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October 27, 2021

Celia M. Witten, Ph.D., M.D.
Deputy Director
Center for Biologics Evaluation and Research
Food and Drug Administration
WO-71, Room 7230
Silver Spring, MD 20993-0002

RE: Advisory committee composition for the upcoming hearing on the Center for Drug Evaluation and Research's proposal to withdraw approval of Makena (hydroxyprogesterone); Docket No. FDA-2020-N-2029

Dear Dr. Witten:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, is writing to express its views regarding the composition of the Food and Drug Administration's (FDA's) Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) for the upcoming hearing on the proposal to withdraw approval of Makena (hydroxyprogesterone) to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth, an action that we requested in our October 8, 2019, citizen petition to the agency.[1]

To ensure the integrity of the hearing process and public trust in the advice and recommendations provided by BRUDAC, the composition of the committee for the hearing must be fairly balanced in terms of the points of view represented; constituted in a manner to ensure independent judgment; and the members must have both relevant expertise and diverse professional education, training, and experience.

To that end, we strongly endorse the Center for Drug Evaluation and Research's (CDER's) position, stated in its October 7, 2021, letter to you,[2] that the BRUDAC membership for the hearing "should be composed of experts with scientific and medical expertise relevant to the issues involved in CDER's proposed withdrawal of Makena's approval and should have

[1] Public Citizen. Citizen petition to the Food and Drug Administration to withdraw the approval of all medications containing hydroxyprogesterone caproate, including the brand name product Makena, and to place this drug on the list of drug products that may not be used in pharmacy compounding. October 8, 2019. https://www.citizen.org/wp-content/uploads/2493.pdf. Accessed October 23, 2021.

[2] Hunt CB. Letter from the Center for Drug Evaluation and Research to the Food and Drug Administration's Celia Witten, Presiding Officer, regarding Docket No. FDA-2020-N-2029 (Makena); CDER response regarding advisory committee composition. October 7, 2021. https://www.regulations.gov/document/FDA-2020-N-2029-0079. Accessed October 23, 2021.

balanced representation of relevant scientific disciplines and perspectives." We also agree with CDER that a balanced committee for the hearing must include multiple members with expertise in biostatistics — including at least one member with expertise in meta-analysis — as well as members with expertise in epidemiology, neonatology, understanding real world evidence, and the regulation of pharmaceuticals.

Because of the need for such a balanced committee, it is imperative that you reject Covis Pharma GmbH's (Covis') proposal to essentially stack the jury in its favor by significantly expanding the BRUDAC roster for the hearing with individuals whom the company believes will be sympathetic to its view that Makena should remain on the market despite the lack of substantial evidence of the drug's effectiveness. In its October 7, 2021, letter to you,[3] Covis asserted that the hearing proceedings "[require] a significant proportion of practicing obstetricians who are maternal-fetal medicine (MFM) sub-specialists, including physicians with experience treating minority and high-risk patient populations." In earlier correspondence to the FDA, Covis requested the following:

> The hearing should include the participation of a new advisory committee with a greater proportion of representatives having substantial experience as treating obstetricians. Fewer than half of the prior Advisory Committee members were practicing obstetricians, let alone MFM…specialists. FDA and the public would benefit from an advisory committee with greater hands-on experience in the treatment of high-risk pregnancies and the use of Makena in U.S. populations, including minority and socioeconomically disadvantaged women.[4]

The BRUDAC composition for the hearing certainly should include practicing obstetricians who are MFM subspecialists, including physicians with experience treating minority and high-risk patient populations. However, Covis' apparent desire for at least half of the committee to be composed of such individuals would result in a committee that is not fairly balanced and thus would fail to ensure the integrity of the hearing process and public trust in the advice and recommendations provided by BRUDAC.

We recommend that no more than one-third of the voting members of the BRUDAC for the hearing be practicing obstetricians. We further recommend that if any of the practicing obstetricians on the committee currently prescribe hydroxyprogesterone to reduce the risk of preterm birth and of physicians, there should be an equal number of obstetricians on the committee who do *not* prescribe the drug for this purpose.

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[3] Wood RK. Letter from Sidley Austin LLP to the Food and Drug Administration's Celia Witten, Presiding Officer, regarding Docket No. FDA-2020-N-2029. https://www.regulations.gov/document/FDA-2020-N-2029-0077. Accessed October 23, 2021.

[4] Hinton DM. Letter from RADM Denise Hinton, Chief Scientist, Food and Drug Administration to Rebecca K. Wood, Sidley Austin LLP, and Vincent Amatrudo, Office of Chief Counsel, Food and Drug Administration, regarding FDA-2020-N-2029 (Makena). https://www.regulations.gov/document/FDA-2020-N-2029-0072. Accessed October 23, 2021.

Thank you for your consideration of our views on this important public health issue.

Sincerely,

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group

cc: RADM Denise Hinton, Chief Scientist, Food and Drug Administration