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October 29, 2024

Re: Food and Drug Administration Diversity Action Plans to Improve Enrollment of Participants From Underrepresented Populations in Clinical Studies; Draft Guidance for Industry; Availability, Best Practices for Meeting Management; Public Workshop; Request for Comments, 89 *Fed. Reg.* 54010-54012 (June 28, 2024); Docket No. FDA– 2021–D–0789[1]

Dear Sir or Madam:

The Consumer Healthcare Products Association[2] ("CHPA") is pleased to submit these comments to Docket No. FDA-2021-N-0789 regarding Diversity Action Plans to Improve Enrollment of Participants From Underrepresented Populations in Clinical Studies; Draft Guidance for Industry; Availability (Draft Guidance).[3] The stated goal of the guidance is to assist sponsors conducting certain clinical trials for drugs, biological products, and devices to meet the requirements to submit Diversity Action Plans (DAPs) based on the Food and Drug Omnibus Reform of 2022 (FDORA) in a specified form. CHPA supports the Agency's directive to increase enrollment of participants from historically underrepresented populations in clinical trials to improve the strength and generalizability of the evidence to demonstrate safety and/or effectiveness of FDA-regulated medical products.[4] CHPA requests FDA clarification for, and makes recommendations on, the following points.

[1] FDA Diversity Action Plans to Improve Enrollment of Participants From Underrepresented Populations in Clinical Studies; Draft Guidance for Industry; Availability, Best Practices for Meeting Management; Public Workshop; Request for Comments. 89 *Fed. Reg.* 54010-54012 (June 28, 2024). Accessed from https://www.govinfo.gov/content/pkg/FR-2024-06-28/pdf/2024-14284.pdf on August 27, 2024. CHPA recognizes that the formal comment period on the Draft Guidance closed on September 26, 2024, for comments to be considered before work begins on the final version of the guidance. However, CHPA is submitting these comments for the Agency's consideration as we raise additional points that may not have been addressed in other comments to the docket.

[2] The Consumer Healthcare Products Association (CHPA), founded in 1881, is the national trade association representing the leading manufacturers and marketers of consumer healthcare products, including over-the-counter (OTC) medicines, dietary supplements, and OTC medical devices. CHPA is committed to empowering self-care by ensuring that Americans have access to products they can count on to be reliable, affordable, and convenient, while also delivering new and better ways to get and stay healthy. Visit www.chpa.org.

[3] FDA Diversity Action Plans to Improve Enrollment of Participants From Underrepresented Populations in Clinical Studies; Draft Guidances for Industry (June 2024). Accessed from https://www.fda.gov/media/179593/download on September 9, 2024.

[4] For purposes of these comments, FDA-regulated products mean human OTC drugs and medical devices. The comments indicate when suggestions are related to a specific product category (*i.e.,* drugs or medical devices).

Most OTC drugs and medical devices should be exempt from Diversity Action Plan (DAP) requirements.

CHPA members manufacture and market over-the-counter (OTC or nonprescription) drugs and medical devices. OTC human drugs and medical devices are available to the general population for purchase in the retail marketplace but may be intended for use by a subset of the population at-large. These products are intended to be purchased and used by consumers without oversight or intervention of a healthcare professional (HCP), or the need for a prescription. Manufacturers of nonprescription drugs and medical devices typically conduct well-controlled clinical trials to demonstrate safety and efficacy, or actual use studies (AUS) to show that users and caregivers understand how to appropriately select and use OTC medical products without a learned healthcare intermediate.[5,6]

As part of the approval process for OTC medical products, sponsors most commonly conduct AUS to evaluate if consumers can appropriately select and use the medicine or device according to the label directions. For OTC medicines and devices, selection of the product does not necessarily reflect the end users. For example, menstrual products are available for retail purchase by both men and women, but are used by women able to bear children. However, the results from self-selection studies are evaluated to ensure appropriate decisions are being made, with these results submitted to the Agency in the final study report. Although most OTC medicines are intended for use by the population at-large (depending on the directions for use), the active ingredient is not typically new to the U.S. market and has been demonstrated to be safe and effective for use in diverse populations under prescription use.

Actual use studies for OTC drugs have typically enrolled several hundred to a couple thousand subjects.[7,8] In contrast, subject enrollment for clinical studies conducted to approve prescription drugs (to treat non-rare diseases or conditions) can exceed 10,000

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[5] Actual use studies are described on FDA's website Drug Application Process for Nonprescription Drugs New Drug Application (NDA) and Abbreviated New Drug Application (ANDA). Accessed from https://www.fda.gov/drugs/types-applications/drug-application-process-nonprescription-drugs#:~:text=Consumer%20behavior%20studies%20are%20used%20to%20evaluate%20how,comprehension%2C%20self-selection%2C%20actual%20use%2C%20and%20human%20factors%20studies on October 10, 2024.

[6] See FDA Over-the-Counter (OTC) Medical Devices: Considerations for Device Manufacturers. Accessed from https://www.fda.gov/medical-devices/products-and-medical-procedures/over-counter-otc-medical-devices-considerations-device-manufacturers on October 10, 2024.

[7] FDA Joint Meeting of the Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive and Urologic Drugs Advisory Committee Meeting (May 9-10, 2023). See Sponsor's presentation posted on FDA's website. Access from https://www.fda.gov/media/167980/download on September 12, 2024.

[8] FDA Meeting of the Nonprescription Drugs Advisory Committee Meeting Announcement. See Sponsor's presentation posted on FDA's website. Accessed from https://public4.pagefreezer.com/browse/FDA/04-03-2022T19:30/https://www.fda.gov/advisory-committees/advisory-committee-calendar/september-18-2019-meeting-nonprescription-drugs-advisory-committee-meeting-announcement-09182019#event-materials on September 12, 2024.

patients.[9] OTC drugs or OTC medical devices that are designated as non-significant risk (NSR) devices may enroll fewer than 100 subjects in their clinical studies. Depending on the study criteria, it may be difficult to routinely achieve the anticipated DAP goals. However, OTC drug and device manufacturers do routinely enroll subjects from diverse subpopulations in such studies but with much smaller enrollment goals when compared to prescription medical products.

CHPA requests that OTC human drug products be exempted from DAP requirements if the active ingredient in the human drug product was previously sold in the U.S. as a prescription drug. In the rare instances when a sponsor is seeking a direct-to-OTC status approval (*i.e.,* marketing approval for a drug product that was not previously sold as a prescription drug) and Phase III studies are needed to support safety and efficacy, the sponsor should anticipate the need to submit a DAP that would be similar to one submitted for prescription drugs. The sponsor and FDA should discuss whether a DAP is needed early in the drug development program and be determined on a case-by-case basis. Lastly, CHPA requests OTC NSR medical device clinical studies also be exempted from DAP requirements.

The draft guidance notes that "…'medical products' refers to human drugs (including biological products that are regulated as drugs)…"[10] However, it is unclear whether OTC drug products were inadvertently or intentionally considered within scope of the draft guidance. As noted on lines 147-149 of the Draft Guidance, FDA expects to require a DAP for a clinical investigation of a new drug that is a Phase III trial or other pivotal clinical study of a drug (that is not a bioavailability or bioequivalence study). In many instances, Phase III actual use studies for OTC drugs enroll all-comers (*i.e.,* limited or minimal exclusion criteria for subject participation) and mimic the U.S. census data for enrollment of racially and ethnically diverse subjects. The targeted subject population for study enrollment and the final subject demographics and other baseline characteristics are collected and usually reported in the study results for OTC medical products when the application is submitted to the Agency for review.

CHPA recommends a waiver process appropriate for OTC drugs and OTC NSR medical devices if the Agency rejects our recommendation for exemption as outlined above.

In the event the Agency disagrees with CHPA's recommendation for most OTC drugs and OTC NSR medical devices to be exempt from the DAP requirement, we strongly urge the FDA to adopt a waiver process appropriate for the risk-level of these selfcare products. Section VIII of the Draft Guidance ("Requesting Diversity Action Plan Waivers") addresses the process for requesting a waiver for a DAP. However, the statutory criteria to receive a waiver are focused on the U.S. prevalence or incidence of a disease or condition, when it would be impractical to conduct a clinical investigation in accordance to a DAP, or to

[9] FDA Cardiovascular and Renal Drugs Advisory Committee Meeting (December 13, 2022). See Sponsor's presentation posted on FDA's website. Accessed from https://www.fda.gov/media/163892/download on September 12, 2024.

[10] See footnote 8 in the Draft Guidance. Accessed from https://www.fda.gov/media/179593/download on October 10, 2024.

protect the public health during a public health emergency (see lines 629-638). None of these criteria seem to apply to the OTC environment where OTC drugs, in particular, do not typically treat rare diseases. FDA should establish criteria for a DAP waiver process for studies related specifically to medical products used in an OTC environment. CHPA offers its expertise in conducting clinical studies for OTC medical products to help establish reasonable and relevant criteria for the proposed new waiver process, such that the DAP process is not unnecessarily burdensome.

FDA should clarify the effective date for the Diversity Action Plan (DAP) requirements

FDORA requires the DAP to apply to clinical studies that commence 180 days from the publication of the final version of the guidance (see lines 50-51). However, CHPA asks that FDA clarify if there will be an exact compliance date published when the final guidance is announced in the *Federal Register*. We recognize that a sponsor may voluntarily comply with the final DAP requirements ahead of the compliance date but those that do not implement the DAP before the established date should not be penalized.

FDA should notify the sponsor of any concerns with the proposed DAP identified during its review of the study protocol.

The Draft Guidance notes that FDA recommends the DAP be submitted when a sponsor is seeking feedback during the applicable clinical study for a drug (typically at the end of Phase II meetings) or be included in the investigational device exemption (IDE) application (see lines 443-447). The Agency should flag any concerns with the proposed DAP during its review of the protocol or application and convey this information to the sponsor prior to commencement of the study. The Agency should also inform the sponsor of the point in the product development timeline that it expects to enforce the DAP.

FDA should streamline the documents required to be submitted to the Agency when a modified Diversity Action Plan is necessary.

Under Section VII of the Draft Guidance ("Procedures for Submitting the Diversity Action Plan and Receiving Feedback"), FDA has indicated that once an initial DAP has been submitted, a sponsor may submit a modified DAP. The Draft Guidance states that the submission must include a copy of the DAP with tracked changes, a clean version, and a summary of the modification and justification outlining the changes and the rationale for these changes (*i.e.,* three separate documents) (see lines 495-501 for drugs and lines 561-567 for medical devices). CHPA understands the need to have the red-line and clean versions of the modified DAP to facilitate efficient review and comparison. However, the information that would be provided in the summary document can be submitted with the tracked change version as comments where the changes occur, therefore eliminating the need for the summary section of the DAP. This allowance would have minimal adverse risk to public health. Furthermore, the reviewer would see the change and rationale for the edit without having to locate the related information in the summary section.

FDA should clarify the process for sponsors to engage in dialogue when the criteria of the DAP cannot be met.

The final version of the DAP guidance should explain or implement a mechanism for dialogue between a sponsor and the Agency if, despite best efforts, the sponsor cannot meet the DAP compliance date. FDA should also include details for how a sponsor should continue its development plan if it is unable to achieve the requested targets within the DAP after applying good faith efforts to do so. If other data exists to support the safety or efficacy of an OTC drug or device product, failure to attain the DAP target(s) alone should not be sufficient to deny approval for the nonprescription drug or medical device.

The DAP for a prescription drug approval should extend to the application for OTC drug approval if the same target population or intended use applies.

Prescription-to-nonprescription (Rx-to-OTC) drug switches typically use data previously reviewed and accepted to demonstrate the safety and efficacy of the prescription version of the medicine. If the holder of the original approved application included information for the DAP, those results should also apply to the switch application unless the product is expected to be used for a condition or subpopulation not anticipated at the time of the prescription approval. FDA should indicate its agreement with this position (*i.e.,* that the DAP information from the initial drug approval will apply to the OTC switch application under review) in the final version of the guidance once it is issued. If the Agency disagrees with CHPA's recommendation, the Agency should explain its position and engage in dialogue with the OTC drug industry to identify a reasonable approach for nonprescription drugs without compromising consumer safety.

The DAP should not carry undue weight in the assessment of the safety and efficacy data for approval of a nonprescription medicine or clearance of an OTC medical device.

Sponsors will be expected to and should undertake legitimate efforts to reach the their recruiting goals outlined within their DAPs for pre-market studies in support of safety or efficacy of the medical product as well as post-market studies once the drug or device has been approved. In the application for approval, a sponsor may include information about its efforts to attain its DAP goals in the final study report. If the sponsor has outlined reasonable efforts to enroll diverse subjects in clinical studies to demonstrate or support a safety or efficacy determination, the review process should not be adversely impacted if there is other information (*e.g.*, literature, study data) that is adequate and scientifically-sound to warrant approval of the pending application. The DAP information should not have equal weight as other data generated for condition of approval or clearance. As mentioned above, failure to reach the recruitment goals of the DAP should not be a stand-alone deciding factor during the Agency review process.

Thank you for the opportunity to provide recommendations to ensure the submission of Diversity Action Plans is effective yet not overly burdensome for sponsors. We believe these suggestions, if implemented, will accomplish the intent of the statute in a manner that is reasonable yet limits risk to end users of OTC medical products. Questions may be directed to me at the email address or phone number below.

Sincerely,

Marcia D. Howard, Ph.D., CAE

Digitally signed by Marcia D. Howard, Ph.D., CAE
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