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American Epilepsy Society (AES)

Written Comments to Norman E. "Ned" Sharpless, MD, Acting Commissioner of Food and Drugs, U.S. Food and Drug Administration (FDA), Department of Health and Human Services (HHS)

on Docket ID# FDA-2019-N-1482, *Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds; Public Hearing; Request for Comments*

Submitted on: July 16, 2019

AES Written Comments were approved by the AES Board of Directors on July 16, 2019, and were prepared by an ad hoc AES work group comprised of the following AES members who have no conflicts of interest to disclose.

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Introduction

On April 3, 2019, the US Food and Drug Administration (FDA) announced a public hearing on May 31, 2019 and a call for written comments on the topic of cannabis and cannabis-derived compounds.[1] Kevin Chapman, MD, spoke on behalf of the American Epilepsy Society (AES) at the public hearing. Transcripts of comments, including those by Dr Chapman, are available through the FDA website.[2]

Additionally the AES submitted written comments on July 16, 2019, in response to the FDA call for Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds.[1] At the request of the AES Board of Directors, official AES written comments were authored by Council on Clinical Activities Chair, Timothy Welty, PharmD, along with Edward Faught, MD, Kevin Chapman, MD, and Robert Kotloski, MD. These representatives were selected for their diverse expertise on the topic and freedom from conflicts of interest. These comments, approved by the AES Board, align with the AES Position Statement on Cannabis as a Treatment for Patients with Epileptic Seizures, Revised February 19, 2019[3] and provide additional, selected supporting documentation on related key points of interest to FDA. The AES comments, along with other public comments submitted to FDA, are also publicly available via the FDA online docket.[4]

After the public comment period closed, FDA issued statements highlighting key outstanding questions and points of concern that include misleading and false claims.[5] The FDA reiterated its continuing evaluation of regulatory frameworks for products containing cannabis and cannabis-derived compounds and its intent to approach the outstanding questions "as

a science-based regulatory agency committed to our mission of protecting and promoting public health."[6]

As a service to AES members, the official AES written comments are being published in *Epilepsy Currents*. Information provided in these comments should be helpful to AES members in making decisions about cannabis or cannabis-derived compounds and in educating patients and caregivers on these products.

About the AES

The AES appreciates the opportunity to provide comments to the FDA on questions related to cannabidiol (CBD) and cannabis-derived compounds. As the professional society for health-care professionals committed to epilepsy research and care of individuals afflicted with epilepsy, the AES consists of approximately 4000 members. The membership is composed of physicians, nurses, advanced practice providers, pharmacists, psychologists, social workers, and basic scientists focused on epilepsy. Our commitment is to research and deliver evidence-based care to individuals with epilepsy.

American Epilepsy Society Position on CBD and Cannabis-Derived Compounds

At the beginning of 2019, the AES revised its position statement on CBD and cannabis-derived compounds. The full statement is available in Supplemental Appendix A (available online).[3] Basically, our position is that pharmaceutical grade CBD demonstrates moderate efficacy in specific types of seizures, that CBD does have important adverse effects, that CBD has several important drug interactions, and that further research is needed on CBD and cannabis-derived compounds. While outside the purview of the FDA, we advocate for the Drug Enforcement Agency to reschedule CBD and cannabis-derived compounds to allow for increased research of these products in epilepsy and other diseases.

Given the current patchwork of legislation and regulations at the federal, state, and local levels, the AES recognizes that there is great confusion in a number of areas related to these products. Patients are uncertain about the legal status of products and have poor to no understanding of the products they are purchasing or consuming. Health-care professionals lack sufficient information about the various products flooding the market, are uncertain of how to advise patients on CBD and cannabis-derived compounds, are unaware of products that their patients may be consuming, and are unable to appropriately monitor patients taking CBD or cannabis-derived compounds due to these factors. The public is confused about the true scientific evidence for the safety and efficacy of CBD and cannabis-derived compounds in epilepsy or other diseases.

The AES advocates that CBD and cannabis-derived compounds be viewed as drugs, as defined by the FDA. This would place CBD and cannabis-derived compounds under the full regulatory control of the FDA. It would ensure that CBD and cannabis-derived compounds are marketed based on the highest scientific standards for safety and efficacy and ensure that these products are produced under the highest manufacturing standards. However, the AES also recognizes that such action might jeopardize patient access to some CBD products that our patients believe to be beneficial in controlling their epilepsy. If steps are taken to regulate CBD and cannabis-derived compounds as drugs, the FDA should consider ways to ensure that individuals with epilepsy are not denied access to products they believe to be beneficial or they can be easily transitioned to FDA-approved products without suffering adverse financial consequences.

With this perspective, the AES provides the following comments in response to the questions on scientific data and information about products containing cannabis or cannabis-derived compounds posed by the FDA for the public hearing and request for comments.

Significant Health and Safety Risk Considerations

Adverse effects. While there is a general public perception that CBD is without risk, this is not entirely true. Adverse effects of CBD reported in clinical trials with Epidiolex®, which are more common than with placebo, include somnolence, nausea, diarrhea, and poor appetite; 5% to 14% of patients in clinical trials stopped taking CBD because of adverse effects. It is likely that these effects are dose-dependent. Epidiolex® was also associated with a higher risk of hepatotoxicity necessitating recommended scheduled liver function testing in patients starting the medication. The recommended dosing for Epidiolex® is 10 to 20 mg/kg, but some trials used higher doses of 25 mg/kg body weight, with a maximum of 50 mg/kg.

We suggest that the FDA consider a recommended maximum daily dose of CBD from all nonprescription sources. Perhaps a nonprescription dose limit of 5 mg/kg/d would be appropriate. This is at the lower range of effective doses in clinical trials of CBD for epilepsy. Since toxicity is likely dose-related (see below), higher doses should be taken only under medical supervision. In addition, ingesting CBD with fatty meals, as opposed to ingestion without food, may increase its absorption and blood levels up to 4 times.[7] Therefore, if an individual were to take a dose of 5 mg/kg/d with a fatty meal, their level may be similar to the upper limit dosing of 20 mg/kg/d Epidiolex®.

Besides the concern with a maximal dose of CBD, there is an additional concern related to the composition of many oral CBD products. Being essentially insoluble in water, many oral preparations of CBD are compounded in an oil (eg, olive, peanut, cottonseed). Higher doses of CBD can expose patients to a higher load of oil leading to increased gastrointestinal or other adverse effects. Many other cannabis-derived compounds are also insoluble in water, raising similar concerns to oral preparations of CBD. Also, as noted earlier, the absorption of CBD is increased 4- to 5-fold when taken with a high fat content meal. This difference in absorption would make a 5 mg/kg/d nonprescription dose similar to the maximum recommended

prescription dose of CBD. This approach to nonprescription dosing of CBD is consistent with the FDA's approach to doses of other nonprescription medications.

Drug interactions. Cannabidiol is an inhibitor of the hepatic enzymes, cytochrome P450 3A4 and 2C19. These enzymes are involved in the metabolism of many commonly used medications. Drug interactions do occur with a variety of medications, which could be clinically significant. Supplemental Appendix B (available online) presents literature search results illustrating the variety of potential drug interactions.

Serum levels of the following antiseizure medications rise when CBD is taken with them: desmethylclobazam (an active metabolite of clobazam), topiramate, zonisamide, rufinamide, and eslicarbazepine. When CBD is taken with valproate, there is an increased incidence of abnormally elevated liver function tests, although it is not known whether there is an increased risk of liver dysfunction. Valproate and topiramate are widely used for the prophylaxis of migraine and valproate is used in psychiatry, so the possible interactions extend to nonepilepsy populations as well.[8]

Many medications undergo metabolism in the liver through these enzyme systems and may be associated with altered metabolism that is clinically significant. For example, there are multiple reports of an interaction between the critical drug warfarin and CBD, resulting in a greatly increased risk of bleeding.[9,10]

Likewise, there is the potential for interactions that alter the absorption and metabolism of CBD. It is well-documented that taking CBD orally with a fatty meal results in a 4- to 5-fold increase in CBD absorption and concentrations.[7] Other drugs may inhibit or induce the metabolism of CBD, resulting in increased toxicity or decreased efficacy.

Outside of the limited understanding of CBD interactions, little is known about drug–drug or drug–food interactions with cannabis-derived products. Given what is known about CBD interactions, it is likely that interactions with cannabis-derived products occur.

Documented and potential drug–drug and drug–food interactions with CBD or cannabis-derived compounds necessitate management of CBD and cannabis-derived compounds under the supervision of a physician and other health-care professionals. In addition, the public should be educated on these interactions and their harmful effects.

Pregnancy and pediatric risk. There is limited information about the effects of cannabis-derived products on the developing brain. Brain development starts early in pregnancy, often before the mother is aware that she is pregnant. With 2-5% of mothers self-reporting marijuana use during pregnancy[11] and a greater availability of marijuana, there are concerns that an even larger number may utilize cannabis-derived products during the earliest critical stages of development. Limited studies in neonates following in utero marijuana exposure are inconsistent but raise concern for fetal growth and early neonatal behaviors.[11] Longitudinal studies of marijuana-exposed neonates suggested concerns for neurodevelopmental and behavioral outcome, although confounders such as cigarette use may question an independent effect. There is limited to no data regarding cannabis-derived products in this same population. Similarly, chronic marijuana use in adolescents and young adults has demonstrated alterations in functional magnetic resonance imaging compared to controls.[12] While there are limited data on long-term outcomes in cannabis-derived products, multiple studies raise concerns about potential negative effects on neurocognitive and behavioral development over time. Highlighting these potential risks to the public in this vulnerable population through labeling and supervision by their physician may help prevent potentially harmful exposure.

Increased risk of overdose. Following legalization of marijuana products in Colorado, there has been a 34% increase in unintended pediatric exposures per year from 2009 to 2015.[13] Edible products were responsible for 52% of cases, while in 9%, the product was not in child-resistant containers. Similar findings were found in Oregon following legalization with 253 cases of acute cannabis toxicity over a 16-month period. Children and teens comprised 44% of patients with the majority unintentionally ingesting edible products. Symptoms in children were typically related to excessive sedation, while adults experienced neuroexcitation (anxiety, hallucinations, agitation, etc). Eight patients required intensive care and 1 patient died. Ingestion of concentrated products, such as liquid concentrates or resins, was associated with a higher rate of intensive care unit admission and intubation.[14] Packaging and labeling strategies need to be implemented to reduce unintended exposure to cannabis-derived products, particularly in children. Concentrated products warrant additional warnings of adverse effects.

Potential substitution for effective treatment. Given the perception that cannabis-derived products are more natural, there is real concern that patients and caregivers may substitute medications with scientifically proven medical benefit for cannabis-derived products with unsubstantiated claims. A recent study demonstrated that nearly 50% of subjects had substituted cannabis for a prescription medication.[15] With social media allowing for personal stories extolling marijuana products for life-threatening diseases, such as epilepsy and cancer, we need to implement strategies highlighting the risks of avoiding or demonizing scientifically proven or FDA-approved treatments. One example is a cannabis-derived product sold online purportedly to abort seizures: https://www.trulieve.com/shop/nasal-spray.[16] Given the substantial risk of injury from prolonged seizures and clear data supporting earlier treatment using benzodiazepines for first-line therapy to abort seizures, using cannabis-derived products in this manner is, at best, misguided and more likely to be negligent.

Product Variability and Lack of Standards in Manufacturing and Product Quality

In the current environment, CBD and cannabis-derived compounds are available through 3 different marketing avenues.

There is the FDA-approved CBD product, Epidiolex®, other FDA-approved cannabis-derived compounds (eg, Marinol, Syndros, Cesamet), state-authorized CBD or cannabis-derived compounds, and artisanal or completely unregulated products.

Types of available products. As noted, there are FDA-approved CBD and cannabis-derived compounds that are available to patients through the traditional prescriptive process. We will not comment on these products, as they meet FDA standards and regulation.

Several states, like Minnesota (https://www.health.state.mn.us/people/cannabis/index.html),[17] Iowa (https://idph.iowa.gov/cbd/Medical-Cannabidiol-Board),[18] and Ohio (https://medicalmarijuana.ohio.gov/)[19] have developed their own programs for authorization of products of CBD or cannabis-derived compounds. Laws and regulations for these programs and the products vary greatly from state to state, with Iowa being one example.[20] However, the programs usually require some type of physician authorization for a patient to obtain CBD or cannabis-derived compounds; state authorization of the CBD or cannabis-derived compound products available to patients; state monitoring of quality, purity, and manufacturing of the CBD or cannabis-derived compound products; governance or oversight of the cannabis program by a medical and regulatory board; and use of state licensed or authorized dispensaries for distribution of CBD and cannabis-derived compounds. Minnesota has one of the longest records in operating a state-authorized cannabis program and has a good amount of data on the use of cannabis for various medication conditions.

Publicly available data on the use of CBD and cannabis-derived compounds in Minnesota are available at https://www.health.state.mn.us/people/cannabis/about/medicalcannabisstats.html.[21] We were able to obtain data from the Iowa CBD program, and these data are presented in Appendix A. It is important to note from the Iowa data that the most frequently purchased products were those containing higher amounts of tetrahydrocannabinol than CBD. Reasons for this observation are unclear but are most likely due to a lack of understanding about the differences between CBD and tetrahydrocannabinol, lack of effect from CBD, or individuals being more interested in obtaining tetrahydrocannabinol than in getting CBD. While not necessarily operating in accordance with FDA guidance and regulations, the state-authorized cannabis programs do appear to provide some assurance to the public that CBD and cannabis-derived compounds obtained through these programs have achieved some standard for content and purity of the products. These programs can also be a rich source of good quality data on the use of products of CBD and cannabis-derived compounds

The other way in which patients may obtain products of CBD or cannabis-derived compounds is through what may be termed artisanal products. At the current time, these products are produced and sold with little or no regulatory control. The products are commonly available in dispensaries operated in states that do not regulate the cannabis industry or through Internet sites and sources. Even in states that have attempted to regulate CBD and cannabis-derived compounds, the artisanal sources of these products may be available to patients.

Product standards and assays. Multiple assay methods for CBD and cannabis-derived compounds are available in the published medical literature. Various assay techniques have been used to detect CBD, cannabis-derived compounds, impurities, and degradation products. Examples of CBD identification and analysis techniques are summarized in a World Health Organization (WHO) 2018 report.[22] Efforts are underway to develop highly sensitive and selective analytic methods for qualitative and quantitative determination of cannabinoids.[23] However, none of these assays have been tested and validated to be the standard assay for product content, purity, and stability. To date, the United States Pharmacopeia has not set an official standard assay and quality standard for CBD or cannabis-derived compounds. Without this standard, it is impossible to ensure the content, quality, and purity of products of CBD or cannabis-derived products.

Additionally, the FDA has not set standards that regulate the cultivation, growth, or manufacturing of products of CBD or cannabis-derived compounds. To ensure the quality and consistency of CBD or cannabis-derived compounds, regulation of production must begin with the growth and cultivation of plants that are used for production of the final products. Dealing with botanical-based products presents a number of challenges to ensure consistent content of active ingredients. One source that provides excellent recommendations and guidance on this aspect of use of botanical products is the WHO Guidelines on Good Agricultural and Collection Practices for Medicinal Plants (GACP).[24] Although this document is somewhat dated, it does highlight the issues associated with medicinal plants and can form the basis for development of regulations and guidance on agricultural and collection practices as part of oversight of the production of cannabis-based drugs or other botanical sources of phytocannabinoids. We note that the FDA has a guidance document on Botanical Drug Development,[25] but this does not appear to include regulations around the agricultural and collection practices of botanical products, such as CBD or cannabis-derived compounds. Without these regulations on the agricultural and collection practices, it is impossible to truly ensure the quality and content of products of CBD or cannabis-derived compounds.

Manufacturing practices. Vital to access and availability of high-quality, consistent and reliable products of CBD and cannabis-derived compounds is the application of Good Manufacturing Practice (GMP) to their manufacturing and production. The FDA does have well-developed standards for drug products.[26] While these regulations address the issues surrounding the manufacturing and production of drug products, there are 2 concerns regarding GMP as they apply to products of CBD and cannabis-derived compounds. The first is that many of the regulations are dependent on standard, validated assays for drug product, content, purity, and stability. As noted above,

standard assays for products of CBD and cannabis-derived compounds have not been established. The first step in applying GMP to production of products of CBD and cannabis-derived products is setting standard assay techniques and parameters. A second concern is evaluating GMP standards in relationship to botanical products, and specifically to CBD and cannabis-derived products, to ensure that any supporting documents, explanations, and expectations account for the unique issues in the manufacturing and production of these drugs.

Additionally important to the manufacturing of CBD and cannabis-derived compounds is the health and safety of individuals who work with these products. There have been several reports in the literature concerning the health and welfare of individuals who work with cannabis and hemp products.[27,28]

While generally outside the jurisdiction of the FDA and the direct interests of the AES, this issue increases the concern with unregulated manufacturing of CBD and cannabis-derived compounds.

Variability of products. The criticality of addressing product variability issues cannot be overemphasized. As noted in multiple published reports, currently available products of CBD and cannabis-derived compounds are frequently mislabeled, misbranded, or adulterated.[29-32] Artisanal products were most tested in this regard. Many CBD products contain much different amounts of CBD than what are noted on the label, usually lower quantities of CBD. Several of these CBD products contained other cannabinoids, including tetrahydrocannabinol, in addition to CBD. In many cases, the quantities of the other cannabinoids were at levels that could produce a pharmacological effect. Additionally, many of the products were contaminated with microbes, fungi, herbicides, pesticides, heavy metals, and other pharmaceutical products. The extent of the documented problems with currently available products is sufficient to advise patients and caregivers to avoid purchasing and using the artisanal products of CBD and cannabis-derived compounds.

In summary, the AES believes that the highest standards of assay techniques, agricultural practices for botanical products, GMPs, and other measures to ensure the quality and consistency of products of CBD and cannabis-derived products must be implemented. Without this surveillance and regulation, the risk of harm and confusion to the public is great.

Need for Better Accuracy and Consistency in Marketing/Labeling/Sales

Based upon the above concerns, our clinical experience, and the regulatory measures of states, we advise that labeling for all cannabis and cannabis-derived compounds contains accurate measures of cannabinoid ingredients including CBD, delta-9-tetrahydrocannabinol cannabidiolic acid, and tetrahydrocannabinolic acid, with accurate concentrations provided in milligrams, for both the entire package and per dose/serving.

The intended route of administration should be clearly stated on the label. This information is critical to the safe use of the product by the consumer and for appropriate counseling by the physician. If third-party testing is reported, the detailed analysis should be available to the consumer. Inclusion of a batch number would allow for detailed tracking of products.

Regarding the packaging itself, given the concern for accidental overdose, especially in children, we recommend child-proof packaging and limitation of the single packaged dose to 250 mg (equal to the starting dose of 5 mg/kg for a 50-kg individual in clinical trials of CBD for childhood epilepsies). This amount is about half of the minimal effective dose and is consistent with current FDA practices for nonprescription versions of prescription drugs. For nonprescription versions, the container should not contain more than a 30-day supply.

Selected labels in Supplemental Appendix C (available online) illustrate some of the inconsistencies, inaccuracies, and confusion resulting from current labeling regulation for CBD and cannabis-derived compounds that underlie AES concerns and prompt its recommendations.

Regarding potential adverse effects both directly and indirectly from cannabis and cannabis-derived compounds, we advise labeling should include mention of hepatotoxicity, depression, nausea, diarrhea, somnolence, and appetite disturbance, as well as interactions with multiple medications. Given the frequent use of cannabis and cannabis-derived compounds for the treatment of epilepsy, the abundant interactions with antiseizure medications should be highlighted. Labeling should advise the consumer to discuss the use of the product with a pharmacist or physician. Labeling should also include warnings for use in children and in women who are pregnant, planning to become pregnant, or breastfeeding.

AES recommends that FDA actively encourage health-care providers and the public to report all overdoses, toxicity, and adverse effects via FDA's MedWatch program[33] at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm. Additionally, problems with labeling can also be reported to the Institute for Safe Medication Practices[34] at https://www.ismp.org/report-medication-error.

One review[35] summarizes public health regulation best practices lessons from tobacco control that may be worthy of FDA consideration in the context of cannabis and cannabis-related compounds regulation. Recommendations include prominent warning labels, rotating health warnings using pictorial content, plain packaging that curtails label use as a marketing tool, reducing appeal to minors, and limiting potency on products easily confused with non-cannabis products.

Finally, labeling should clearly state that the product is not FDA approved, and no claims of health benefits of these untested products should be allowed.

Conclusion and Recommendations

There is sufficient evidence to argue for regulation of CBD and cannabis-derived compounds as drugs by the FDA. The AES

believes that these compounds need to be under the full regulatory control of the FDA and that distribution should be limited to the well-developed legend drug process. While drug regulation is desired, in the interim, the following equally important steps should be taken to assure continuous and safe access to CBD products for patients who are currently benefiting from them.

Until regulation of CBD and cannabis-derived compounds as drug is accomplished, AES recommends that FDA implements the following steps to help ensure patient and consumer safety:

- Require labeling of common and serious adverse effects and symptoms of overdose.
- Require label warnings about interactions with other medications.
- Require label warnings with considerations for special populations such as children and women who are pregnant, planning to become pregnant, or breastfeeding.
- To enable health professionals to monitor and manage drug interactions and be alerted to potential symptoms of overdose or toxicity in patients, require a label warning that encourages consumers to report use of CBD and cannabis-derived products to their physicians; for example, "Please inform your physician if you are taking this medication."
- Encourage the public and health-care professionals to report problems with CBD and cannabis-derived compounds to the FDA MedWatch program[33] at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm and to report errors and problems with labeling to the Institute for Safe Medication Practices[34] at https://www.ismp.org/report-medication-error.
- Determine a recommended maximum daily dose for nonprescription use.
- Require clear and accurate labeling of dose or strength per unit.
- Require clear disclosure of the amounts of each cannabinoid in a product.
- Develop standards for product quality assay techniques.
- Enforce the highest GMP levels possible.

Thank you for the opportunity to provide comments as FDA considers regulatory options and weighs the many significant factors involved in ensuring safe and effective use of cannabis and cannabis-related products including CBD. American Epilepsy Society remains available to answer questions, provide additional information, offer clinical or scientific expertise, or otherwise serve as a resource to FDA.

Appendix A

Iowa CBD Program Data

These data (T. Welty, e-mail communication, June 2019) reflect the use of cannabidiol (CBD) products under the Iowa state-authorized CBD program. Availability of CBD products through the state program started in December 2018, so these data reflect the first 6 months of product availability through the program.

Number of Patients Authorized to Purchase CBD Products Through the State Program.

2698 patients
456 caregivers who can purchase on behalf of a patient
3154 total individuals who are authorized to purchase CBD products

Indications for CBD Use.

Indication	Number of Patients (Percent of Total Patients Authorized to Obtain CBD)
Amyotrophic lateral sclerosis	26 (1%)
Acquired immune deficiency/human immunodeficiency virus	25 (1%)
Autism	10 (1%)
Cancer with cachexia or sever wasting	54 (2)
Cancer with nausea or chronic pain	265 (9%)
Crohn disease	101 (3%)
Multiple sclerosis	238 (8%)
Parkinson disease	178 (6%)
Seizures	185 (6%)
Terminal illness with pain	16 (1%)
Terminal illness with cachexia or wasting	5 (<1%)
Terminal illness with nausea or vomiting	4 (<1%)
Untreatable pain	1906 (61%)
Ulcerative colitis	11 (<1%)

How Many Patients Return to a Dispensary for a Second Visit?. A total of 51.6% of individuals who purchased CBD on an initial visit have returned to a dispensary for a second purchase. However, several confounding factors need to be considered when looking at this data point. These include the short period of time that the program has been operational and only 5 dispensaries are authorized state-wide to sell these products. Many individuals had to travel long distances, so they may have purchased sufficient quantities of CBD products to last for several months.

Reports of Adverse Effects or Drug Interactions. No CBD adverse effects have been reported to the program. Individuals taking products that contain tetrahydrocannabinol have reported the psychoactive effects. No emergency department visits have been reported.

Product Usage Based on CBD:delta-9-Tetrahydrocannabinol (THC) Content.

Dosage Form	CBD:THC Ratio	Percent of Sales
Capsule		45%
	1:1	16%
	1:20	24%
	20:1	5%
Tincture		46%
	1:1	20%
	1:20	15%
	20:1	11%
Cream	2:1	9%

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Supplemental Material

Supplemental material for this article is available online.

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