Meena Aladdin, MS, PhD
Sidney M. Wolfe, MD
Michael A. Carome, MD
Public Citizen's Health Research Group
1600 20th Street NW
Washington, DC 20009

October 5, 2020

Re: Docket No. FDA-2019-P-4683

Dear Drs. Aladdin, Wolfe, and Carome:

This letter responds to your citizen petition received on October 8, 2019 (Petition). Your Petition requests that the Food and Drug Administration (FDA or the Agency) immediately: (1) withdraw approval of all medications containing hydroxyprogesterone caproate (HPC), which is currently approved and marketed under the brand name Makena and multiple generic formulations; and (2) place HPC on the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness and therefore may not be compounded under the exemptions provided by sections 503A(a) or 503B(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353a and 353b).[1] You state that you request these actions because the postapproval confirmatory trial required as a condition of accelerated approval for the new drug application (NDA) for Makena (NDA 021945) failed to verify that the drug provides clinical benefit. More specifically, you state that the confirmatory trial "failed to demonstrate that hydroxyprogesterone caproate is effective for its approved indication of reducing the risk of preterm birth in women with a singleton pregnancy and a history of singleton spontaneous preterm birth or . . . that it decreases the risk of fetal and neonatal morbidity or mortality."[2]

We carefully have considered the Petition, as well as the comment submitted by Makena's sponsor, AMAG Pharmaceuticals, dated January 21, 2020. For the reasons explained below, we are denying your request that we "immediately" take the two actions requested in your Petition. FDA's Center for Drug Evaluation and Research (CDER) is initiating proceedings to withdraw approval for Makena on the grounds that the confirmatory trial failed to verify clinical benefit, and that Makena is not shown to be effective. If withdrawal is contested by the sponsor of Makena, the ultimate decision regarding withdrawal will be made by the Commissioner or his designee.[3] If that process results in withdrawal of approval of Makena, withdrawal of the generic formulations that reference Makena will follow.[4] CDER declines to take any action at this time regarding the approval of generic HPC products referencing an HPC product other than

[1] Petition at 1.

[2] Id.

[3] Section 506(c)(3); 21 CFR 314.530.

[4] See generally sections 505(e) and (j)(6); 21 CFR 314.151.

Makena, which are not approved for reducing the risk of preterm birth. Finally, whether drug products containing HPC may be added to the withdrawn or removed list under sections 503A and 503B of the FD&C Act would depend on whether such drug products have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective. Currently, drug products containing HPC have approved applications in effect and remain marketed. Moreover, the addition of drug products containing HPC to the withdrawn or removed list would require rulemaking. For these reasons, FDA denies your request to immediately place drug products containing HPC on the withdrawn or removed list.

I. BACKGROUND

A. Approved HPC Products

1. Makena and ANDAs Citing Makena as the Reference Listed Drug (RLD)[5]

On February 3, 2011, FDA approved NDA 021945 for Makena (hydroxyprogesterone caproate injection, 250 milligrams (mg) per milliliter (mL), once weekly) under the accelerated approval pathway (section 506(c) of the FD&C Act and § 314.510 (21 CFR part 314, subpart H)) to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.[6]

The Makena NDA relied on data from the Maternal Fetal Medicine Unit (MFMU) Network (referred to as "Trial 002") for primary support of efficacy and safety.[7] The primary efficacy endpoint in Trial 002 was the proportion of pregnant women delivering prior to 37 weeks gestation, a surrogate endpoint considered reasonably likely to predict clinical benefit (reduced morbidity and mortality) to the neonate. Trial 002 showed that Makena reduced the proportion of women who delivered less than 37 weeks gestation (55 percent with placebo versus 37 percent with Makena).

FDA's February 3, 2011 approval letter for NDA 021945 described the following postmarketing confirmatory study requirements: (1) completion of a clinical trial of HPC in women with a singleton pregnancy who had a previous spontaneous preterm birth (Protocol #17P-ES-003); and (2) completion of the clinical follow-up study (Protocol #17P-FU-004) of children born to

[5] A *listed* drug is a drug that FDA has approved (21 CFR 314.3). A *reference listed drug* is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (§ 314.3(b)). RLDs are identified the Orange Book, available at http://www.accessdata.fda.gov/scripts/cder/ob/.

[6] See Makena's approved labeling at 1-2, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021945s000lbl.pdf.

[7] Meis, PJ, M Klebanoff, E Thom, MP Dombrowski, et al., 2003, Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate, N Engl J Med, 348(24):2379-2385.

women who participated in Protocol #17P-ES-003.[8] Eight approved ANDAs referenced Makena as the basis of submission, and, accordingly, the products approved under those ANDAs have the same labeling as Makena: ANDAs 210724, 210723, 211777, 211071, 210877, 211070, 210618 and 208381.

2. Delalutin and ANDAs Citing Delalutin as the RLD

HPC first was approved by FDA in 1956 under the name Delalutin injection, 125 mg/mL and 250 mg/ml (NDA 010347), last held by Bristol-Myers Squibb (BMS).[9] The last approved labeling for Delalutin (1991)[10] states the indications as follows:

> 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.[11]

Delalutin was not indicated to reduce the risk of preterm birth in any population.

By letter dated September 13, 1999, BMS, stating that Delalutin had not been marketed for several years, requested that FDA withdraw its approval. FDA announced in the *Federal Register* of September 13, 2000, that it was withdrawing approval of NDAs 010347 and 016911, effective September 30, 2000.[12] In June 2010, FDA published its determination that Delalutin was not withdrawn from sale for reasons of safety or effectiveness (relisting determination).[13]

Accordingly, Delalutin continues to appear in FDA's *Approved Drug Products with Therapeutic Equivalence Determinations* (the Orange Book), which includes, among other things, drug products that have been discontinued from marketing for reasons other than safety or

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[8] See the Accelerated Approval letter, p. 2, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/021945s000ltr.pdf.

[9] Delalutin (NDA 010347) originally was approved based on safety information and was later reviewed for efficacy under the Drug Efficacy Study Implementation (DESI) program (see 36 FR 18115, September 9, 1971; 38 FR 27947, October 10, 1973). In 1970, a supplement to NDA 010347 was submitted for an additional indication for control and palliation of advanced adenocarcinoma of the corpus uteri. Because this supplement proposed a new indication, in accordance with FDA policy at the time, FDA reviewed it as an original NDA (NDA 016911) and approved it as safe and effective in 1972. Both NDA 010347 and NDA 016911 cover the same drug product, Delalutin.

[10] Both NDAs 010347 and 016911 utilize the same labeling (see 75 FR 36419 at 36420, June 25, 2010).

[11] 75 FR 36419, June 25, 2010.

[12] 65 FR 55264, September 13, 2000 (see also 75 FR 36419 at 36420, June 25, 2010).

[13] 75 FR 36419, June 25, 2010.

effectiveness. FDA's relisting determination for Delalutin further indicated that ANDAs that refer to Delalutin may continue to be approved by the Agency as long as they meet all relevant legal and regulatory requirements.[14]

FDA has approved two ANDAs that referenced Delalutin: ANDAs 200271 and 211142. These ANDAs are labeled with the same indications as Delalutin. Importantly, neither ANDA 200271 nor ANDA 211142 is labeled with an indication regarding the risk of preterm birth.

B. Statutory and Regulatory Framework

1. Accelerated Approval Pathway

Accelerated approval allows for expedited approval of drugs intended to treat serious diseases or conditions that generally provide a benefit over available therapy. Accelerated approval can be based on a drug's effect on a surrogate or intermediate clinical endpoint that is "reasonably likely . . . to predict [a drug's] clinical benefit."[15] For purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but it is not itself a measure of clinical benefit.[16]

Accelerated approval generally is subject to the requirement that "the sponsor conduct appropriate postapproval studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit."[17] Under section 506(c)(3) of the FD&C Act and § 314.530, FDA may withdraw approval of a drug approved under accelerated approval if, among other reasons, a required postapproval confirmatory study fails to verify and describe clinical benefit.

2. ANDA Approval Pathway

The ANDA approval process established by the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) is set forth in section 505(j) of the FD&C Act. To obtain approval, an ANDA applicant is not required to submit evidence establishing the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the RLD is safe and effective. To rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its drug

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[14] 75 FR 36419 at 36421, June 25, 2010.

[15] Section 506(c)(1)(A) of the FD&C Act (21 U.S.C. 356(c)(1)(A))(see also § 314.510 (21 CFR 314.510)).

[16] See FDA's guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014) (Expedited Programs Guidance) at 17. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[17] Section 506(c)(2)(A) of the FD&C Act; 21 CFR 314.510.

product is bioequivalent to the RLD.[18] In addition, an ANDA must contain, with certain exceptions not relevant here, information to show that the proposed drug has the same active ingredient(s), indications for use, route of administration, dosage form, strength, and labeling as the RLD.[19]

3. Withdrawn or Removed List

Section 503A of the FD&C Act describes the conditions under which a human drug product compounded by a licensed pharmacist or licensed physician for an identified individual patient based on a prescription is exempt from three sections of the FD&C Act: (1) section 501(a)(2)(B) (concerning current good manufacturing practice); (2) section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and (3) section 505 (concerning the approval of new drugs under NDAs or ANDAs).[20] One of the conditions that must be satisfied to qualify for the exemptions under section 503A of the FD&C Act is that the licensed pharmacist or licensed physician does not compound a drug product that appears on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective (see section 503A(b)(1)(C) of the FD&C Act). Section 503A(c)(1) of the FD&C Act also states that the Secretary shall issue regulations to implement section 503A, and that before issuing regulations to implement section 503A(b)(1)(C) pertaining to the withdrawn or removed list, among other sections, the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health.

Section 503B of the FD&C Act describes the conditions under which human drugs compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility are exempt from three sections of the FD&C Act: (1) section 502(f)(1); (2) section 505; and (3) section 582 (concerning drug supply chain security requirements).[21] One of the conditions in section 503B of the FD&C Act that must be satisfied to qualify for the exemptions is that the drug does not appear on a list published by the Secretary of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective (see section 503B(a)(4)). To be eligible for the exemptions in section 503B, a drug must be compounded in an outsourcing facility in which the compounding of drugs occurs only in accordance with section 503B, including as provided in section 503B(a)(4) of the FD&C Act.

Given that nearly identical criteria are described in section 503A(b)(1)(C) and section 503B(a)(4) of the FD&C Act, these conditions have been implemented through the publication of a single list in the *Federal Register* of drug products that have been withdrawn or removed from the

[18] Section 505(j)(2)(A)(iv) of the FD&C Act.

[19] Section 505(j)(2)(A) of the FD&C Act.

[20] Section 503A(a) of the FD&C Act.

[21] Section 503B(a) of the FD&C Act.

market because such drug products or components of such drug products have been found to be unsafe or not effective.[22] This list (referred to as ''the withdrawn or removed list'' or ''the list''), which has been developed through the notice-and-comment rulemaking process, is codified in the Code of Federal Regulations (CFR) at 21 CFR 216.24.

Regulations are issued from time to time to revise the withdrawn or removed list.[23] Before regulations to amend the withdrawn or removed list are issued, the FDA Pharmacy Compounding Advisory Committee (PCAC) is convened and consulted, unless a determination is made that the issuance of such regulations before consultation is necessary to protect the public health.[24] A *Federal Register* notice is published to announce the intention to convene and consult the PCAC to discuss proposed inclusion of specific drug products on the withdrawn or removed list.[25] As announced in the *Federal Register* notice, interested persons are invited to present data, information, or views in writing on issues pending before the committee. All electronic and written submissions can be made at the addresses listed in the *Federal Register* notice.

Additionally, interested parties have the opportunity to present relevant data, information, or views orally during a portion of the advisory committee meeting referred to as the "open public hearing." The *Federal Register* notice also provides instructions on how interested parties can request time during the open public hearing to deliver a formal oral presentation to the PCAC. During the notice-and-comment rulemaking process, interested parties can comment on a proposal to add drug products to the withdrawn or removed list. Comments received will be reviewed and considered before the issuance of a final rule revising the withdrawn or removed list.

After soliciting public comments and consulting with the PCAC, entries may be added to the list in § 216.24 of drug products that have been withdrawn or removed from the market because the drug products or components of such drug products have been found to be unsafe or not effective.

II. DISCUSSION

A. Makena and ANDAs Citing Makena as the RLD

Under the accelerated approval pathway, Makena's approval is subject to the requirement that its sponsor conduct an appropriate postapproval study to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit. FDA may withdraw approval if, among other reasons, a postapproval study fails to verify the drug's clinical benefit.

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[22] See sections 503A(b)(1)(C) and 503B(a)(4) of the FD&C Act; see also 81 FR 69668 at 69669-70, November 7, 2016; 83 FR 63569 at 63570, December 11, 2018.

[23] See, e.g., 83 FR 63569, December 11, 2018.

[24] See section 503A(c)(1) of the FD&C Act.

[25] See, e.g., 80 FR 29717, May 22, 2015.

In late 2018, AMAG Pharmaceuticals completed the post-approval confirmatory trial for Makena (Trial 003) intended to verify and describe the clinical benefit associated with the use of the drug. Trial 003 evaluated the co-primary endpoint of neonatal composite index (a clinical outcome measuring neonatal morbidity and mortality) and gestational age at delivery (delivery less than 35 weeks gestation, a surrogate endpoint). The trial failed to demonstrate a statistically significant difference between Makena and placebo arms for the coprimary endpoint of proportion of women delivering prior to 35 weeks (11 percent with Makena versus 12 percent with placebo, p=0.72) or proportion of neonates experiencing at least one event comprising the neonatal composite index[26] (5.4 percent with Makena versus 5.2 percent with placebo, p=0.84).[27] In the exploratory subgroup analyses, there was no statistically significant treatment difference or interaction between treatment effect and race, region or other elements that may increase PTB risk like substance use in pregnancy, years of education or partnership status.[28]

AMAG Pharmaceuticals publicly acknowledged, in a March 8, 2019 press release, that this confirmatory trial did not demonstrate a statistically significant difference between the Makena and placebo arms for the co-primary endpoints.[29]

On October 29, 2019, FDA convened a meeting of its Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) to consider the findings of Trial 003 in the context of AMAG Pharmaceuticals' confirmatory study obligation.[30] This meeting was open to the public, and Dr. Aladdin, representing Public Citizen, and Dr. Urato, among others, provided comments to the committee. All 16 voting members of the BRUDAC concluded that the findings from Trial 003 failed to verify the clinical benefit of Makena on neonatal outcomes. The BRUDAC further concluded, by a vote of 13 to 3, that, based on the findings from Trial 002 and Trial 003, there is not substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth. Nine members of the BRUDAC voted that FDA should pursue withdrawal of Makena

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[26] The neonatal composite index assesses neonatal morbidity and mortality and includes diseases and conditions frequently seen in infants born premature. The neonatal composite index includes neonatal death, Grade 3 or 4 intraventricular hemorrhage (bleeding in the brain), respiratory distress syndrome, bronchopulmonary dysplasia (abnormal lung development in the infant), necrotizing enterocolitis (bacterial infection in the intestine), and proven sepsis (life-threatening condition caused by the body's response to infection). A neonate with one or more these events of the composite neonatal index counts towards the co-primary endpoint of the proportion of neonates experiencing the neonatal composite index.

[27] Blackwell, SC, 2020, 17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG Study): A Multicenter, International, Randomized Double-Blind Trial, Am J Perinatol, 37(2):127-136.

[28] See Meeting materials available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/october-29-2019-meeting-bone-reproductive-and-urologic-drugs-advisory-committee-meeting-announcement#event-materials.

[29] "AMAG Pharmaceuticals announces topline results from the PROLONG trial evaluating Makena®" (AMAG Pharmaceuticals press release, March 8, 2019). See https://www.globenewswire.com/news-release/2019/03/08/1750567/0/en/AMAG-Pharmaceuticals-Announces-Topline-Results-From-the-PROLONG-Trial-Evaluating-Makena-hydroxyprogesterone-caproate-injection.html.

[30] Meeting materials available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/october-29-2019-meeting-bone-reproductive-and-urologic-drugs-advisory-committee-meeting-announcement#event-materials.

from the market, while seven voted that Makena should remain on the market while a new confirmatory trial is conducted.

Advisory committee members generally provide the Agency with their informed judgment after thorough review of background materials and consideration of comments made by the applicant, FDA, and the public. FDA highly values the expertise of the independent experts on the committee and carefully considers their advice; however, advisory committee votes and recommendations are not binding on the Agency. In this case, CDER has decided to pursue withdrawal of approval. Simultaneous with issuance of this petition response, CDER is issuing a notice of opportunity for hearing (NOOH) on its proposal to withdraw approval of NDA 021945 for Makena. See Docket No. FDA-2020-N-2029, available at www.regulations.gov. Upon withdrawal of the Makena NDA (NDA 021945), CDER would also withdraw approval of the ANDAs that reference Makena.

Whether the approvals of Makena and the ANDAs that reference it are withdrawn will depend on whether AMAG Pharmaceuticals requests a hearing in response to the NOOH, whether any hearing request is granted, and, if a hearing takes place, the Agency's decision at the conclusion of the hearing. Your request that FDA immediately withdraw approval of Makena and the generic products referencing Makena is denied while CDER instead initiates the NOOH process described above.

B. ANDAs 200271 and 211142 Citing Delalutin as the RLD

As explained above, ANDAs 200271 and 211142 referenced Delalutin, rather than Makena, as their RLD. Accordingly, these ANDA products are not approved to reduce the risk of preterm birth. Your Petition does not specify reasons why FDA should withdraw approval of these HPC drug products lacking the preterm birth indication. The outcome of Trial 003, required as a condition of Makena's accelerated approval to verify and describe its clinical benefit, has no bearing on the effectiveness of generic HPC products that do not rely on Makena as their RLD and lack its preterm birth indication. Accordingly, to the extent that your Petition's first requested action (that FDA immediately withdraw approval of all medications containing HPC) extends to ANDAs 200271 and 211142, that request is denied.

C. Placement of HPC on the Withdrawn or Removed List

Your Petition asks FDA to immediately place HPC on the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness and therefore may not be compounded under the exemptions provided by sections 503A(a) or 503B(a) of the FD&C Act. As with your first requested action, the Agency denies your request to take this action immediately. Whether drug products containing HPC may be added to the withdrawn or removed list would depend on whether such drug products have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective. As described above, the approvals of Makena and generic drug products referencing Makena remain in effect and such products have an active marketing status. Also, the addition of drug products containing HPC to the withdrawn or removed list would depend on the initiation and outcome of a notice-and-comment rulemaking process to

revise the withdrawn or removed list. Accordingly, we are denying your Petition's second requested action at this time.

In addition, to the extent the Petition seeks placement of HPC products not labeled with Makena's preterm birth indication on the withdrawn or removed list, it is denied. Among other reasons, this is based on FDA's determination that Delalutin was not withdrawn from sale for reasons of safety or effectiveness.[31]

III. CONCLUSION

For the reasons described herein, after carefully considering the Petition, we are denying your request that we undertake two specific actions: (1) immediate withdrawal of approval of all medications containing HPC; and (2) immediate placement of HPC on the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness and may not be compounded. As described above, CDER instead, simultaneously with issuance of this petition response, is initiating the NOOH process that may result in withdrawal of the approval of NDA 021945 for Makena and ANDAs that rely on NDA 021945 as their RLD. We are also denying your request to withdraw approval of the generic products approved under ANDAs 200271 and 211142 referencing Delalutin as their RLD. Finally, whether HPC drug products may be added to the withdrawn or removed list would depend on whether such products have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective. Additionally, whether HPC drug products may be added to the withdrawn or removed list would depend on the outcome of a notice-and-comment rulemaking process.

Sincerely,

Patrizia A. Cavazzoni -S

Patrizia Cavazzoni, M.D.
Acting Director
Center for Drug Evaluation and Research

[31] See supra note 11 and accompanying text.