsky M.D. FACOG , ABHM

(Diplomate of the American Board of Holistic Medicine)

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Website e-mail dr@doctorallan.com

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CELL 914 400 7380

EDUCATION

Queens College of CUNY, Queens, New York, BA 1969, Phi Beta Kappa, Magna Cum Laude

Downstate Medical Center, of SUNY, Brooklyn, NY, M.D. 1973

Long Island Jewish Medical Center, Queens, NY

Internship (Rotating) -1973-1974

Residency (OB/GYN) -1974-1976

Chief Residency (OB/GYN) -1976-1977

WORK EXPERIENCE

Private practice in Obstetrics and Gynecology (Conventional and Holistic OB/GYN) on Long Island, NY 1977-March ,2000

Associate attending at Long Island Jewish Medical Center, Long Island campus for Albert Einstein Medical Center

Director of the Women's Program, Beth Israel's Continuum Center for Health and Healing, New York, NY April '00 –October '03

Private practice in Integrative Holistic Women's Health October '03 – 8/06 in NYC

Private practice in Integrative holistic women's healthcare in Bethesda, MD 8/06 – 6/08

Private practice in integrative holistic health care in Rye, NY 6/08 - present

PROFESSIONAL ORGANIZATIONS/ACHIEVEMENTS

Director Emeritus, American Board of Holistic Medicine (ABIHM) 1998-present

Created 1st board certification exam in Holistic Medicine –given Dec. 2000, and then 2x/year since then

Board of Directors, American Holistic Medical Association (AHMA) 1997-2000

member American Board of Obstetrics and Gynecology

Fellow American College of Obstetrics and Gynecology

Board of Advisors, Xymogen Professional Formulas 4/10 - present

Board of advisors, Sharpe Again Naturally - (Alzheimer's education group)

Author

"Healing Fibroids- a Doctors Guide to a Natural Cure"- published by Simon and Schuster

"Women at Risk"– coauthored with Dr. Gregory Henderson, published by Penguin abnormal pap smears, HPV, Holistic approach

Textbook of Integrative Medicine, University of Wisconsin Integrative Medicine

Dr. Allan Warshowsky is a board certified Ob-Gyn who had been in private practice from 1977 –present in the New York City area. He spent the last ten years developing a practice of integrative holistic women's healthcare. He has expanded his practice to include men and teens located in Rye, NY.

His practice therapies range from the conventional to the purely holistic. Some of these holistic modalities include: nutritional therapy, vitamin and herbal treatments, lifestyle changes, visualization and imagery, and other stress modification therapies.

He has had great results treating the discomforts and problems of menopause using natural, bio-identical hormones and other integrative, holistic approaches.

Dr. Warshowsky has been very successful as a facilitator of optimal health to those in need. His book "Healing Fibroids - A Doctors Guide to a Natural Cure", published by Simon and Schuster, describes Dr. Warshowsky's holistic program for fibroid tumors of the uterus.

Dr Warshowsky was a founding physician and director of the Women's Program at Beth Israel's Continuum Center for Health and Healing form 2000 -2003

Dr Warshowsky is a Founding Diplomat of and Director Emeritus of the American Board of Integrative Holistic Medicine

Exhibit 1-Q

David J. Watson,
Bruce R. Derr,
Jeannie Kay,
Katherine Tiedt,

Statement From David Watson, M.D., FACOG

Qualifications

My name is Dr. David Watson, MD, FACOG. My professional background is as follows. I earned my undergraduate degree in zoology from the University of Arkansas and earned my Doctor of Medicine from the University of Arkansas School of Medical Sciences. I graduated from medical school in 1988, having received the Elvin Shuffield Award in Excellence. I completed my internship and residency at St. Joseph Hospital in Denver, Colorado in 1992.

I began practicing medicine, specifically obstetrics and gynecology, at Littleton Gynecology & Wellness in 1992. I am credentialed by the American Board of Obstetrics and Gynecology. I am skilled in traditional pelvic surgery as well as DaVinci robotic surgery, and I am co-chairman of the Robotics Committee at Littleton Adventist Hospital. I became a certified BioTF medical practitioner in 2014.

Experience With Treatment Of Compounded Bio-Identical Hormone Therapy

I have over 20 years of experience in hormone management for my patients, and it is my professional medical judgment that compounded Bio-Identical Hormone Therapy ("*BHRT*") is a better course of treatment than commercially available hormone replacement therapy. Since 2014, I have provided hormone pellet therapy to both of my male and female patients, and I currently treat virtually all of my patients with individualized forms of compounded BHRT.

When I first began practicing medicine, I treated my patients with conventional, commercially available hormone therapies. Unfortunately, I did not see the health of these patients improve, and often these patients returned with health decline, exhibiting conditions and symptoms such as Type II Diabetes, bone loss, general decline in wellbeing, and cardiovascular issues, among others. I made the decision, based on my medical judgment, to switch to treating patients with compounded BHRT, and I saw a near immediate improvement in these patients' overall health, which is further discussed below. It simply made sense to me—put the missing bioidentical hormones back into the body and tailor them to the individual and mimic how the body managed the hormones. I now effectively treat over 400 patients per month with compounded BHRT.

Medical Conditions and Patient Populations Treated with Compounded BHRT

I treat a variety of medical conditions in my male and female patients with compounded BHRT. In men specifically, I prescribe compounded BHRT to treat erectile dysfunction. In women, I prescribe compounded BHRT to treat all menopausal symptoms. In both men and women, I prescribe compounded BHRT to treat the following medical conditions:

- Anxiety
- Cardiovascular issues and function
- Depression
- General health decline
- Diabetes
- Erectile dysfunction in men
- Fatigue
- Mild Alzheimer's disease

7750 South Broadway, Suite #200 • Littleton, CO 80122
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www.rightbalancehormonehealth.com

right balance
for mental health

- Joint pain
- Libido and sexual health issues in women
- Mental illness
- Osteopenia
- Osteoporosis
- Symptoms of menopause
- Vaginal dryness

Why is Compounded BHRT Preferred Over Commercially Available BHRT?

Using my professional medical judgment, I prefer to treat my patients with compounded BHRT instead of the commercially available hormone replacement therapy. I treat my patients according to the "Five Rights of Medicine" – that is, the Right patient, the Right drug, the Right dose, the Right route, and the Right time– a practice that is only possible with the individualized treatment available from a personalized, compounded medication rather than the one-size-fits-all, commercially available treatment.

Based on my professional medical experience, it seems the conventional medical industry has made the false assumption that all estrogens, all progestins, and all androgens behave the same in all human bodies. This is akin to assuming that all alcohols behave the same within the body, whereas consumption of ethanol versus consumption of a standard cocktail cause vastly different reactions in the human body.

When the Five Rights of Medicine are applied to hormone replacement therapy, it is clear that compounding the hormone medication (i.e., tailoring the dosage strength and form of administration to the individual patient) is the only appropriate way to treat hormone imbalance within patients. For example, when certain testosterone is converted into methyl-testosterone and absorbed in the gastrointestinal tract, it is converted by the liver into estrogens that have been proven to contribute to risks of breast cancer. However, when treating a patient with bioidentical testosterone in the dosage form of pellet therapy, the hormone is absorbed into the bloodstream and bypasses the liver –this has resulted in a 70% reduction in breast cancer risk in patients where pellet therapy was the right dosage form for him or her.

All patients are different, and therefore each patient has different sensitivities, tolerances, and reactions to hormone therapy that must be monitored throughout treatment so that the dosages and/or combinations of hormones can be adjusted appropriately. The commercially available BHRT does not, in my experience and medical judgment, allow me to effectively treat my patients the same way and to the same degree to that of compounded BHRT. There are no commercially available BHRT options that can adhere to the Five Rights of Medicine like pellet therapy. Especially now, when physicians have access to compounding facilities that adhere to very strict compounding standards, there is no reason physicians would not want this treatment option available for their patients.

It is critical that hormone levels be monitored in patients and tailored to an individual. For instance, a patient with an estrogen receptor positive breast tumor should not receive systemic

estrogen, or a patient with a history of endometriosis might require lower doses of estrogen to avoid re-igniting the disease. Further, if a patient's skin type does not allow proper absorption of hormone cream, pellet therapy would be a better option in order to receive the full benefit of the hormone therapy. Or, a patient may require a smaller dose of hormone in the pellet as time goes on. Being able to make these BHRT adjustments for patients is only possible with compounded BHRT—the commercially available BHRT cannot be tailored in this way, and therefore cannot treat patients to the same degree of effectiveness and success that the compounded version can. Individualization of therapy is tantamount to good outcomes, and these outcomes are difficult, at best, to achieve with current commercially available BHRT products.

I routinely witness severe osteopenia and osteoporosis completely reversed in patients after appropriate treatment with compounded BHRT. This is quite logical as it is when sex hormones are depleted which can be iatrogenic with the use of GNRH analogs or surgical removal of gonads or spontaneous as in menopause that we see the greatest degree of bone loss. It requires synergy between testosterone which promotes osteoblastic activity and estrogen which modulates osteoclastic activity in bone that we see the greatest results. No drug on the market can make that claim.

I commonly see my patients require less medication after being treated with compounded BHRT—for example, these patients are no longer relying on mood stabilizers, erectile dysfunction medication, pain medication, and sleep aids. Specifically, one of my patients was being treated with numerous medications and prednisone for eight years to treat joint pain, but this medication regimen was ineffective. Since this patient began treatment with compounded BHRT in pellet form, this patient's joint pain has been completely resolved and the patient is no longer taking prednisone. When the pellet treatment wears off, the joint pain returns but quickly dissipates when the pellets are reinserted. Further, compounded BHRT has proven invaluable for aiding in opioid addiction. And, as testosterone is an excellent insulin receptor sensitizer, I have witnessed better diabetic control in patients than before they were treated with compounded BHRT. Compounded BHRT is real, it is effective, and it should be here to stay.

Sincerely,

s *David Watson, M.D*

Exhibit 2

MHB
MEN'S HEALTH BOSTON
Beth Israel Lahey Health
Performance Network

Abraham Morgentaler, MD, FACS
Founder/President-Men's Health Boston
Associate Clinical Professor of Urology
Harvard Medical School
Urology/Andrology

200 Boylston Street, A309 | Chestnut Hill, MA 02467 | p. 617-277-5000 | f. 617-277-5444 | www.menshealthboston.com

October 31, 2019

Statement regarding compounded testosterone pellets from Abraham Morgentaler, MD

To whom it may concern,

I have extensive experience using testosterone pellets for the treatment of male hypogonadism over more than ten years. In that time I have had the occasion to use the FDA-approved pellet (Testopel) as well as compounded pellets from several sources. Whereas early in my experience it was my impression that challenges in the production of pellets were likely to make compounded pellets less reliable, this is no longer the case. In my current practice we routinely use compounded pellets. They are consistent in appearance, firmness, and resistance to breakage, and our clinical experience with them is excellent, based on follow-up testosterone levels and duration of response.

Compounded pellets are a critical part of the treatment armamentarium for men suffering from hypogonadism. I make this assessment based on: my own clinical experience; serving as President of the Androgen Society, an international, multidisciplinary organization dedicated to excellence in research, education, and clinical practice regarding testosterone deficiency and its treatment, where I interact with experts from around the world; serving as co-author on three sets of international society clinical recommendations for the management of testosterone deficiency, including lead author on one, and peer-reviewer for the Guidelines published by the American Urological Association in 2018. It would be damaging to the health and well-being of many men across the United States if new restrictions were placed on the use and availability of compounded testosterone pellets.

Sincerely,

Abraham Morgentaler, MD

Exhibit 3

Kimzey LM, Gumowski J, Merriam GR, Grimes GJ Jr, Nelson LM. (1991). Absorption of micronized progesterone from a nonliquefying vaginal cream. *Fertility and Sterility, 56*(5), 995-996.

Population: 8 healthy women with regular menses

Intervention: During the follicular phase of their menstrual cycle, five women inserted 3.3 grams of compounded micronized progesterone in Unibase at a concentration of 100 mg per 1.1 gram and five women took 3 compounded micronized progesterone in oil suspension in gelatin capsules at 100 mg per capsule (2 women received both interventions during different c ycles).

Comparison: Serum progesterone levels at 1, 2, 4, 6, 8, 12, 16, 20, and 24 hours after administration.

Outcome: See figure below for serum progesterone levels. Vaginal progesterone and oral progesterone were absorbed at differing rates, but both showed absorption into serum at appreciable levels.

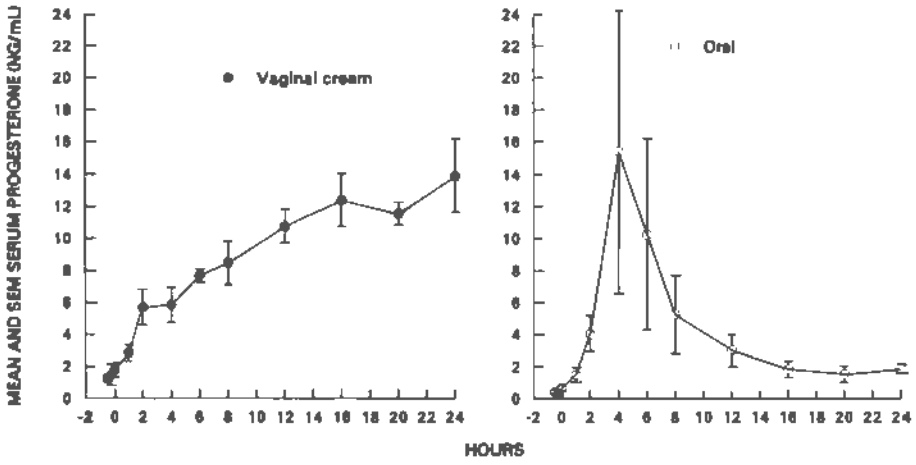

Figure 1 Serum P concentrations after vaginal applicator administration of 300 mg of micronized P in a nonliquefying cream and after oral administration of gelatin capsules containing 300 mg of micronized P in oil.

Maxson WS, Hargrove JT. (1985). Bioavailability of oral micronized progesterone. *Fertility and Sterility, 44*(5), 622-626.

Population: Nine health postmenopausal women and one male. Five women were receiving estrogen supplementation, one woman had previously received a progestogen, but all subjects had not taken any progestin within 3 week of onset of study.

Intervention: After fasting, all subjects were given 2 capsules of 100 mg of compounded micronized progesterone in a gelatin capsule

Comparison: Blood was drawn at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, and 24.0 hours after administration.

Outcome: Various serum concentrations were measured and compared. Progesterone reached maximum absorption approximately 4 hours after administration.

Table 2. *Serum Concentrations of Steroids, Enzymes, and Lipids in Female Subjects (n = 9) Receiving Oral Micronized P 200 mg at Time 0*

Test	Units[a]	Time				
		0	2	4	6	24
				hrs		
P	ng/ml	0.2 ± 0.1[b]	7.5 ± 3.1[c]	9.1 ± 2.2[d]	3.2 ± 4.1[d]	0.6 ± 0.1
E_2	pg/ml	72 ± 24	57 ± 16	60 ± 18	62 ± 19	56 ± 14
DHEA-S	ng/ml	1603 ± 614	1488 ± 578	1646 ± 611	1713 ± 590	1860 ± 688
FSH	mIU/ml	70 ± 11	63 ± 13	65 ± 11	73 ± 12	73 ± 12
LH	mIU/ml	68 ± 13	69 ± 12	69 ± 12	73 ± 10	74 ± 13
Cortisol	μg/dl	12 ± 3				11 ± 2
Aldosterone	ng/dl	18 ± 4				18 ± 2
Cholesterol[e]	mg/dl	284 ± 19				279 ± 20
HDL[e]	mg/dl	43 ± 4				43 ± 4
Triglycerides[e]	mg/dl	190 ± 23				188 ± 19
Alkaline phosphatase[e]	Bodansky U/dl	4.3 ± 0.8				4.3 ± 0.5
SGPT[e]	IU/l	11 ± 0.2				11 ± 1
Bilirubin[e]	mg/dl	0.2 ± 0.1				0.2 ± 0.1

[a] All values are recorded as mean ± SEM.
[b] Statistical comparison of baseline values to subsequent measurements by Student's *t*-test. All comparisons not significant ($P > 0.05$), except as noted.
[c] $P < 0.05$.
[d] $P < 0.001$.
[e] Values include one male subject ($n = 10$).

Tzingounis VA, Aksu MF, Greenblatt RB. (1978). Estriol in the Management of Menopause. *JAMA, 236*(16), 1638-1641

Population: Fifty-two postmenopausal women split into 4 different dosage groups.

Intervention: Oral estriol at dosages of 2 mg per day, 4 mg per day, 6 mg per day, and 8 mg per day for 6 months.

Comparison: Improvement in menopausal symptoms using the menopausal index of Kupperman, as well as comparison of various hormone serum levels over time.

Outcome: Improvement in menopausal symptoms for all dosages (see figure below).

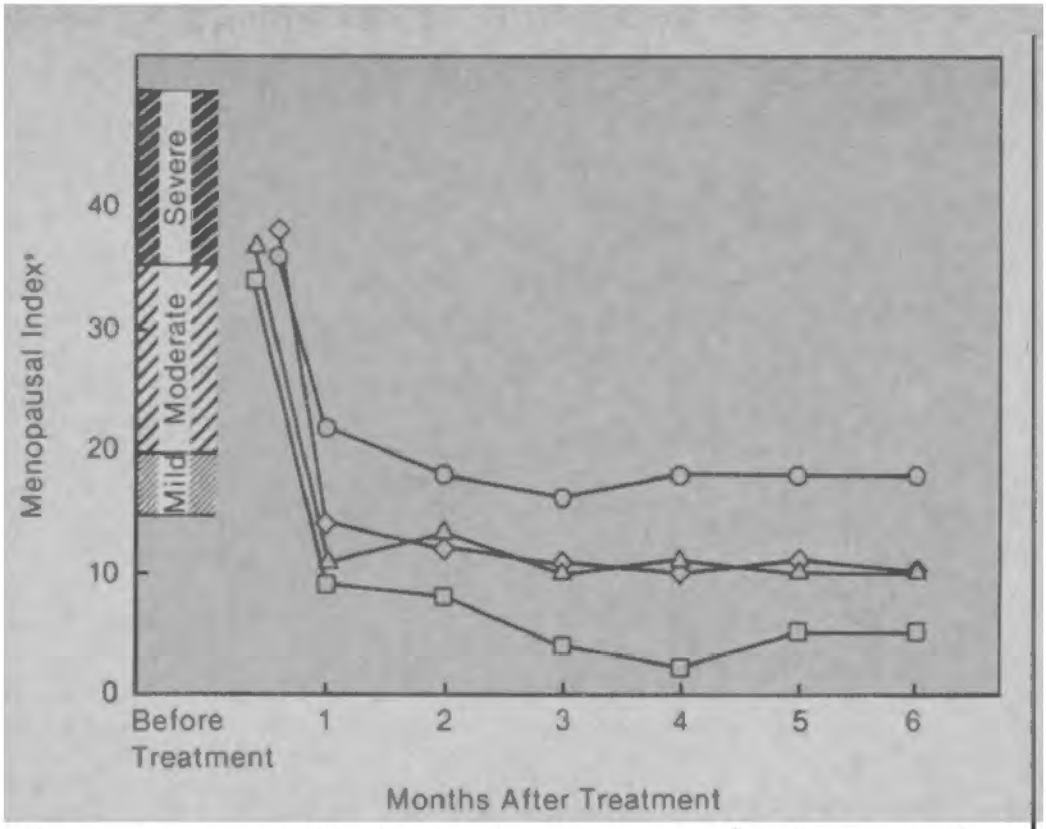

Fig 1.—Menopausal index by Kupperman et al[9] before and after treatment. Circles indicate group A (20 women; 2 mg estriol); diamonds, group B (16 women; 4 mg); triangles, group C (8 women; 6 mg); and squares, group D (8 women; 8 mg).

Devogelaer JP, Lecart C, Dupret P, De Nayer P, Nagant De Deuxchaisnes C. (1998). Long-term effects of percutaneous estriol on bone loss and bone metabolism in postmenopausal hysterectomized women. *Maturitas, 28*, 243-249.

Population: Forty-three postmenopausal women who have had hysterectomies and may or may not have had oophorectomies.

Intervention: Compounded estriol gel at a dose of 1.5 mg daily cyclically with a placebo tablet versus placebo gel with a 2 mg estriol tablet daily cyclically.

Comparison: Bone mineral density via DXA measurement every 3 months

Outcome: Bone mineral density increased in the lumbar spine in the estriol gel group as compared to a decrease in density in the estriol tablet group. Bone mineral density also decreased in the proximal femur in the estriol tablet group, where there was no significant loss or gain in the estriol gel group.

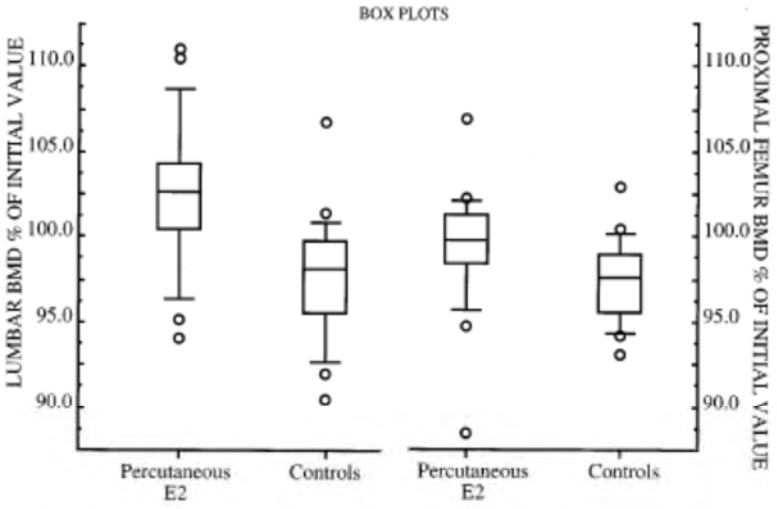

Fig. 2. Box plots: percentage changes at 24 months as compared to the initial value of BMD of lumbar spine and proximal femur in the percutaneous E_2 group and in the control-E_3 group. The midline of the box correponds to the median of BMD changes. The upper extremity of the box corresponds to percentile 75, and the lower extremity to percentile 25. The upper whiskers correspond to percentile 90, while the lower ones correspond to percentile 10.

Hargrove JT, Maxson WS, Wentz AC, Burnett LS. (1989). Menopausal hormone replacement therapy with continuous daily oral micronized estradiol and progesterone. *Obstetrics & Gynecology, 73*(4), 606-612.

Population: Ten menopausal women

Intervention: Five women were given 0.625 mg of oral conjugated (manufactured) estrogens with 10 mg of oral medroxyprogesterone acetate (manufactured) daily for first 10 days of each calendar month for 12 months. The other 5 women were given a compound of 0.35 mg of micronized estradiol combined with 100 mg of micronized progesterone in an oil base in gelatin capsules, 1 capsule in the morning and 1 or 2 capsules in the evening daily for 12 months.

Comparison: Patients were seen at 0, 1, 3, 6, and 12 months, where symptoms were assessed and labs were drawn. Mammograms were obtained at 0 and 12 months.

Outcomes: Symptoms improved significantly in the compounded group versus the manufactured group (see figure below).

Table 1. Estrogen Replacement Therapy: Effect on Symptoms

	E2 and progesterone (N = 10)		Conjugated estrogens and medroxyprogesterone (N = 5)	
Symptom	Baseline	12 mo	Baseline	12 mo
Hot flashes	9	0	5	3
Night sweats	6	0	4	3
Insomnia	4	1	3	1
Decreased libido	6	0	2	0
Dyspareunia or vaginal dryness	5	0	3	2
Anxiety	6	3	3	1
Depression	1	1	3	0

E2 = estradiol.
Data are presented as number of patients with symptom. Symptom severity is scored as none, mild, moderate, or severe. Only moderate and severe symptoms were considered positive.

Wright DW, Kellermann AL, Hertzberg VS, Clark PL, Frankel M, et al. (2007). ProTECT: A randomized clinical trial of progesterone for acute traumatic brain injury. *Annals of Emergency Medicine, 49*(4), 391-402.

Population: One hundred adult traumatic brain injury patients who arrive to the ER within 11 hours of injury

Intervention: Seventy-seven patients received compounded IV progesterone with a loading dose of 0.71 mg/kg for 1 hour, the continuous infusion at 0.5 mg/kg for next 11 hours, then 5 additional 12-hour maintenance infusions for a total of 3 days of treatment was compared to 23 patients who received a placebo infusion.

Comparison: Measurements such as duration of time to awakening from coma, duration of posttraumatic amnesia, and mortality within 30 days of injury.

Outcome: Patients in the progesterone group had lower 30-day mortality rate than control. Additionally moderate traumatic brain injury survivors had better outcomes if they received progesterone compared to placebo.

Miller BE, De Souza MJ, Slade K, Luciano AA. (2000). Sublingual administration of micronized estradiol and progesterone, with and without micronized testosterone: effect on biochemical markers of bone metabolism and bone mineral density. *Menopause, 7*(5), 318-326.

Population: Fifty seven postmenopausal, healthy women who either had hysterectomies or had an intact uterus.

Intervention: The women who had hysterectomies were randomized into 1 of 2 groups: compounded sublingual micronized estradiol 0.5 mg or compounded sublingual micronized estradiol 0.5 mg + micronized testosterone 1.25 mg. The women with intact uteri were randomized into 1 of 2 groups: compounded micronized sublingual estradiol 0.5 mg + micronized progesterone 100 mg or compounded sublingual micronized estradiol 0.5 mg + micronized progesterone 100 mg + micronized testosterone 1.25 mg. The women took 1 compounded tablet twice a day

Comparison: Blood was drawn at baseline, 2 months, 6 months, and 12 months. Bone mineral density was measured using DXA at baseline and 12 months.

Outcome: Bone mineral density in the lumbar spine increased over the 12 months in both groups, and total hip bone mineral density increased in the non-testosterone group, while it was only maintained in the testosterone group.

Stephenson K, Neuenschwander PE, Kurdowska AK, Pinson B, Price C. (2008). Transdermal progesterone: Effects on menopausal symptoms and on thrombotic, anticoagulant, and inflammatory factors in postmenopausal women. *International Journal of Pharmaceutical Compounding, 12*(4), 295-304.

Population: Thirty healthy postmenopausal women

Intervention: The women were split into 2 groups, one group received a compounded progesterone 20 mg per day cream to apply transdermally daily for 4 weeks, followed by a 4 week washout period where no cream was applied, then a 4 week period where a placebo cream was applied. The other group received a placebo cream to apply transdermally for 4 weeks, followed by a 4 week washout period where no cream was applied, then a 4 week period where a compounded progesterone 20 mg per day cream was applied transdermally daily for 4 weeks.

Comparison: Blood was drawn at baseline, after 4 weeks, and at the end of the study, as well as menopausal symptoms using the Greene Climacteric Scale.

Outcome: Neither group had a significant increase in blood levels that would effect clotting or inflammation after use of the progesterone. Administration of the progesterone also improved menopausal symptoms in both groups.

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March 4, 2021

By Electronic Submission On www.regulations.gov

Food and Drug Administration
Department of Health and Human Services
Compounding of Human Drug Products Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act; Establishment of a Public Docket
Docket No. FDA-2015-N-0030

RE: Supplement to August 17, 2020 Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy"

To Whom It May Concern:

On behalf of a coalition of traditional compounding pharmacies and FDA-registered outsourcing facilities (the "*Coalition*"), we are hereby submitting this supplement to our August 17, 2020 comment to the Food and Drug Administration ("*FDA*" or "*Agency*") regarding The National Academies of Sciences, Engineering, and Medicine ("*NASEM*") Report addressing the clinical utility of compounded bioidentical hormone replacement therapy ("*cBHRT*").[1] As set forth below, materials recently produced by FDA in response to a lawsuit filed by Reed Smith LLP ("*Reed Smith*") demonstrate that FDA was in stark violation of the Federal Advisory Committee Act ("*FACA*") in FDA's management and control of the NASEM Committee. The documents produced by FDA thus far provide further support for the Coalition's position that ***FDA cannot, in any way, adopt or rely on any of the conclusions or recommendations*** published by NASEM in its Report, and should FDA adopt or rely on any of the conclusions or recommendations in the Report in crafting policy on cBHRT, FDA will threaten the health of the millions of patients across the U.S. who rely on this medication.

As illustrated in our initial comment, the Report is merely a conduit through which FDA is baselessly attempting to discredit critical and life-sustaining compounded therapies in favor of FDA-approved hormone medications. The Report itself is rife with bias in favor of such FDA-approved hormone therapies, and in order to get a comprehensive understanding of just how deep this bias went, on July 31, 2020, Reed Smith submitted an extensive Freedom of Information Act ("*FOIA*") request to FDA requesting communications between FDA (including FDA's Center for Drug Evaluation and Research),

[1] We hereby incorporate by reference our comment to FDA submitted on August 17, 2020, including all defined terms set forth therein. See enclosed as Exhibit 1.

NASEM, and other relevant individuals and entities within a specified timeframe.[2] FDA had 20 working days to respond to the FOIA request—yet, the statutory response deadline came and went, and FDA still withheld the Agency's records.[3] Ultimately, Reed Smith filed a FOIA Complaint against FDA on October 1, 2020, requesting that FDA produce all records responsive to the FOIA request.[4]

Nearly two months after filing the Complaint, FDA proposed to Reed Smith that the Agency produce responsive documents on a rolling basis, starting with documents from two allegedly primary FDA custodians, i.e., Ms. Gabrielle Cosel and Ms. Elizabeth Hankla. Reed Smith agreed to this process, while reserving the right to identify additional custodians after review of FDA's initial production from Ms. Cosel and Ms. Hankla.[5] Based off this initial production, it is abundantly clear that the bias present throughout the Study and the Report was no coincidence—the initial production revealed that FDA steered the NASEM Committee in violation of FACA.

Therefore, as it stands, in the interest of time and due to the threat the Report ***presently*** poses to the health of millions of Americans should FDA adopt it in its current state, we are submitting this supplemental comment now urging FDA to reject the conclusions and recommendations proffered in the Report, because FDA violated FACA in at least the following ways:

- Before the Study even began, FDA provided one-sided information to NASEM on compounded medications, particularly hormone medications, that profoundly shaped the NASEM Committee's position on cBHRT;

- As the Study began to materialize, FDA played a role in determining who should serve on the NASEM Committee and who NASEM should rely on as cBHRT subject-matter "experts";

- During the course of the Study, FDA and the NASEM Committee consistently collaborated over substantive aspects of the Study; and

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[2] Specifically, the FOIA request asked for responsive documents concerning the following subjects: (1) The National Academies of Sciences, Engineering, and Medicine or NASEM; (2) Bioidentical hormones; (3) Compounded bioidentical hormone therapy (otherwise known as "cBHT" or "cBHRT"); (4) Difficult to compound; (5) Clinical Utility; (6) Pharmacy Compounding Advisory Committee (otherwise known as "PCAC"); (7) Jane Axelrad; and (8) Axelrad Solutions, LLC. *See* FOIA request, submitted July 31, 2020, enclosed herein as Exhibit 2.

[3] 5 U.S.C. § 552(a)(6)(A).

[4] *See* Complaint For Injunctive Relief, enclosed herein as Exhibit 3.

[5] *See* Joint Status Report, enclosed herein as Exhibit 4. Further, on February 9, 2021, Reed Smith identified four additional custodians with responsive documents: (1) Gail Bormel; (2) Sara Rothman; (3) Amy Akparewa; and (4) Lesley-Anne Furlong. FDA agreed to release responsive non-exempt records from Ms. Bormel and Ms. Akparewa by March 26, 2021, and responsive non-exempt records from Ms. Rothman and Ms. Furlong by May 31, 2021. This email is enclosed herein as Exhibit 5. We therefore reserve the right to submit a second supplemental comment upon receipt of additional responsive records from FDA. We would also like to further note that, should we deem it necessary, we will be pursuing litigation under FACA in order to participate in the kind of discovery permitted in FACA litigation. *See Alcresta Therapeutics, Inc. v. HHS*, Civil Action No. 18-243 (Aug. 2018) (order permitting discovery on a plaintiff's FACA count).

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- Finally, FDA was given the opportunity to review and comment on the Report before it was published—a Report that was supposed to be advice independent from FDA.

Overall, despite FDA's stated goal of commissioning a study that would deliver the "independent advice of unparalleled objectivity of the highest quality," the actual Study and corresponding Report were anything but independent and objective. Rather, the materials that FDA has produced thus far under FOIA demonstrate that FDA effectively inserted itself as a voice in the NASEM Committee, as a presenter throughout the Study, and as a writer of the Report. This Study was never independent of FDA, and FDA's management and control of the NASEM Committee violated FACA.

I. FDA Took Steps To Steer The NASEM Study From Its Inception By Providing One-sided Information To NASEM On Compounded Medications, Particularly Hormone Medications, That Inevitably Shaped The NASEM Committee's Position On cBHRT.

The initial materials produced by FDA thus far under FOIA demonstrate that FDA steered the NASEM Study from its inception in direct violation of FACA. As set forth in our initial comment to FDA, FACA is the legal foundation that defines and sets parameters for how federal advisory committees operate. As such, FACA prohibits a federal agency from managing or controlling an advisory committee and, in essence, prohibits that agency from manipulating the advisory committee while the committee develops its advice or recommendations.[6]

Despite FDA's tacit acknowledgement of FACA's applicability, FDA's manipulation of the Study was rampant. FDA went to great lengths from the start of the Study to manage and control the NASEM Committee and thereby steer the Study toward the conclusions and recommendations FDA desired—which is peculiar, given the emphasis FDA initially placed on a need for Study independence. That is, before the Study even began, in order for FDA to obtain federal funding from the Department of Health and Human Services ("*HHS*") to award the Study contract to NASEM, FDA had to submit a Department of Health and Human Services Acquisition Plan (the "*Acquisition Plan*") to HHS, which set out, among other things, FDA's goals for the Study, reasons why NASEM was the appropriate committee to engage the Study, and anticipated costs.[7] FDA stated in its Acquisition Plan to HHS that, due to the nature of the Study:

> [I]t is ***in the public interest to receive the independent advice of unparalleled objectivity*** of the highest quality that provides an inherent degree of acceptability. Considering the volunteer nature of committee members as well as the ***independence, objectivity, quality and acceptance of [NASEM] recommendations***, [NASEM] represents a cost effective means for examining the critical issues of this project.[8]

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[6] In pertinent part, FACA states that "[a]n agency may not use any advice or recommendation provided by the National Academy of Sciences . . . that was ***developed by use of a committee created by that academy under an agreement with an agency***, unless . . . the committee was not subject to any ***actual management or control*** ***by an agency*** or an officer of the Federal Government . . . ." 5 U.S.C. app. 2 § 15(a)(1) (emphases added).

[7] *See* HHS Acquisition Plan, at FDACDER_002307, enclosed herein as Exhibit 6.

[8] HHS Acquisition Plan, at FDACDER_002308, Exh. 6 (emphasis added).

Thus, in order to even obtain the federal funding to contract the Study out to NASEM (which, at $1,345,719.00, was no small price for federal taxpayer dollars to cover) FDA had to explain to HHS that this Study needed to reflect independence and objectivity because that was in the best interest of the public.

Yet, FDA destroyed any semblance of Study independence almost immediately. Notwithstanding FDA's professed need for independence, FDA inserted dangerous bias and mischaracterizations into its Acquisition Plan, essentially telling NASEM how the Study should go and which conclusions should be made, especially as they relate to the regulation of cBHRT and pellets. Specifically, FDA stated in its Acquisition Plan that "compounded drugs are subject to a ***lower regulatory standard*** than FDA-approved drugs,"[9] and stated that one of the reasons the Study was needed was because FDA had:

> recently became aware of many ***adverse events associated with compounded implantable hormone pellets***. For example, during an inspection FDA discovered that one marketer collected more than 4,000 reports of adverse events associated with these products over approximately four years. These adverse events concerned endometrial cancer, prostate cancer, stroke, heart attack, deep vein thrombosis, breast cancer, cellulitis, and pellet extrusions. FDA is currently reviewing these cases.[10]

This means that before the NASEM Committee had a chance to review any relevant materials or form its own opinion or even ***initiate*** the Study, FDA had already told NASEM that all compounded medications were less safe than FDA-approved drugs and that hormone pellets, in particular, were problematic. FDA offered no variety in opinions besides its own regarding the regulation of compounded medications. And, with respect to the inspection referred to above, ***none*** of the information collected actually reflected serious complications or unexpected adverse events associated with cBHRT. The "adverse events"[11] FDA referred to were either coincidental randomly occurring events or possible secondary reactions from treatment with cBHRT (e.g., acne, rashes, etc.)—they were ***not*** serious and/or unexpected adverse events.

These unfounded claims profoundly shaped NASEM's outlook on these issues, which is evidenced in part by the fact that NASEM wrote a White Paper echoing FDA's opinions on compounded medications and pellets shortly after FDA prepared its Acquisition Plan and nearly ***nine months*** before the Study began.[12] In other words, NASEM seemingly formed its opinion on cBHRT based ***only on*** FDA's Acquisition Plan and nine months before the NASEM Committee held its first open session to hear from any other industry stakeholders besides FDA, the Study sponsor. And NASEM understood the importance of independence, as NASEM conceded in its White Paper that it had developed policies to implement certain portions of FACA, and therefore NASEM "must provide ***independent, unbiased advice*** without actual or perceived interference or management of the outcome (findings and recommendations)" during

[9] HHS Acquisition Plan, at FDACDER_002320, Exh. 6 (emphasis added).
[10] HHS Acquisition Plan, at FDACDER_002319, Exh. 6 (emphasis added).
[11] The marketing company FDA referred to is unable to determine where FDA obtained the number of allegedly adverse events referenced in its Statement. This company's records do not reflect 4,202 separate events.
[12] "Clinical Utility of Treating Patients With Compounded 'Bioidentical Hormone Replacement Therapy,'" hereinafter referred to as NASEM's White Paper, at FDACDER_002255, FDACDER_002262 (emphasis added), enclosed herein as Exhibit 7.

the Study and in the Report.[13] However, nearly a year before the Study opened its doors to public input, the NASEM Committee had already spent at least nine months listening to only one biased voice—FDA.

II. FDA Provided Recommendations To NASEM On Who Should Serve On The NASEM Committee And Who NASEM Should Rely On As cBHRT Subject-Matter "Experts."

Once the Study parameters were finalized, FDA began making recommendations to NASEM as to who should serve on the NASEM Committee, i.e., who should be the judges of the Study and ultimate writers of the Report,[14] and who it should hear from as subject-matter "experts" on cBHRT. First, FDA sent an entire list of individual recommendations to NASEM setting out who should serve on the NASEM Committee to analyze the clinical utility of cBHRT. One of the individuals recommended by FDA, Adel H. Karara, actually served on the NASEM Committee. Another individual, Nanette Santoro, published literature that was considered by the NASEM Committee in forming its conclusions and recommendations. And, two other individuals that FDA proffered to NASEM, James H. Liu and Jane Axelrad, actually served as Report reviewers and were able to provide substantive comments and revisions to drafts of the Report before it was published.

FDA's attempt to have Ms. Axelrad serve on the NASEM Committee was particularly surprising given FDA's stated assertion in its Acquisition Plan that it wanted a committee of "independence" and "objectivity."[15] Despite the wealth and variety of non-FDA industry stakeholders from which FDA could have chosen, FDA initially sought out Ms. Axelrad, the Agency's former lead on compounding for over two decades. Although Ms. Axelrad operates her own consulting firm now, her perspectives and voice cannot be separated from FDA—and FDA knew this and tried to capitalize on it. However, when asked, Ms. Axelrad disclosed that she had a client conflict of interest that prohibited her from participation on the NASEM Committee, as reflected in the following timeline of email communications:

November 9, 2018, 6:35 AM **FDA to Ms. Axelrad**	"NASEM have asked us to recommend people for their consideration for their expert committees for the [the Study]. Among other experts, they are looking for people with knowledge of regulatory matters. ***If you are open to it, we'd like to include your name in our recommendations to them***."[16]
November 9, 2018, 10:00 AM **Ms. Axelrad to FDA**	"I don't think I can do it as ***I have a client interested in bioidentical hormones***. I nominated 5 people for that, 5 outside doc experts and one I would think that would be a conflict. Maybe I could do pain creams?"[17]

[13] NASEM's White Paper, at FDACDER_002255, FDACDER_002262 (emphasis added), Exh. 7.
[14] *See* FDA recommendations for NASEM Committees, at FDACDER_000010, enclosed herein as Exhibit 8.
[15] HHS Acquisition Plan, at FDACDER_002308, Exh. 6.
[16] E-Mail Correspondence between FDA and Ms. Axelrad, at FDACDER_000006, enclosed herein as Exhibit 9.
[17] E-Mail Correspondence between FDA and Ms. Axelrad, at FDACDER_000007, Exh. 9.

However, despite this apparent conflict, FDA still made sure Ms. Axelrad was on NASEM's radar from the get-go:

> **November 9, 2018, 6:49 PM**
> **FDA to NASEM**
>
> "Ms. Axelrad was formerly the associate director for Policy, Center for Drug Evaluation and Research, Food and Drug Administration for 25 years. Following the fungal meningitis outbreak, Axelrad was the agency lead on drug compounding. ***We are recommending Ms. Axelrad for the Committee on compounded topical pain medications, as she has indicated she may have a current business conflict with regard to hormone therapy***."[18]

Conflicts aside, FDA wanted Ms. Axelrad's voice to be part of the Study. So, once Ms. Axelrad said "no" to committee participation, her involvement pivoted to presenting to the NASEM Committee, participating in the Study, and serving as a Report reviewer, which allowed her to have substantive influence over the Report's conclusions and recommendations. One such recommendation published in the Report was that the Pharmacy Compounding Advisory Committee ("*PCAC*") review certain bioidentical hormone therapies and pellets as candidates for FDA's Difficult to Compound List—a recommendation that came ***directly*** from Ms. Axelrad's presentation to the NASEM Committee, and an assertion that was identical to the position she took as FDA's compounding lead during meetings with PCAC in 2015.[19]

FDA cannot assert that Ms. Axelrad's presentation that hormones are too difficult to compound—the same position she took while at FDA—was in any way independent from FDA. And, given Ms. Axelrad's decades-long tenure with FDA, there is truly no way to separate her opinions from those of the Agency when even her presence in a room implies that FDA has arrived. Because her opinions and

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[18] FDA recommendations for NASEM Committees, at FDACDER_000014, Exh. 8. We also note that even though FDA formally recommended Ms. Axelrad for inclusion on a committee for a different NASEM study on pain creams, FDA provided committee recommendations to NASEM for both the cBHRT Study and the pain cream study in the same single email, thereby ensuring that NASEM would know Ms. Axelrad's name and experience while NASEM reviewed the recommendations for the NASEM Committee on cBHRT.

[19] In a 2015 presentation by FDA to PCAC, on behalf of FDA, Ms. Axelrad asserted that compounders are not equipped to compound certain medications based on their alleged level of difficulty. Specifically, she stated: "[W]e have seen drugs and categories of drugs that even drug manufacturers have difficulty getting right . . . So I think that there may be certain drugs on the list that we don't think that even a highly skilled compounding operation could do successfully . . . [W]e want to eliminate risks to public health that might be associated with compounding difficult-to-compound drugs that we don't think, in most cases, can be compounded safely or provide a safe and effective product." Thursday, June 18, 2015 PCAC meeting, pages 67-92. The medications Ms. Axelrad was referring to in the 2015 meeting were substances that had already been submitted to FDA's public docket FDA-2013-N-1523 (which was seeking nominations for FDA's Difficult to Compound List) and thus were already on FDA's radar. Among the nominations received by the Agency through this docket, ***nine*** were hormones or categories of hormones that the NASEM Committee, in its Report, suspiciously recommended PCAC to review. That is, of the 11 hormones or categories of hormones the NASEM Committee recommended PCAC to review, ***nine were already nominated for FDA's Difficult to Compound List in 2014 when Ms. Axelrad served as the FDA lead on compounding***. *See* Nominations to the Difficult to Compound List or comments submitted in response to FDA's December 4, 2013 Federal Register notice were submitted to docket FDA-2013-N-1523.

the issues about which she presented are all intrinsically and undeniably tainted by FDA, FDA in effect recommended ***itself*** for the Study, which is an alarming violation of FACA.

In addition to NASEM Committee member recommendations, FDA also told NASEM who the subject-matter experts for cBHRT were and provided scientific literature to the NASEM Committee from these alleged "experts." FDA's cBHRT "expert" recommendations included: The North American Menopause Society; American College of Obstetricians and Gynecologists; Endocrine Society; American College of Physicians; National Association of Nurse Practitioners in Women's Health; HealthyWomen; and National Women's Health Network.[20] Not a single "expert" represents an active prescriber of cBHRT, nor are any of these groups considered specialists in the intricacies of prescribing and treating with cBHRT—they merely offer opinions without the expertise of actual prescribers. Notably, at one point FDA even acted as its own "subject-matter expert" by presenting to the NASEM Committee on compounding and, specifically, the differences between compounding according to Section 503A and Section 503B of the Federal Food, Drug, and Cosmetic Act. It is of course important for a committee like the NASEM Committee to work with experts in the field, but NASEM was supposed to act as an "independent advisor" to FDA and to "partner with experts, representing ***various areas of expertise*** in medical product development, ethics, clinical investigation, clinical care, law, and patient perspectives."[21] FDA was not supposed to intervene in the Study and steer the NASEM Committee toward the groups only FDA deemed to be "experts." Moreover, at no time does it appear that FDA ever suggested to the NASEM Committee that it should hear from active clinical cBHRT prescribers or other compounding industry stakeholders.[22]

III. <u>As The Study Progressed, FDA And The NASEM Committee Consistently Collaborated Over Substantive Aspects Of The Study.</u>

As the Study progressed, the documents produced by FDA reveal that FDA and the NASEM Committee frequently collaborated over substantive aspects of the Study, steadily chipping away at the independent advice the NASEM Committee was initially called upon to give and blurring the lines as to who was actually running the Study. For example, when the NASEM Committee asked FDA for guidance on the regulatory oversight of compounding, it was FDA who presented on and discussed the subject.[23] And, FDA consistently forwarded FDA resources to the NASEM Committee for its consideration. Moreover, as it relates just to adverse events, FDA actually told NASEM, directly and indirectly, on ***three*** separate occasions that it was FDA's belief that there were significant adverse events associated with pellets. Recall that prior to the Study's inception, FDA had already told NASEM through FDA's

[20] *See* FDA recommendations for NASEM Committees, at FDACDER_000015, Exh. 8.
[21] FDA Justification for Other than Full and Open Competition, at FDACDER_002340, FDACDER_002341, enclosed herein as Exhibit 10 (emphasis added).
[22] We note that, when the Coalition became involved in the Study, FDA balked at the idea of other industry opinions. Email correspondence between FDA and the Study coordinator indicated concern over stakeholder involvement late in the Study. Specifically, the Study coordinator told FDA that the Study had a "substantial amount of late stakeholder interest and we're not exactly sure as to why . . . only in the last few months have these stakeholders expressed interest in providing comments to the committee." To which FDA replied, "I'm not sure why some of those stakeholders were late in expressing interest, one of the speakers as you may know is a well-known attorney (in our wonky world, haha) who represents compounders so perhaps she had a hand in organizing the outreach to you." *See* February 6-7, 2020 Email Correspondence, at FDACDER_001801, FDACDER_001802, enclosed herein as Exhibit 11.
[23] *See* April 2019 Email correspondence, at FDACDER_000889, enclosed herein as Exhibit 12.

Acquisition Plan that FDA had become aware of "adverse events associated with compounded implantable hormone pellets."[24] Then in July 2019, which was approximately halfway through the Study, FDA told the NASEM Committee that cBHRT in pellet form was a particular problem by stating that it is FDA's "understanding that most if not all of the [adverse] events relate to drugs formulated as ***pellets*** . . . ."[25] Then, to make sure that the NASEM Committee had not forgotten FDA's position on pellets, in September 2019, right in the middle of the Study, FDA published a press release that grossly mischaracterized cBHRT and pellets as unsafe and/or ineffective and implied that the compounding of cBHRT is inherently risky.[26]

IV. FDA Was Handed The Pen To Revise The Report Before It Was Published—A Report That Was Supposed To Be Advice Independent From FDA.

FDA's influence over the NASEM Committee did not cease when the Study ended—rather, FDA continued to exercise broad management and control over the NASEM Committee even as it was drafting its ultimate Report. FDA did so by proposing revisions to a Report that was supposed to represent "independent advice of unparalleled objectivity" from an institution that provided the public "an inherent degree of acceptability."[27] Given FDA's involvement throughout the Study and given that FDA was offered the pen in writing the Report, it frankly begs the question of, what is the worth of this Study?[28] It appears that FDA merely wanted to mask its longstanding opinions on cBHRT and pellets under the guise of NASEM—a well-known public institution that is inherently trusted by the public. Regardless of FDA's true intentions with this Study, there is absolutely no way that the Report can be considered independent of FDA's management and control.

We are continuing to receive and review materials from FDA under FOIA. Nevertheless, from what we have received so far, we have seen enough to conclude that it is abundantly clear that FDA had actual management and control over the NASEM Committee, which made it impossible for the NASEM Committee to publish an independent, unbiased Report. Therefore, FDA must disregard this Report in its entirety—FDA ***cannot*** adopt ***any*** of the conclusions or recommendations in the NASEM Report because FDA's interference with the Report violated FACA.

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[24] HHS Acquisition Plan, at FDACDER_002319, Exh. 6.
[25] July 2019 Email correspondence, at FDACDER_001378, enclosed herein as Exhibit 13 (emphasis added).
[26] FDA Statement on improving adverse event reporting of compounded drugs to protect patients, September 9, 2019, enclosed herein as Exhibit 14.
[27] FDA Justification for Other than Full and Open Competition, at FDACDER_002340, Exh. 10.
[28] FDA also steered the definition of "clinical utility" by providing literature to NASEM on what constitutes "clinical utility." "What Is Clinical Utility and Why Should We Care?" Dr. Granley. Further, NASEM's Policies explicitly state that, "[s]ponsors are not given an opportunity to suggest changes in reports," i.e., NASEM's Policies forbid sponsors from serving as reviewers to NASEM's reports. Our Study Process https://www.nationalacademies.org/about/our-study-process (last visited March 4, 2021).

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V. Conclusion.

In conclusion, FDA violated FACA by inserting itself into the NASEM Committee and steering the Study from its inception. Therefore, ***FDA must reject the NASEM Committee's Report*** and all the conclusions and recommendations therein, in favor of keeping cBHRT, a critical, life-saving therapy, available for the millions of patients that rely on this therapy.

Very truly yours,

/s/ Rachael G. Pontikes

Rachael G. Pontikes
For Reed Smith LLP

RGP:rl