Ms. Jill Gilbert Escher
Escher Fund for Autism
1590 Calaveras Avenue
San Jose, CA 95126

FEB 14 2018

RE: Docket No. FDA-2015-P-0876

Dear Ms. Escher:

This letter responds to your citizen petition received on March 19, 2015 (Petition). In that Petition, you request that the Food and Drug Administration (FDA or the Agency) withdraw approval of 17-alpha hydroxyprogesterone caproate (17-HPC),[1] including the drug product Makena, as a drug used in pregnancy, pending assessment of potential deleterious impacts to the fetal germline. We have also reviewed the comments submitted by you to the docket, dated May 5, 2016, February 13, 2017, May 25, 2017, and February 5, 2018.

FDA has considered the information submitted in the Petition, the subsequent comments, and other relevant data. Based on our review of this information and for the reasons described below, the Petition is denied.

I. BACKGROUND

A. 17-alpha Hydroxyprogesterone Caproate

In 1956, 17-HPC was first approved as Delalutin (hydroxyprogesterone caproate) injection under new drug application (NDA) 010347, with labeling stating that the drug "appears to be useful in conditions generally responding to progestogens." In light of the statutory requirements for approval in place at the time, this approval was based solely on a finding of safety. Delalutin was later reviewed under the Drug Efficacy Study Implementation program, and certain indications were found to be effective (36 FR 18115, September 9, 1971; 38 FR 27947, October 10, 1973). In 1972, an indication for "control and palliation of advanced adenocarcinoma of the corpus uteri" was approved under NDA 016911.

The last approved labeling for Delalutin (1991)[2] stated the indications as follows:

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[1] In the Petition, the name of the drug substance was abbreviated as "17-OHPC," and that term was used throughout the Petition. We have used the abbreviation "17-HPC" for accuracy.

[2] NDA 010347 and NDA 016911 utilized the same labeling.

> Hydroxyprogesterone Caproate Injection USP is indicated in non-pregnant women: for the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV); in the management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer; as a test for endogenous estrogen production ("Medical D and C"); and for the production of secretory endometrium and desquamation.

On September 13, 1999, the sponsor requested withdrawal of approval of both NDAs (010347 and 016911). In 2000, FDA announced in the Federal Register that it was withdrawing approval of NDAs 010347 and 016911 effective September 30, 2000 (65 FR 55264, September 13, 2000). In 2010, FDA published its determination that Delalutin was not withdrawn for reasons of safety or effectiveness[3] (75 FR 36419, June 25, 2010).

A generic version of Delalutin, abbreviated new drug application (ANDA) 200271, was approved in 2015. This ANDA is labeled with the same indications as Delalutin, which, as noted above, did not include indications for use in pregnancy.

FDA has approved two other NDAs for products that contain 17-HPC as the active ingredient (NDA 017439 and NDA 018004); however, the available records indicate that NDA 017439, which has been discontinued from marketing, was not approved for use in pregnancy, and approval of NDA 018004 was withdrawn in 1995 (60 FR 50626, September 29, 1995). There were previously two other generic 17-HCP products, ANDA 089330 and ANDA 089331, but both were withdrawn in 1992 at the request of the application holder.[4]

In 2011, FDA approved NDA 021945 for Makena (hydroxyprogesterone injection), administered as a weekly intramuscular injection of 250 milligrams of 17-HPC. Makena was approved under the Agency's accelerated approval regulations, 21 CFR part 314, subpart H, and, under 21 CFR 314.510, the applicant was required to complete two clinical trials to verify and describe the product's clinical benefit. Makena is indicated to reduce the risk of preterm birth in women with a singleton pregnancy and who have a history of singleton spontaneous preterm birth. A preservative-free version of Makena was approved in February 2016. Makena is not indicated for use in the first 15 weeks of pregnancy.

B. Regulatory Framework

FDA only approves drug products for marketing in the United States if those products have been shown to be safe and effective for their proposed indication(s).[5] After an approved drug enters the marketplace, FDA may reassess its safety and consider whether changes in the available information concerning the product's risk-benefit profile call for regulatory action. Because the

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[3] The Petition indicates that withdrawal of approval of the NDA for Delalutin was associated with concerns about its effectiveness (Petition at 9). However, as reflected in the June 25, 2010, determination, FDA thoroughly reviewed the available information, including relevant literature and data for adverse event reports, and concluded that Delalutin was not withdrawn for reasons of either effectiveness or safety.

[4] 57 FR 6228 (Feb. 21, 1992).

[5] See section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)).

goal of postmarketing safety surveillance is to identify and prevent or mitigate emerging safety concerns before they can cause significant harm to patients, FDA may consider a broad range of new information relevant to a drug's potential serious risks or signals of serious risks (safety signals), including adverse event reports, peer-reviewed biomedical literature, and any other scientific data deemed appropriate by FDA.[6] FDA's assessment of postmarketing safety signals is governed by the same risk-benefit analysis and similar criteria as those used for drug approvals.[7]

If FDA concludes that a product's risk-benefit profile is unfavorable, it may take steps to withdraw approval of that application. Section 505(e)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)[8] (21 U.S.C. 355(e)(2)) authorizes FDA to withdraw the approval of a drug when consideration of new evidence of clinical experience, not contained in the NDA or not available until after the application was approved, or tests by new methods not deemed reasonably applicable when the application was approved, together with the evidence available to FDA when the application was approved, indicate that the drug "is not shown to be safe for use under the conditions of use upon the basis of which the application was approved."[9]

The criteria and procedures for withdrawing an approved application are detailed in FDA's regulations at 21 CFR part 314. In particular, § 314.150(a) permits FDA to initiate a formal withdrawal proceeding if it finds that new evidence, evaluated together with the evidence available at the time of approval, reveals that the drug is not shown to be safe for use under the conditions upon the basis of which it was approved.[10] Alternatively, FDA has the option of notifying an applicant that it "believes a potential problem associated with a drug is sufficiently serious that the drug should be removed from the market" and asking the applicant to (1) permit

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[6] See section 505-1(b)(5) and (b)(6) of the FD&C Act (separately defining "serious risk" and "signal of a serious risk"); section 505-1(b)(1) and (b)(6)(B) (distinguishing "adverse event" from a signal "derived from" adverse event information). Additional information on FDA's postmarketing surveillance programs can be found at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm090385.htm.

[7] FDA applies the same standards in both premarketing and postmarketing safety determinations because the underlying legal question in each case is the same: whether the drug product meets the statutory standard of safety. See, e.g., section 505-1(a)(1) to (2)(A) of the FD&C Act (21 U.S.C. 355-1(a)(1) to (2)(A)) (applying same risk-benefit analysis to unapproved and approved drug products), and compare FD&C Act sections 505(d) and 505(e) (applying similar requirements for refusing to approve an NDA and withdrawing an approved NDA on grounds of safety).

[8] Section 505(e)(1) of the FD&C Act authorizes withdrawal of approval when evidence shows that the drug is unsafe for use under the conditions of use upon the basis of which the application was approved.

[9] We note the statement on page 2 of the Petition that it is made "pursuant to 21 U.S.C. Sec. 355-1(b)(3) to present to the FDA 'new safety information' regarding a particular drug." Section 505-1(b) of the FD&C Act gives definitions of key terms used in section 505-1, which pertains to Risk Evaluation and Mitigation Strategies. Thus, while the definitions in that section are informative as to what types of safety information FDA considers, they do not on their own constitute a basis for withdrawal of approval of an application. Rather, FDA uses the standard articulated in section 505(e)(2) of the FD&C Act to withdraw approval of a product based on new evidence of clinical experience.

[10] Section 314.150(a)(2)(ii). "New evidence" can include clinical or other experience not contained in the application or not available to FDA when the application was approved, as well as tests by new methods or methods that were not deemed reasonably applicable when the application was approved.

FDA to withdraw approval of the product's NDA or ANDA, (2) waive its opportunity for a hearing under § 314.200,[11] and (3) voluntarily remove the product from the market.[12]

II. DISCUSSION

The Petition asks FDA to withdraw approval of 17-HPC, including the drug Makena, as a drug used in pregnancy, pending assessment of potential deleterious impacts to the fetal germline. In support of this request, the Petition explains the pharmacology of 17-HPC and its "hormone signal-disrupting properties," the history of the use of 17-HPC in obstetric practice, and that fetal germlines are vulnerable to epimutation caused by "hormone signal disruptors" such as 17-HPC. In light of this background, the Petition states that 17-HPC is a pregnancy medication that "drug[s] the DNA" of grand offspring (Petition at 2) and that "gametes exposed to [17-HPC] during the period of early germline programming are at increased risk of producing neurodevelopmental abnormalities in resulting offspring" (Petition at 14). The Petition focuses on the relationship between use of 17-HPC during pregnancy and autism and related neurodevelopmental abnormalities in subsequent generations.[13]

Note that Makena is currently the only approved drug product containing 17-HPC that is indicated for use in pregnancy,[14] and therefore we interpret the Petition's request as a request that FDA withdraw approval of Makena.

As explained in the Background section above, FDA will withdraw approval of a drug if new evidence shows that the drug is not safe, or not shown to be safe, under the conditions of use described in the approved labeling.[15] When FDA approves a drug, the Agency relies on "substantial evidence" derived from "adequate and well-controlled investigations" conducted by qualified experts, from which such experts could "fairly and responsibly" conclude that the drug

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[11] Section 314.200 sets out the procedures to be followed in withdrawing approved applications, including drug applicants' rights of notification, participation, and appeal.

[12] Section 314.150(d). See also 21 CFR 314.530, which provides withdrawal procedures for NDAs approved under 21 CFR 314.510 and 314.520.

[13] In the Petition, the action you request the Agency to take is to withdraw approval of 17-HPC as a drug used in pregnancy (Petition at 2). However, you also mention a number of other regulatory actions FDA could consider taking in response to the evidence presented, including issuing a general warning about the risks of 17-HPC and "other hormone signal-disrupting drugs"; taking steps to require that medical records permanently contain information about exposure to 17-HPC; and funding, mandating, or conducting certain studies. (Petition at 21-22). For the same reasons explained in this response, at this time there is insufficient evidence upon which the Agency would base the other listed regulatory actions regarding the use of 17-HPC in pregnancy. Similarly, with respect to your suggestion that the Agency "convene an expert committee to add the fetal germline to the scope of FDA testing protocols" (Petition at 22), we have not identified sufficient evidence that at this time would warrant convening an advisory committee to discuss whether and the extent to which this issue should be studied in clinical trials of the drug products we regulate. Finally, we also note that some of the options you reference in the Petition may be outside the scope of FDA's regulatory authority.

[14] As discussed above, the Agency has approved other 17-HPC products, including ANDAs. All previously approved NDAs and ANDAs that contained 17-HPC have either been withdrawn or were not indicated for use in pregnancy.

[15] See section 505(e)(1) and (e)(2) of the FD&C Act.

is effective under the conditions of use suggested in its labeling.[16] To assess a drug's safety, FDA examines evidence from "all methods reasonably applicable to show whether or not such drug is safe,"[17] including "pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs."[18] As discussed in the Background section of this response, FDA would rely on similar information to withdraw approval of a drug.[19]

In support of your request for withdrawal of approval, the Petition discusses studies, including those of the effects of 17-HPC on the first generation born to women who received it during pregnancy (the "F1" generation), case reports of incidents of autism in the grand offspring of women who received 17-HPC during pregnancy (the second or "F2" generation), temporal associations between the use of 17-HPC and the incidence of autism, consistency with autism etiology, and the germline effects of other synthetic hormone drugs. Nothing in the Petition (or any of the subsequent comments submitted by the Petitioner) provides a basis for FDA to change its prior finding that Makena (17-HPC) is safe and effective for its approved indication.[20] The

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[16] Section 505(d) of the FD&C Act. The characteristics of adequate and well-controlled studies are set forth in FDA regulations at 21 CFR 314.126. As stated in the regulation, these criteria were developed over many years of scientific and regulatory experience and are recognized by the scientific community as the essential elements of adequate and well-controlled investigations.

[17] Section 505(d)(1) of the FD&C Act (requiring FDA to deny any application lacking such information).

[18] 21 CFR 314.50(d)(5)(vi)(*a*); see also § 314.50(d)(5)(iv) (description and analysis of "any other data or information relevant to an evaluation of the [drug's] safety and effectiveness . . . from any source . . . including information derived from clinical investigations . . . commercial marketing experience, reports in the scientific literature, and unpublished scientific papers); 314.50(d)(2) (requirement for submission of nonclinical toxicology and pharmacology data).

[19] See notes 5 through 11 above.

[20] In your February 5, 2018, comment to the docket (Feb. 5, 2018, Comment), you assert that "the evidence is now clear that 17-HPC is ineffective at reducing preterm birth." Feb. 5, 2018, Comment at 1. In support of that position, you cite to a 2017 prospective cohort study, Nelson DB, McIntire DD, McDonald J, et al. 17-alpha Hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study. American Journal of Obstetrics and Gynecology, 2017:216(6):600.e1-600.e9. We disagree with your interpretation of that observational study and its implications because it has significant limitations that preclude reliable interpretation of the study findings. For example, the study uses a historical control, which is highly problematic as the basis for studying the effect of a drug in preterm delivery. Obstetric practices are constantly changing and frequently vary in different regions of the country, so in this clinical area, standards of care often differ between a historical control group and the study cohort. In addition, the study is also not generalizable to the broader population because it was conducted at only one center and the study cohort was mostly comprised of individuals of the same ethnicity. Because of these limitations, among others, the Nelson et al. study does not provide reliable evidence that 17-HPC is ineffective for its indicated use.

The Agency has determined that Makena is safe and effective for reducing the risk of preterm birth in women with a history of a preterm delivery when used in accordance with its approved labeling; as described in the Response, we have found no persuasive evidence that would call this determination into question, either in this study or elsewhere in the recent literature. We also disagree with the assertion in the Feb. 5, 2018, Comment that daily vaginal progesterone has been found to be a safer and preferable alternative to 17-HPC. There are no approved applications for vaginal progesterone for the same indication and population as Makena. Additionally, a 2016 study found that vaginal progesterone was not associated with reduced risk of preterm birth or composite neonatal adverse outcomes. Norman JE, Marlow N, Messow C-M, et al. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM

evidence relied upon in the Petition (and the subsequent comments), considered either individually or collectively, does not show that Makena is unsafe under its approved conditions of use and does not meet the statutory standard in section 505(e)(2) of the FD&C Act for withdrawal of approval based on new evidence of clinical experience.

A. Studies on Fetal Germline Vulnerability and Effects in the Proximal Generation

After reviewing the pharmacology of 17-HPC and the history of its use in obstetrics, the Petition discusses fetal germline vulnerability to adverse epigenetic effects ("epimutations") caused by "hormone signal disruptors" (Petition at 10-12). You assert that the administration of 17-HPC affects "the delicate process of fetal germline synthesis"—that is, that 17-HPC disrupts development of the "molecular material of heritability within fetal germ cells (egg and sperm precursors) that gives rise to the subsequent generation" (Petition at 1-2). According to the Petition, this disruption "drugs the DNA" of grand offspring (Petition at 2). In the Petition you state that "[b]ased on ever-accumulating evidence, there is now no question that hormone signal-disrupting substances can cause F1 germline epimutation via F0 gestational exposure" (Petition at 11). You cite a large number of studies in support of that statement (Petition at 11-12). After listing these studies, you state:

> In sum, fetal germline synthesis is an epigenetically dynamic and vulnerable phase of the human lifecycle, and research has repeatedly demonstrated that fetal germline programming is vulnerable to epimutations caused by steroid hormone signal disruptors. Not only is [17-HPC] a hormone signal disruptor, it is one introduced into the uterine environment in intentionally heavy, consistent doses during a dynamic phase of germline synthesis.

Petition at 13.

After discussing fetal germline vulnerability generally, your Petition turns to 17-HPC specifically, beginning with a discussion of studies of proximal fetal effects in the first (F1) generation (Petition at 14). The Petition states that adverse effects to the first generation of offspring of women who receive 17-HPC and "similar progesterone-like compounds" have been known since the 1970s (Petition at 14). You cite two studies, one from 1977[21] (in which you state you were a subject) and the other from 2007,[22] along with the classification of Makena as a "Category D" drug,[23] in support of your statement that 17-HPC is known to cause adverse fetal

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study): a multicentre, randomised, double-blind trial. *Lancet (London, England)*. 2016;387(10033):2106-2116. doi:10.1016/S0140-6736(16)00350-0).

[21] Reinisch JM, Karow WG. Prenatal exposure to synthetic progestins and estrogens: effects on human development. Arch Sex Behav. 1977;6:(4):257-288.

[22] Christian MS, Brent RL, Calda P. Embryo-fetal toxicity signals for 17alpha-hydroxyprogesterone caproate in high-risk pregnancies: a review of the non-clinical literature for embryo-fetal toxicity with progestins. J Matern Fetal Neonatal Med. 2007;20(2):89-112.

[23] Pregnancy categories are no longer used in drug labeling (79 FR 72064, 72073; December 4, 2014) and were removed effective June 30, 2015. Before the categories were removed, "Category D" was defined as follows:

effects in the first generation (Petition at 14). In your February 5, 2018, Comment, you also cite to a 2016 study that "documented adverse long-term consequences of 17-OHPC exposure during development on cognitive behavior of offspring."[24]

Your Petition also states that timing of administration of 17-HPC, in the second and third trimesters of pregnancy, not the first, is "of little relevance to the question of germline vulnerability" (Petition at 14, note 19).

FDA Response

We have thoroughly reviewed the many scientific articles cited in the Petition and the subsequent comments. We have also conducted our own independent search for relevant information on any association between administration of 17-HPC and development of autism spectrum disorder (ASD).

Based upon the scientific data currently available, we agree with the Petition that 17-HPC crosses the placenta.[25] Hormonally active compounds (endocrine disruptors), such as 17-HPC, have been demonstrated to induce epigenetic changes that are passed to subsequent generations.[26] However, the fact that placental transfer occurs does not in and of itself imply an effect on the fetal germline, and not all hormone signal disruptions result in clinically relevant adverse effects. We found no evidence that any placental transfer of 17-HPC is causally linked to adverse effects to the fetal germline.

Of the many articles you cite in the Petition, only one, the 2007 article by Christian et al., specifically addresses 17-HPC and its effects on fetal development.[27] That article reviewed existing nonclinical literature on 17-HPC and discussed two studies that reported a signal for embryo-fetal toxicity in animals. However, results of the two studies discussed are limited by study design, including that too few animals were used, animal strains were used for which there

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> there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).

73 FR 30831 at 30832 (May 29, 2008).

[24] Willing J, Wagner CK. Exposure to Synthetic Progestin, 17α-Hydroxyprogesterone Caproate During Development Impairs Cognitive Flexibility in Adulthood. Endocrinology 2016;157(1)1:77-82.

[25] Caritis SN, Sharma S, Venkataramanan R, et al. Pharmacology and placental transport of 17-hydroxyprogesterone caproate in singleton gestation. Am J Obstet Gynecol. 2012;207(5):398.e1-8; Hemauer SJ, Yan R, Patrikeeva SL, et al. Transplacental transfer and metabolism of 17-alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol. 2008;199(2):169.e1-5.

[26] Tammen SA, Friso S, Choi S-W. Epigenetics: the link between nature and nurture. Molecular Aspects of Medicine 34:753-764 (2013); Skinner MK. Role of epigenetics in developmental biology and transgenerational inheritance. Birth Defects Research (C) 93:51-55 (2011); Gluckman PD, Hanson MA, Low FM. The role of developmental plasticity and epigenetics in human health. Birth Defects Research (C) 93:12-18 (2011).

[27] See note 22, above. We note that this study did not address the effect of 17-HPC on subsequent generations.

are minimal historical data, and the studies did not conform to clinical use in dose, route of administration, or timing of administration. Given these limitations of the studies, among others, the authors concluded that the relationship between clinical and nonclinical findings is unclear. We also note that the Christian et al. article does not review any F2 generation data and does not comment on any potential effects of 17-HPC on subsequent generations.

The 1977 Reinisch and Karow study that you reference in the Petition[28] examined exposure to combinations of synthetic progestins and estrogen, which, according to the Petition, included 17-HPC in your case. However, that study did not conclude that there were any adverse effects from exposure to 17-HPC or other progestins. Rather, the study concluded that there was no difference in IQ between the three treatment subgroups. The study determined that progestin-exposed subjects were characterized as more independent, sensitive, self-assured, individualistic, and self-sufficient.

The 2016 Willing et al. study discussed in your Feb. 5, 2018, Comment described an evaluation of rats that were postnatally exposed to 17-HPC. Willing et al. concluded that the exposed rats suffered impaired cognitive flexibility in adulthood.[29] However, that study evaluated the effects of postnatal exposure rather than the prenatal exposure for which Makena is approved. The nonclinical and clinical data submitted with the Makena NDA, which were found to support approval of the NDA, did not suggest adverse neurodevelopmental outcomes related to exposure to 17-HPC.

In light of the foregoing, neither the 2007 Christian et al. article, the 1977 Reinish and Karow study, nor the 2016 Willing et al. study provides evidence that Makena is not safe for its approved conditions of use.

The studies described in the other articles you cite in the Petition were not specific to 17-HPC[30] or its association with ASD, if any. We note that the assessment of any link between maternal exposure to 17-HPC and ASD in subsequent generations is challenging given that women who are given 17-HPC are at risk of preterm delivery for various reasons, and premature birth itself

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[28] See note 21, above.

[29] See note 24, above.

[30] The Petition acknowledges that "there are no clinical trials of germline effects of 17-OHPC known to Petitioner, or any third-generation phenotype studies to date" (Petition at 20). However, the Petition states that this lack of data is "a sign of the incomplete risk paradigm employed by the FDA and the broader medical/pharmaceutical community, and not suggestive of any inherent lack of germline risk posed by this endocrine disrupting chemical" (Petition at 20). While we are not aware of circumstances where FDA has required drug applicants to conduct clinical trials of germline effects, we disagree that failure to require such studies represents an "incomplete risk paradigm." As described in this response to your Petition, FDA has not identified evidence of risk that would justify requiring applicants to conduct clinical trials of germline effects of 17-HPC or multigenerational clinical trials. Although it is not possible to identify all safety concerns related to a drug product either prior to approval or based on post-approval clinical trials, FDA requires postmarketing safety data collection and risk assessment. When new risks are identified from postmarketing use (or from additional clinical or nonclinical trials conducted post-approval), FDA will take the necessary steps to reevaluate findings of safety and effectiveness, including convening an advisory committee if appropriate. As discussed in this response, to date, we have not identified such risks here.

has been associated with adverse neurodevelopmental outcomes.[31] It might also be possible that offspring of women with gestational diabetes or other metabolic conditions in pregnancy might have an increased risk of ASD.[32]

We also do not agree with your assertion that the timing of administration of 17-HPC is "of little relevance to the question of germline vulnerability." Epigenetic[33] mechanisms are critical during the first trimester of pregnancy, when the zygote transforms to become the blastocyst, gonads are differentiated, and prespermatogonia and primary oocytes are formed.[34] The critical window for any exogenous environmental effects, including that of a hormone signal disruptor, is during the first trimester (i.e., 12 weeks of pregnancy).[35] As noted above in the Background section, Makena is not indicated for use until 16 weeks of gestation.

The Petition notes certain embryo-fetal toxicity data observed in clinical and nonclinical trials of 17-HPC. The labeling of Makena contains accurate and current evidence regarding embryo-fetal toxicity. The labeling also provides the results of the follow-up study with Makena referenced above, in which 194 children of Makena-treated women were compared with control subjects. That study found that the proportion of children who met the screening threshold for developmental delay was similar for each treatment group. The risks associated with the use of

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[31] Hwang YS, Weng SF, Cho CY, Tsai WH. Higher prevalence of autism in Taiwanese children born prematurely: a nationwide population-based study. Res Dev Disabil. 2013 Sep;34(9):2462-2468; Lampi KM Lehtonen L, Tran PL, et al. Risk of autism spectrum disorders in low birth weight and small for gestational age infants. J Pediatr. 2012 Nov;161(5):830-836; Schendel, D., Bhasin TK. Birth Weight and Gestational Age Characteristics of Children With Autism, Including a Comparison With Other Developmental Disabilities, Pediatrics 2008;121(6):1155–1164; Larsson, HJ, Eaton WW, Madsen KM, et al. Risk Factors for Autism: Perinatal Factors, Parental Psychiatric History, and Socioeconomic Status. Am J Epidemiol 2005;161(10):916–925.

[32] Xu G, Jing J, Bowers K, et al. Maternal diabetes and the risk of autism spectrum disorders in the offspring: a systematic review and meta-analysis. J Autism Dev Disord. 2014 Apr;44(4):766-775; Xiang AH, Wang X, Martinez MP, et al. Association of maternal diabetes with autism in offspring. JAMA. 2015 Apr 14;313(14):1425-1434.

[33] "Epigenetics" has been defined as "molecular factors and processes around DNA that regulate genome activity independent of DNA sequence and are mitotically stable." Skinner MK, Manikkam M, Guerro-Bosagna C. Epigenetic transgenerational actions of endocrine disruptors. Reprod. Toxicol. 2011; 31:337-343. See also Berger SL, Kouzarides T, Shiekhattar R, Shilatifard A. An opertational definition of epigenetics.Genes & Development. 2009.23:781-783 ("An epigenetic trait is a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence.").

[34] Messerschmidt DM, Knowles BB, Solter D. DNA methylation dynamics during epigenetic reprogramming in the germline and preimplantation embryos. Genes Dev. 2014;28(8):812-828.

[35] E.g., Skinner MK. Role of epigenetics in developmental biology and transgenerational inheritance. Birth Defects Research (C) 93:51-55 (2011); Hales BF, Grenier L, Lalancette C, Robaire B. Epigenetic programming: From gametes to blastocyst. Birth Defects Research (a) 91:652-665 (2011); Inbar-Feigenberg M, Choufani S, Butcher DT, Roifman M, Weksberg R. Basic concepts of epigenetics. Fertility and Sterility 99(3):607-615 (2013); McCarrey JR. The epigenome as a target for heritable environmental disruptions. Molecular and Cellular Endocrinology 354:9-15 (2012); O'Rahilly R, Muller F. Human Embryology and Teratology. Wiley-Liss, New York NY (1992).

Makena that you point out in the Petition are fully disclosed in the labeling, which allows health care providers to weigh the risks and benefits of prescribing Makena to their patients.[36]

In sum, in our review of the studies cited in the Petition, as well as in the course of our independent research, we found no evidence from published literature describing either animal or human data that supports the Petition's claim that 17-HPC is not safe for use in pregnancy. There is no evidence in the cited studies or that we are aware of in the published literature that would cause FDA to reevaluate its prior determination that Makena is safe and effective for its indicated use or to withdraw approval of Makena..

B. Case Reports Discussed in the Petition

In addition to discussing scientific literature on proximal fetal effects in the Petition, you support the claim that there are adverse effects in subsequent generations in part by pointing to case reports of autism and other neurodevelopmental disorders in subsequent generations born to women who you state were administered 17-HPC during pregnancy (Petition at 14-16). Specifically, you list 15 children who you assert have been diagnosed with autism or related disorders and who you state have grandmothers who were treated with 17-HPC (Petition at 15). You further state that these individuals' families had no history of autism or developmental abnormalities (Petition at 15). You claim that these case reports support the argument that "gametes exposed to 17-OHPC during the period of early germline programming are at increased risk of producing neurodevelopmental abnormalities in resulting offspring" (Petition at 14).

FDA Response

We have reviewed the information submitted with the Petition,[37] and we disagree that the case reports described in the Petition, either individually or collectively, indicate a safety signal associated with the use of Makena in pregnancy. It is important to note that ASD is a neurodevelopmental disorder with no known causes at present, and it is likely to have multifactorial causes.[38] Spontaneous reports such as those in the Petition cannot explain the

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[36] We note your assertion in the Feb. 5, 2018, Comment that the Nelson study, Nelson DB, McIntire DD, McDonald J, et al. 17-alpha Hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study. American Journal of Obstetrics and Gynecology, 2017:216(6):600.e1-600.e9, shows that 17-HPC "increases the risk of maternal diabetes in the exposed mother." Feb. 5, 2018, Comment at 2. For the reasons described above, the conclusions of the 2017 Nelson study are not reliable. Further, the Makena labeling currently describes the numerical imbalance in gestational diabetes in Makena-treated women from the adequate and well-controlled phase 3 trial that supported the initial approval of Makena. This information in the labeling provides adequate notice to health care practitioners on this issue.

[37] Under 21 CFR 10.20(c), a citizen petition is required to contain all relevant information on which the petitioner relies.

[38] An, J.Y. and C. Claudianos, Genetic heterogeneity in autism: From single gene to a pathway perspective. Neurosci Biobehav Rev, 2016. 68: p. 442-453; DiLalla, L.F., M. McCrary, and E. Diaz, A review of endophenotypes in schizophrenia and autism: The next phase for understanding genetic etiologies. Am J Med Genet C Semin Med Genet, 2017. 175(3): p. 354-361.

genetic causes of autism, if any, and do not provide a sufficient basis to conclude that there is a causal association between ASD and the use of 17-HPC in pregnancy.

Although spontaneous adverse event reports are not the best source of information for linking adverse events to exposures that may have occurred across generations, we searched the FDA Adverse Event Reporting System (FAERS)[39] for any reports of ASD associated with 17-HPC. None of the reports identified as part of that search indicated ASD associated with the use of 17-HPC, nor were any outcomes reported for subsequent generations. We also conducted a postmarketing safety review for Makena under section 915 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), which did not identify any new safety concerns, including autism, not already reflected in the approved labeling.[40]

In light of the foregoing, there is insufficient evidence from any case reports upon which to base a change to FDA's previous determination that Makena is safe and effective for its approved conditions of use, or that would lead FDA to withdraw approval of Makena.

C. Temporal Associations

According to the Petition, a third arena of evidence supporting withdrawal of Makena's approval is the temporal association between its use and a dramatic increase in cases of autism (Petition at 16-18). You state that 17-HPC was first introduced in 1956, with births of the first subsequent generation approximately 22 years later, followed by births of the second generation after another 23 years (Petition at 16). You point out that the number of cases of autism rose dramatically between 1956 and 1980, and you describe data on cases of autism in California at length (Petition at 14-15). Your Petition also states that there is evidence of increased autism prevalence in areas where you assert synthetic hormone drugs were more commonly used, including West Los Angeles and New Jersey (Petition at 18).

FDA Response

When interpreting reported incidence and prevalence rates for ASD, it is important to take into consideration the historical context of changes in the conceptualization of ASD over time. While the first studies of the prevalence of autism were published during the 1960s, the diagnostic criteria for autism were not formalized until the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) was published in 1980. Over time, ASD has come to be understood as embodying a heterogeneous set of behavioral characteristics and a wide range of levels of functional impairment. The diagnostic criteria for ASD changed in 1994 with the

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[39] We acknowledge that, due to the voluntary nature of adverse event reporting, FDA does not receive all adverse event reports that occur with a product, and the number of patients actually using a product is frequently difficult to determine. Consequently, FAERS data cannot be used to calculate the incidence or occurrence rate of an adverse event in the population or to compare products to determine the safety of different product dosages or formulations.

[40] See https://wayback.archive-it.org/7993/20170111133810/http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm465730.htm. More information about Postmarket Drug and Biologic Safety Evaluations conducted under section 915 of FDAAA is available at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/ucm204091.htm.

publication of the fourth edition of the DSM, and again in 2013 with publication of the fifth edition of the DSM. Some patients who met the criteria for the diagnosis of ASD at one point in time may not have qualified for the diagnosis under previous classification systems. There has also been an increase in awareness of autism in the general public. Training in recognizing the signs of autism has increased in health care, educational, and social service settings. The Centers for Disease Control and Prevention (CDC) now recommends that all children be screened by a pediatrician for autism three times by the age of 3 years. It is possible that these historical changes have contributed in part to increased recognition and reporting of the diagnosis of ASD.[41]

We agree that the rise in the number of Californians with ASD (a rise of 1,148% between 1987 and 2007) is significant, and that the trend is continuing. We note that the report on California data that you cite in the Petition includes this disclaimer:

> The information presented in this report is purely descriptive and should not be used to draw scientifically valid conclusions about the incidence or prevalence of ASD in California. Numbers of people with ASD described in this report reflect point-in-time counts and do not constitute formal epidemiological measures of incidence or prevalence. The information contained in this report is limited by factors such as case finding, accuracy of diagnosis, hand entry, and possible error, by case workers of large amounts of information onto state forms.[42]

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[41] You state in the Petition that studies have repeatedly shown that the dramatic increase in autism is not due to better ascertainment or more awareness. Petition at 17-18. We believe it is important to recognize the historical context of changes in diagnosis and recognition of autism, while at the same time acknowledging that the reasons for the increase in autism prevalence remain unclear. See, e.g., Autism and Developmental Disabilities Monitoring Network, Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. MMWR Surveill Summ, 2012. 61(3): p. 1-19 (stating that "the extent to which these increases reflect better case ascertainment as a result of increases in awareness and access to services or true increases in prevalence of ASD symptoms is not known"; Wazana, A., M. Bresnahan, and J. Kline, The Autism Epidemic: Fact or Artifact? Journal of the American Academy of Child & Adolescent Psychiatry, 2007. 46(6): p. 721-730 (analysis suggesting that broadening diagnostic criteria, younger age at diagnosis, and improved efficiency of case recognition could result in variations in the measured frequency of ASD over time); Leonard, H., et al., Unpacking the complex nature of the autism epidemic. Research in Autism Spectrum Disorders, 2010. 4(4): p. 548-554 (discussing multiple possible explanations for the apparent increase in the frequency of diagnosis of ASD, including changes in diagnostic criteria, earlier age at diagnosis, differing methodologies across studies for confirming a diagnosis after initial screening, differing statistics used to estimate ASD prevalence, and the phenomenon of diagnostic substitution); Shattuck, P.T., The Contribution of Diagnostic Substitution to the Growing Administrative Prevalence of Autism in US Special Education. Pediatrics, 2006. 117(4): p. 1028 (noting that the apparent increase in prevalence of ASD from 1994 to 2003 was associated with corresponding declines in the use of other diagnostic categories, suggesting a potential influence of diagnostic substitution on changes in prevalence rates); Matson, J.L. and A.M. Kozlowski, The increasing prevalence of autism spectrum disorders. Research in Autism Spectrum Disorders, 2011. 5(1): p. 418-425 (concluding that the change in diagnostic criteria over time has had a significant influence on reported prevalence rates of ASD).

[42] Cal. Dept. Developmental Services. Autistic Spectrum Disorders, Changes in the California Caseload, An Update: June 1987-June 2007, at 3, available at http://www.dds.ca.gov/Autism/docs/AutismReport_2007.pdf.

We also agree that the prevalence of children in New Jersey with ASD cited in the Petition is notable (1 in 45, compared with an average of 1 in 69 in all areas of the United States where the CDC tracks ASD).[43]

However, we found no data to support a connection between this rise and the use of 17-HPC. In the absence of data, any connection between the use of 17-HPC and the increase in the incidence of ASD is speculative at best. As noted above, there is no known cause of autism, and the observed trends of rising rates of autism could be explained by many other factors.

In light of the foregoing, the temporal associations cited in the Petition do not provide evidence that would cause FDA to reevaluate its prior determination that Makena is safe and effective for its indicated use or to withdraw approval of Makena.

D. Consistency with Autism Etiology

In the Petition, you next discuss the etiology of autism. You state that epigenomic marks play an important role in brain development, and that neurological development "may be particularly affected by even subtle alterations in DNA methylation" (Petition at 18). You further state that "[e]vidence is mounting that epigenetic dysregulation in the germline contributes to autism risk," and you cite several studies in support of that statement (Petition at 19). You contend that ASD risk increases with parental endocrine abnormalities and that grandparental associations to ASD in the F2 generation have been observed (Petition at 19).

FDA Response

To date, there is no known etiology of autism. We do not agree that the Petition's description of the etiology of autism indicates a safety signal or otherwise raises a concern about the relationship between administration of 17-HPC during pregnancy and the incidence of ASD in offspring.

As noted above, we have thoroughly reviewed the many scientific articles cited in the Petition and subsequent comments and independently searched for relevant information on any association between administration of 17-HPC and development of ASD. The studies described in the articles you cite in this section of the Petition[44] do not address 17-HPC directly or indirectly and do not provide any evidence that 17-HPC is associated with an increased risk of ASD in subsequent generations. For example, the study that you cite regarding grandparental associations to ASD—a 2013 study of the relationship between grandparental and parental age and the risk for autism—suggests that grandparental age might contribute to certain neurodevelopmental disorders in offspring.[45] You also cite a 2014 study of methylation differences in twins discordant for autism,[46] among various other studies, for the position that

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[43] CDC. Autism Spectrum Disorder (ASD), available at http://www.cdc.gov/ncbddd/autism/addm.html.

[44] See section B.4.b.iii of the Petition, pages 18-19.

[45] Frans EM, Sandin S, Reichenberg A, et al. Autism risk across generations: a population-based study of advancing grandparental and parental age. JAMA Psychiatry. 2013;70(5):516-521.

[46] Wong et al. Methylomic analysis of monozygotic twins discordant for autism spectrum disorder and related behavioral traits. Molecular Psychiatry (2014) 19, 495-503.

"[e]vidence is mounting that epigenetic dysregulation in the germline contributes to autism risk" (Petition at 19). But like the other studies that you reference, neither of these studies assess the relationship between 17-HPC and the development of autism. Similarly, we found no evidence in our independent research linking the two.

Accordingly, there is no evidence from the etiology of autism that would cause FDA to reevaluate its prior determination that Makena is safe and effective for its indicated use or to withdraw approval of Makena.

E. Germline Effects of Other Synthetic Hormone Drugs

Finally, in the Petition you discuss the germline effects of other synthetic hormone drugs, specifically diethylstilbestrol (DES) and dexamethasone (DEX) (Petition at 19-20). You state that DES is the synthetic hormone drug that provides "[t]he best-known case of germline and generational effects of synthetic chemicals," although you acknowledge that neurodevelopmental impacts associated with DES have not been investigated (Petition at 19-20). Your Petition also discusses increases in rate of germ cell death observed with DEX exposure, and you conclude that "fetal exposure to hormone-signal disrupting compounds during the critical period of reproductive organ development and germ cell division has been shown to have deleterious effects" (Petition at 20).

FDA Response

We have reviewed the studies that you cite in the Petition regarding possible effects of DES and DEX on fetal development. We agree that prenatal exposure to DES, a synthetic estrogen that was used in the early first trimester for treatment of miscarriage, has been linked with numerous detrimental effects, including reproductive tract abnormalities and a low but significant increase in vaginal cancer in the F1 generation.[47] Also, studies in rats indicate that DEX has been shown to increase susceptibility to autoimmune disease in the F1 generation.[48] However, we have not found any evidence that these study results for DES or DEX indicate that similar detrimental effects would occur with prenatal exposure to 17-HPC. Moreover, these data are not relevant for FDA's review of the safety of 17-HPC since epigenetic alterations such as those that may be linked to prenatal exposure to DES or DEX occur early in the first trimester of fetal development; however, Makena is not indicated for use during this period of gestation. Therefore, we are not aware of any evidence from the germline effects of DES and DEX that leads FDA to reevaluate its prior determination that Makena is safe and effective for its indicated use or to withdraw approval of Makena.

F. Culmination of All Data

As noted in each of the prior sections of this response, FDA considered all the information discussed in the Petition and evaluated the data carefully when considering whether you had

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[47] Newbold RR. Lessons learned from perinatal exposure to diethylstilbestrol. Toxic Appl Pharmacol. 2004 Sep;199(2):142-150.

[48] Sun Y, Wan X, Ouyang J, et al. Prenatal dexamethasone exposure increases the susceptibility to autoimmunity in offspring rats by epigenetic programing of glucocorticoid receptor. Biomed Res Int. 2016;2016:9409452, 9 p.

presented any evidence of a safety concern associated with the use of Makena. As discussed above, the data you presented in the Petition do not demonstrate a connection, or the possibility of a connection, between 17-HPC and ASD in subsequent generations. We have found no evidence in the Petition, or through the Agency's independent research, that would cause FDA to reevaluate its prior determination that Makena is safe and effective for its indicated use or to withdraw approval of Makena.[49] Thus, your request that FDA withdraw approval of Makena is denied.

However, we share your concern that FDA-approved products be safe and effective for their indicated uses, and the Agency will continue to monitor available evidence concerning the epigenetic effects of products indicated for use in pregnancy, including 17-HPC. Makena currently is being further evaluated through the confirmatory clinical trials required as a condition of its approval. These trials are designed to evaluate a potential signal for early pregnancy loss, as well as to conduct developmental assessment (and where indicated, a neurological evaluation) of infants born to women treated with Makena.[50]

III. CONCLUSION

For the reasons described above, your Petition is denied. FDA will continue to monitor available evidence of safety concerns associated with the use of 17-HPC and other drugs indicated for use in pregnancy, including information concerning the epigenetic effects of the products we regulate, and if warranted, FDA will take appropriate regulatory action to protect the public health.

Sincerely,

/S/ for

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

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[49] Nor, as we noted supra note 13, does any of the information presented in the Petition, or identified by the Agency, support our taking any of the other regulatory actions suggested on pages 21-22 of the Petition.

[50] We acknowledge that this trial is limited to the first generation of offspring and will not evaluate outcomes in subsequent generations.