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through partnership

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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

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).

- 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

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. <i>If you are open to it, we’d like to include your name in our recommendations to them.</i> ” ¹⁶
November 9, 2018, 10:00 AM Ms. Axelrad to FDA	“I don’t think I can do it as <i>I have a client interested in bioidentical hormones</i> . 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 bioequivalent 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

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. As The Study Progressed, FDA And The NASEM Committee Consistently Collaborated Over Substantive Aspects Of The Study.

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.

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).

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