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Citizen Petition

Date: October 8, 2019

On behalf of Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide; Public Citizen's Health Research Group; and Adam C. Urato. M.D., Chief, Maternal-Fetal Medicine, MetroWest Medical Center in Framingham, Massachusetts, the undersigned submit this petition under Sections 505(e), 506(c)(3), 503A, and 503B of the Federal Food, Drug, and Cosmetic Act (FDCA)(21 U.S.C §§ 355(e), 356(c)(3), 353a, and 353b) and under Food and Drug Administration (FDA) regulations at 21 C.F.R §§ 10.30, 314.530, and 216.24 to request that the Commissioner of Food and Drugs immediately (1) withdraw the approval of all medications containing hydroxyprogesterone caproate, including the brand name product Makena, and (2) place hydroxyprogesterone caproate on the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness and therefore may not be compounded under the exemptions provided by sections 503A(a) or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 FDCA.

We request these actions because evidence derived from the FDA-mandated postmarket clinical trial for the new drug application (NDA) for Makena (NDA 21945) failed to verify that the drug provides clinical benefit. In particular, the 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, more importantly, that it decreases the risk of fetal and neonatal morbidity or mortality. Moreover, the drug never should have been approved under accelerated approval in the first place because the data from the single phase 3 premarket trial that was relied on to establish efficacy were seriously flawed.

A. ACTIONS REQUESTED

1. Immediately withdraw approval of all medications containing hydroxyprogesterone caproate (hereafter referred to as hydroxyprogesterone), which is currently marketed under the brand name Makena and multiple generic formulations.

2. Immediately place hydroxyprogesterone on the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness and therefore may not be compounded under the exemptions provided by sections 503A(a) or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 FDCA.

B. STATEMENT OF GROUNDS

1. Background

a. Regulatory history of hydroxyprogesterone prior to approval of Makena

Hydroxyprogesterone is a synthetic progestin.[1] It has been purported for decades to be effective for reducing the risk of preterm birth, but a mechanism of action for this use has never been established.[2]

In 1956, the FDA — based solely on a finding of safety — approved the first NDA for hydroxyprogesterone caproate injection (brand name Delalutin), which was submitted by Bristol-Myers Squibb, for the treatment of several gynecological and obstetrical conditions, including habitual and threatened spontaneous abortions.[3] Years later, the FDA reviewed several of the approved indications of Delalutin for efficacy under the agency's Drug Efficacy Study Implementation program. In 1971, the FDA announced its conclusion that hydroxyprogesterone caproate was "probably effective" for the treatment of habitual and threatened abortions.[4]

In 1973, the FDA reversed course and announced that based on the information submitted by Bristol-Myers Squibb to support the use of Delalutin for the prevention of habitual and threatened abortion, there was a lack of substantial evidence of effectiveness for this indication.[5] Moreover, the agency further concluded that the drug was unsuitable for use in pregnancy-related conditions because of safety concerns, as reflected in the following excerpt from the agency's October 10, 1973, *Federal Register* notice:

> In addition, data have become available which suggest a **possible association of prenatal hormonal treatment of mothers with congenital heart defects in the offspring**… On the basis of these considerations it is concluded that a question of safety is raised by inferential evidence supporting the existence of an association between the administration of progestins during early pregnancy and the occurrence of congenital malformations. **The potential risk of teratogenic effects is considered high enough to warrant removal of pregnancy-related indications from labeling of progestins currently marketed for systemic use.**[6] [Emphasis added]

In 1978, the FDA issued a rule requiring the labeling of progestational drug products to include a warning about an increased risk of birth defects associated with the use of these drugs during the

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[1] AMAG Pharmaceuticals. Label: hydroxyprogesterone caproate injection (MAKENA). February 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021945s013lbl.pdf. Accessed October 4, 2019.
[2] Mesiano SA, Peters GA, Amini P, et al. Progestin therapy to prevent preterm birth: History and effectiveness of current strategies and development of novel approaches. *Placenta*. 2019 Apr;79:46-52.
[3] Food and Drug Administration. Office director memo for NDA 021945. February 3, 2011. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000ODMemo.pdf. Accessed October 4, 2019.
[4] 36 FR 18115-18116.
[5] 38 FR 27947-27949.
[6] *Ibid*.

first four months of pregnancy,[7] but the agency rescinded that rule in 1999 because it concluded that such labeling for all progestogens was not warranted, noting that the diversity of drugs that can be described as progestational and the diversity of conditions these drugs may be used to treat made it inappropriate to consider these drugs a single class for labeling purposes.[8]

On September 13, 1999, Bristol-Myers Squibb submitted a letter to the FDA requesting the withdrawal of the NDA for Delalutin, noting that the drug had not been marketed for several years.[9] On September 13, 2000, the FDA announced that the approval of the NDA for Delalutin would be withdrawn, effective September 30, 2000.[10]

Hydroxyprogesterone remained available exclusively through pharmacy compounding with limited regulatory oversight following the removal of Delalutin from the market.

b. Accelerated approval

The FDA approved Makena under the accelerated approval pathway on February 3, 2011.[11]

Under section 506(c) for the FDCA and FDA regulations at 21 C.F.R. Part 314, Subpart H, the FDA may grant accelerated approval to a new drug that has been studied for safety and effectiveness in treating a serious or life-threatening disease or condition and that provides meaningful therapeutic benefits to patients over existing treatments.

Accelerated approval may be based on *adequate and well-controlled* clinical trials establishing that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. Such approval is subject to the requirement that the NDA applicant conduct a postmarket study to verify and describe the drug's clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit or of the observed clinical benefit to ultimate outcome. FDA may withdraw approval if, among other things, the required postmarketing clinical study fails to verify clinical benefit of the drug or other evidence demonstrates that the drug is not shown to be safe or effective for its conditions of use.

2. National Institute of Child Health and Human Development (NICHD) clinical trial[12]

Makena's approval was based primarily on safety and efficacy data from a single clinical trial (submitted to the FDA as Study 17P-CT-002), which were published by Meis et al. in 2003 in *The New England Journal of Medicine*. This double-blind, randomized, placebo-controlled trial was conducted by the Maternal-Fetal Medicine Units Network of the NICHD and investigated

[7] 43 FR 47178-47181.
[8] 64 FR 62110-62112.
[9] 75 FR 36419-36421.
[10] 65 FR 55264-55265.
[11] Food and Drug Administration. Accelerated approval letter for NDA 21945. February 3, 2011. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/021945s000ltr.pdf. Accessed October 4, 2019.
[12] Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caprote. *N Eng J Med.* 348(24):2379-2385.

the effects of hydroxyprogesterone treatment in pregnant women with a history of spontaneous preterm birth.

The trial investigators enrolled 463 women at 15 weeks to 20 weeks, 3 days of gestation at 19 clinical centers in the U.S. The investigators excluded women with more than one fetus, known fetal anomalies, progesterone or heparin treatments during the current pregnancy, current or planned cervical cerclage (procedures that use sutures or synthetic tape to reinforce the cervix during pregnancy), hypertension requiring medication, seizure disorder, or a plan to deliver outside of one of the participating clinical centers.

The investigators randomly assigned subjects in a 2-to-1 ratio to receive either weekly injections of 250 milligrams (mg) of hydroxyprogesterone dissolved in castor oil (310 subjects) or placebo (castor oil only; 153 subjects) until delivery or 36 weeks of gestation. The primary outcome was preterm delivery before 37 weeks of gestation, a surrogate endpoint.

Subjects who were screened and found eligible for enrollment were excluded from the trial if they did not return for randomization between 16 weeks and 20 weeks, 6 days of gestation.

With respect to the primary outcome, 36.3% of the subjects in the hydroxyprogesterone group experienced preterm delivery prior to 37 weeks of gestation, whereas 54.9% of subjects in the placebo group ($P<0.001$) experienced this outcome. Delivery prior to 35 weeks of gestation occurred in 20.6% of women in the hydoxyprogesterone group and 30.7% of women in the placebo group ($P=0.02$). Furthermore, delivery prior to 32 weeks of gestation occurred in 11.4% of women in the hydroxyprogesterone group and 19.6% of those in the placebo group ($P=0.02$).

Additionally, there were no differences in the rates of hospital visits for preterm labor, use of alternative tocolytic agents, corticosteroid use, cesarean delivery, or chorioamnionitis (bacterial or viral infection of the amniotic sac).

Neonatal assessments revealed a statistically significant decrease in the risk of birth weight less than 2,500 grams in the hydroxyprogesterone group as compared with the placebo group (27.2% versus 41.1%, respectively; $P=0.003$). There were no statisticially significant differences between the hydroxyprogesterone and placebo groups in the rates of fetal death, infant death, infant pulmonary disorders, retinopathy, or patent ductus arteriosus.

The enrolled subjects represented a high-risk population: One-third of the subjects had a history of more than one preterm birth. Notably, the mean number of previous preterm deliveries was higher in the subjects assigned to the placebo group (1.6 ± 0.9) than in those assigned to the hydroxyprogesterone group (1.4 ± 0.7). The proportion of subjects who had more than one preterm delivery prior to enrollment in the trial also was higher in the placebo group (41.2%) than in the hydroxyprogesterone group (27.7%). These differences may have biased the trial.

The trial investigators concluded that in this cohort, weekly treatment with hydroxyprogesterone significantly reduced the rate of preterm birth before 37, 35, and 32 weeks of gestation.

3. Original NDA submission

a. Concerns raised by the FDA prior to submission of the NDA

The initial sponsor, Adeza Biomedical, submitted an investigational new drug (IND) application (IND 68,108) for hydroxyprogesterone and met with the Division of Reproductive and Urologic Products (DRUP; now the Division of Bone, Reproductive and Urologic Products) several times in 2004 to discuss the possible submission of an NDA for hydroxyprogesterone for reducing the risk of preterm birth based on the NICHD trial (designated Study 17P-CT-002).[13]

DRUP expressed concerns about the adequacy of the available data demonstrating safety and efficacy of hydroxyprogesterone in the scientific medical literature and from Study 17P-CT-002.[14] Among other things, DRUP questioned the utility of the primary endpoint used in Study 17P-CT-002 (i.e., delivery prior to 37 weeks) and suggested that delivery prior to 32 weeks is more clinically relevant due to the fact that infants born prior to 32 weeks are at a higher risk of neonatal morbidity and mortality.[15]

On April 20, 2006, Adeza Biomedical submitted NDA 21945 to the FDA for hydroxyprogesterone under the proposed brand name Gestiva for the proposed indication of prevention of preterm birth in women with a history of at least one spontaneous preterm birth. The applicant based this application largely on the clinical data from the NICHD trial (17P-CT-002), which the FDA noted was not designed to support the marketing approval of hydroxyprogesterone.[16] The applicant also submitted data from the initial incomplete efficacy clinical trial known as the Initial Formulation (IF) Study (Study 17P-IF-001) and data from a follow-up study, Study 17P-FU.

b. Clinical trial data submitted for approval of NDA 21945

The first efficacy clincial trial, Study 17P-IF-001, used a trial design similar to the NICHD trial. It began in April 1998 but was terminated prematurely in February 1999 after only 150 subjects had been enrolled because the active drug hydroxyprogesterone being administered to the experimental group subjects was recalled by its manufacturer, at the direction of the FDA, due to manufacturing practice violations that may have affected the drug's potency.[17] No analysis of data from Study 17P-IF-001 had been done, and the FDA considered information from the trial to be of limited value in supporting either the safety or efficacy of hydroxyprogesterone.

As a result, the assessment of NDA 21945 for hydroxyprogesterone was primarly based on safety and efficacy data generated from the NICHD trial.

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[13] Food and Drug Administration. Medical review(s) of NDA 21945. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000MedR.pdf. Accessed October 4, 2019. PDF page 267.
[14] *Ibid*. PDF page 267.
[15] *Ibid*. PDF page 267.
[16] *Ibid.* PDF page 277.
[17] *Ibid.* PDF page 296.

A third clincal study, Study 17P-FU, which was conducted at DRUP's request, assessed long-term outcomes in children aged 2 years or older whose mothers took part in the the NICHD trial. Study 17P-FU investigated the potential differences in developmental milestones and physical health of children born to mothers who were exposed to hydroxyprogesterone (194 children) compared with those whose mothers received placebo (84 children).[18]

c. FDA reviewers' assessments of safety and efficacy – major deficiencies identified

During the FDA's review of the initial submission of NDA 21945, agency reviewers raised serious concerns and identified major deficiencies regarding the nonclinical and clinical trial data submitted in support of the application. The statistical reviewer in particular expressed strong opposition to approval because of these deficiencies.

i. Pharmacology review

The pharmacology reviewers conducted a review of published nonclinical data regarding hydroxyprogesterone and found "significant deficiencies in the scope and quality of the reported nonclinical studies."[19] The supervisory pharmacology reviewer further noted the following:

> Most of the nonclinical studies were old and did not comply with either Good Laboratory Practices or conform to current CDER [Center for Drug Evaluation and Research] or ICH [International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use] guidances. The primary deficiencies in the nonclinical studies included insufficient numbers of animals, use of nonconventional species, lack of any PK/ADME [pharmacokinetics and pharmacology for absorption, distribution, metabolism, and excretion] data, correlation between gestational timing of exposures and pregnancy outcome, and lack of developmental studies in offspring exposed in utero. ***In addition[,] there were conflicting findings in the studies, regarding [hydroxyprogesterone] embryolethality and potential differences in species sensitivity, what have not been adequately addressed and remain safety concerns…***
>
> **Unresolved Toxicology Issues:**
> - Based on the information available in the published literature, ***it appears that high doses of [hydroxyprogesterone] are associated with increased embryo lethality in several species*.** The nonclinical data provided is insufficient to calculate a no adverse effect level (NOAEL) in animals.
> - ***There is insufficient nonclinical information on potential adverse effects on postnatal development including learning, behavior, and reproduction*.**
>
> **Conclusions and Recommendations:** From a Pharmacology/Toxicology standpoint, this NDA is approvable. ***There is insufficient nonclinical data on which to base the safety of***

[18] *Ibid.* See PDF pages 279-280.

[19] Food and Drug Administation. Pharmacology review(s) for NDA 21945. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000PharmR.pdf. Accessed October 4, 2019. PDF page 35.

> ***[hydroxyprogesterone], especially in regards to long-term effects in offspring exposed in utero.*** We recommend that a thorough reproductive and developmental study be performed in accordance with ICH S5A "Guideline for Industry: Detection of toxicity to Reproduction for Medicinal Products". ***A multigenerational study should be designed and conducted to assess potential effects on developmental and reproductive parameters, including learning, behavior and reproductive function, in offspring exposed in utero***.[20]
>
> [Bold with italics added for emphasis]

ii. Statistical review

The FDA statistical reviewer recommended against approval of Makena in October 2006 and reiterated this recommendation in subsequent review cycles. The statistical reviewer made the following overall conclusions in her review of the initial NDA submission:

> **From a statistical perspective, the level of evidence from Study 17P-CT[-]002 is not sufficient to support the effectiveness of [hydroxyprogesterone]. The primary reason is the absence of a second, confirmatory study.** Without a second study, the generalizability of the study results to a larger population cannot be assessed…
>
> **Study 17P-CT[-]002 was not designed for drug approval**.[21]
>
> [Emphasis added]

The statistical reviewer detailed numerous reasons why the substantial deficiencies in the NICHD trial rendered it unsuitable for definitively determining the efficacy of hydroxyprogesterone for preventing preterm birth, including the following:

- *Pitfalls in relying on a single efficacy clinical trial, like the NICHD trial*

Citing the FDA's 1998 guidance titled "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,"[22] the statistical reviewer noted that reliance on a single clinical trial created many challenges when interpreting the data submitted for approval of an NDA:

> **[I]t should also be appreciated that reliance on a single study of a given use, whether alone or with substantiation from related trial data, leaves little room for study imperfections or contradictory (non-supportive) information.** In all cases, it is

[20] *Ibid*. PDF pages 35-36, 38.
[21] Food and Administration. Statistical review(s) of NDA 21945. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf. Accessed October 4, 2019. PDF pages 103-104.
[22] Food and Drug Administration. Guidance for industry: Providing clinical evidence of effectiveness for human drugs and biological products. May 1998. https://www.fda.gov/media/71655/download. Accessed October 4, 2019.

> presumed that the single study has been appropriately designed, that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis, or other factors is judged to be minimal."[23] [Emphasis added]

As the statisticial reviewer explained in great detail, the NICHD trial was not appropriately designed and conducted to jusify reliance on it alone to establish the efficacy of hydroxyprogesterone for reducing the risk of preterm birth.

- *Inadequate prespecified primary endpoint*

Emphasizing that the NICHD trial was not designed for drug approval, the statistical reviewer explained that the prespecified primary outcome for the trial ─ preterm delivery before 37 weeks of gestation — was not an appropriate endpoint to establish the efficacy of the drug and support its approval. In particular, the reveiwer noted the following:

> Study 17P-CT[-]002 was not designed for drug approval. FDA and the applicant did not have the usual meetings and discussions regarding the choice of endpoint needed to establish efficacy in a regulatory environment. As a result, **the primary endpoint for the study – Delivery <37 weeks [of] gestation – is not what the FDA would have advised.**[24] [Emphasis added]

The FDA had determined that the clinical significance of preterm birth with respect to mortality rates and long-term morbidity is most pronounced prior to 32 weeks of gestation and therefore asked the applicant for NDA 21945 to conduct additional analyses using preterm delivery before 35 weeks of gestation and before 32 weeks of gestation.[25] The statistical reviewer noted that the analyses using these outcomes were *post hoc*,[26] which made them more subject to bias.

- *Trial not powered for these* post hoc *secondary efficacy endpoint analyses*

The statistical reviewer stated that the NICHD trial was not powered for endpoints based on preterm delivery prior to 37 weeks of gestation. The reviewer further stated that this "lack of power may explain the weaker results shown" for these secondary endpoints.[27]

- *High likelihood of false-positive results based on appropriately adjusted analyses using secondary endpoints of preterm delivery before 35 weeks and before 32 weeks*

The statistical reviewer reported that the point estimates and 95% confidence intervals (CI) — adjusted for the interim analyses conducted during the NICHD trial — for the differences

[23] Food and Administration. Statistical review(s) of NDA 21945. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf. Accessed October 4, 2019. PDF page 88.
[24] *Ibid*. PDF page 104.
[25] *Ibid*. PDF page 78.
[26] *Ibid*. PDF page 78.
[27] *Ibid*. PDF page 80.

between the hydroxyprogesterone group and the placebo group in the rate of preterm delivery before 35 weeks of gestation and before 32 weeks of gestation were -9.4% [95% CI: -18.7%, -0.2%] and -7.7% [95% CI: -16.1.%, -0.3%], respectively.[28] Importantly, the lower bounds of both CIs were very close to zero.

Of note, to preserve the overall Type I error rate of 0.05, the statistical reviewer used a final p-value boundary of 0.0345 for the adjusted confidence intervals (equivalent to a 96.6% confidence interval).[29] In explaining the importance of doing such an adjustment, the statistical reviewer noted the following:

> All of the secondary endpoints are correlated with the primary endpoint, [preterm birth] <37 weeks [of gestation], which was the basis for stopping the study. **The primary and secondary endpoints [preterm birth <35 weeks and <32 weeks of gestation] are not independent**…
>
> Estimates of treatment effects, which are the basis for early termination of a study, are biased. The observed treatment effects overestimate the "true" effect. **Because the secondary endpoints in this study are correlated with the primary endpoint, they too are overestimates.**
>
> **The results from a single study submission need to be robust in establishing efficacy of a drug product.** If the results of the secondary endpoints from this study were overwhelming, they would remain statistically significant regardless of whether a level of 0.0345 or 0.05 is used to declare significance.[30]
>
> [Emphasis added]

The statistical reviewer concluded that the analyses of the data assessing the efficacy of hydroxyprogesterone based on preterm delivery before 35 weeks and before 32 weeks were not convincing:

> Although the results are statistically significant for Delivery < 35 weeks [of] gestation and Delivery <32 weeks [of] gestation when accounting for interim analyses, **the confidence intervals for the treatment effects are not convincing when considering that only one study was submitted to support the claim of effectiveness for [hydroxyprogesterone]**…
>
> When two studies are submitted, the chance of both studies yielding a false positive result is 1/1600. In the case of a single study, the results must be less than a nominal p-value of 0.00125 to ensure the same false positive rate. In Study 17P-CT[-]002, the only endpoint that meets this criterion is Delivery <37 weeks [of] gestation. Deliveries at times earlier than [of] 37 weeks gestation were not statistically significant at 0.001. **The results of the**

[28] *Ibid*. PDF page 79.
[29] *Ibid*. PDF page 79.
[30] *Ibid*. PDF pages 80-81.

> **analyses of the 32 and 35 week endpoints suggest their false positive rates could be as great as 1/40**.[31]
>
> [Emphasis added]

- *Failure to consider the range of gestational age at study entry and time on drug prior to delivery*

The statistical reviewer noted that the applicant's Kaplan-Meier analyses failed to "accommodate the range of gestational age at study entry and, therefore, the time on study drug prior to delivery."[32] Notably, subjects were enrolled at 16 weeks to 20 weeks of gestation, and approximately 75% of subjects were randomized before 20 weeks of gestation. Therefore, by 20 weeks of gestation, the time on the drug could have ranged from zero to four weeks.

An analysis by the statistical reviewer that accounted for gestational ages at the time of randomization showed that prior to 28 weeks of gestation, subjects assigned to the hydroxyprogesterone group tended to deliver earlier than those assigned to the placebo group.[33] Moreover, another analysis by the statistical review found that through 24 weeks of gestation, the rates of fetal and neonatal deaths among the hydroxyprogesterone-group subjects were much greater than those among placebo-group subjects (see Table 3.2 below, excerpted from the FDA's statistical reviews).[34]

[31] *Ibid*. PDF pages 104-105.
[32] *Ibid*. PDF page 83.
[33] *Ibid*. PDF page 83.
[34] *Ibid*. PDF pages 85-86.

Table 3.2 Estimated Rates of Fetal and Neonatal Deaths, accounting for time on study drug.

Week of Gestation	17P %	Placebo %
16	0.0%	0.0%
17	0.0%	0.0%
18	0.0%	0.0%
19	2.3%	0.0%
20	3.5%	0.0%
21	6.3%	0.8%
22	6.6%	0.8%
23	7.2%	1.4%
24	7.2%	3.3%

Source: Figure 3-2. Time to delivery as a function of gestational age, using staggered entry based on the gestational age at randomization., and Appendix 5.1 Listings of Kaplan-Meier Estimates of Time to Delivery, Incorporating Gestational Age at Randomization as a Left-censored Variable

- *Potential lack of generalizability: The effects of one study site drove major trial findings*

The statistical reviewer noted that of 19 study sites, one site — the University of Alabama — enrolled 126 subjects, accounting for approximately 25% of total enrollment, which was about three times larger than the second largest study site.[35] The statistical reviewer's analyses that separated the data from the University of Alabama from the data for all other 18 study sites revealed that the disproportionately large representation of subjects from the University of Alabama influenced the significance of the overall results, as noted in the following comment:

> [T]he one finding that is notable is the result for delivery <32 weeks [of gestation] among all other centers combined, which is non-significant (p=.197). Moreover, the results for the University of Alabama are statistically significant for this endpoint (p=0.034). **This may suggest that the University of Alabama may be responsible for the overall findings of this endpoint.**[36] [Emphasis added]

[35] *Ibid.* PDF page 90.
[36] *Ibid.* PDF page 91.

Another analysis by the statistical reviewer revealed important differences in time-to-delivery for subjects in the hydroxyprogesterone group enrolled at University of Alabama compared with all other study centers:

> **Among [hydroxyprogesterone]-treated women, the time-to-delivery is longer among women enrolled at the University of Alabama than those enrolled at the other centers.** This difference ranges from 11 to 13 days, depending on the summary statistic used. Note that the confidence intervals for [hydroxyprogesterone] from the University of Alabama do not overlap the confidence intervals from all other centers combined, indicating these differences in the summary statistics are statistically significant.[37]

The statistical reviewer also noted the following regarding the confounding of center and gestational age at randomization:

> The effect of [hydroxyprogesterone] is most pronounced when started at 18 weeks [of] gestation or earlier and does not appear effective when started at 20 weeks of gestation or later. The rate of fetal and neonatal deaths is also most pronounced among women who started study drug at 18 weeks [of] gestation or earlier (10%). The rate decreases to 2% when study drug is started at 20 weeks of gestation or later.
>
> **These results need to be interpreted in the larger context of confounding with study center. The results of my analyses suggest the presence of confounding between center and gestational age at randomization.** For example, the University of Alabama accounts for 44% of subjects enrolled at 18 weeks [of] gestation or earlier and had relatively few patients at later ages. At other centers, the gestational age at randomization is skewed towards later gestational ages at the time of randomization.
>
> Moreover, the University of Alabama accounts for about 50% of the fetal and neonatal deaths that occurred among women who started study drug at 18 weeks of gestation or earlier.
>
> **Thus, the apparent age trends in treatment effect, and fetal and neonatal deaths simply could be unique to the patient population enrolled at the University of Alabama.**[38]
>
> [Emphasis added]

[37] *Ibid.* PDF page 93.

[38] *Ibid.* PDF pages 104-105.

iii. Clinical reviews

The primary clinical reviewer and clinical team leader recommended an approvable action for the initial submission of NDA 21945 for hydroxyprogesterone.[39] Although supportive of potential approval of the drug in the future, contingent on actions stipulated in the approvable letter discussed below, the clinical reviewers echoed many of the same concerns regarding the adequacy of the NICHD trial raised by the statistical reviewer.

The primary clinical review made the following additional points that augment or add to the concerns and deficiencies raised by the statistical reviewer:

- *Miscarriages, stillbirths, and neonatal deaths*

The primary clinical reviewer noted that the incidence of stillbirths was slightly higher in the hydroxyprogesterone group than the placebo group (2.0% versus 1.3%, respectively), whereas the incidence of neonatal deaths was numerically twice as high in the placebo group, but these differences were not statistically significant.[40] Overall, the rates of miscarriages before 20 weeks of gestation, stillbirths, and neonatal deaths combined was similar in the hydroxyprogesterone group (6.2%) and the placebo group (7.2%). Taken together, the primary clinical reviewer concluded that there was "no net benefit regarding survival,"[41] which is the most important clinical outcome.

- *Safety review issues*

The primary clinical reviewer noted that for both Study 17P-IF-001 and the NICHD trial, adverse events were not captured in the typical manner used in studies designed to support drug approval.[42] In particular, assessment of severity or relationship of the adverse events to study drug was not made for nonserious adverse events. The reviewer nevertheless did not think that these deficiencies significantly compromised the application.

The primary clinical reviewer reported that there were numerically higher rates of gestational diabetes, oligohydramnios, and preeclampsia or gestational hypertension in the hydroxyprogesterone-group subjects than in the placebo-group subjects in both the NICHD clinical trial and Study 17P-CT-001.[43]

In addition, the primary clinical reviewer noted the following regarding data on cardiac abnormalities that were collected on children enrolled in follow-up Study 17P-FU:

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[39] Food and Drug Administration. Medical review(s) of NDA 21945. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000MedR.pdf. Accessed October 4, 2019. PDF pages 264 and 295.
[40] *Ibid*. PDF page 327.
[41] *Ibid*. PDF page 327.
[42] *Ibid*. PDF page 334.
[43] *Ibid*. PDF page 345.

> ***The findings of 10 heart murmurs/irregular rhythm in the [hydroxyprogesterone-]exposed children vs. none in the vehicle exposed children warrants further investigation as part of an additional safety study.*** *An increase in cardiac anomalies from [hydroxyprogesterone] is very unlikely since the anatomic development of the heart is complete at 4-5 menstrual weeks [of] gestation. Some of the mothers were aware of the study arm they were assigned to which could have a bias if she informed the examining pediatrician*.[44] [Italics in original; bold emphasis added]

The clinical team leader offered the following overall assessment in her risk-benefit analysis:

> [FDA] Guidance further states that "reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible."
>
> **In the case of NDA 21-945, the clinical and statistical reviews have raised questions as to whether the evidence of efficacy from this single study is convincing and compelling. The clinical trial data did not provide evidence of a clinically meaningful or statistically significant effect on neonatal morbidity or mortality, as measured by a composite endpoint.** However, preterm birth can be considered "a disease with potentially serious outcome," and the trial did succeed in demonstrating efficacy of [hydroxyprogesterone] in preventing preterm birth at <35 and <32 weeks of gestation, cutpoints which the majority of members of the Advisory Committee on Reproductive Health Drugs believed represented adequate surrogates for fetal/neonatal mortality and neonatal morbidity. **There remains some uncertainty as to whether the demonstrated benefit of [hydroxyprogesterone] in prevention of preterm birth at <32 weeks [of gestation] was due largely to the findings from a single large study site, or whether this result generalizes**…
>
> **In addition, the clinical data suggest that there may be more immediate safety issues, particularly involving increased early fetal loss in women treated with [hydroxyprogesterone], a finding that mirrors nonclinical data relating high doses of [hydroxyprogesterone] with increased embryolethality in mice, rats and monkeys.** Therefore, I conclude that, while the Applicant has demonstrated efficacy of [hydroxyprogesterone] in a single trial in reducing the risk of preterm birth at gestational ages that correlate with increased neonatal morbidity and mortality, **these data are not sufficiently robust to support approval at this time**.[45]
>
> [Emphasis added]

[44] *Ibid*. PDF page 362.
[45] *Ibid*. PDF page 265.

d. Advisory committee review

On August 29, 2006, the FDA convened a meeting of its Advisory Committee for Reproductive Health Drugs to discuss the safety and efficacy of hydroxyprogesterone.

A large majority of the committee (16 of 21 members) agreed with the FDA that a reduction in preterm birth before 37 weeks of gestation was *not* an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity.[46] In contrast, a majority of members concluded that preterm birth prior to 35 weeks of gestation would be an adequate surrogate (13 of 21 members), and all but one member concluded that preterm birth before 32 weeks of gestation would be an adequate surrogate.[47]

Slightly more than one-half of the committee (12 of 21 members) agreed that there was substantial evidence that hydroxyprogesterone prevents preterm birth prior to 35 weeks of gestation, but two-thirds concluded there was *not* substantial evidence that hydroxyprogesterone prevents preterm birth prior to 32 weeks of gestation.[48] A large majority of the committee (19 of 21 members) found that there was *not* substantial evidence that hydroxyprogesterone reduces fetal and neonatal mortality or morbidity.[49]

The committee unanimously agreed that further study was needed to evaluate the potential association of hydroxyprogesterone with an increased risk of second-trimester miscarriage and stillbirth.[50] Eight members recommended that this data be obtained prior to approval of the drug.[51]

Finally, the committee unanimously recommended that if hydroxyprogesterone were to be approved for marketing without additional preapproval clinical studies, the applicant should be required conduct a postapproval clinical trial to investigate further the safety and effectiveness of the drug.[52]

e. Final FDA regulatory action on the initial NDA submission

On October 20, 2006, the agency issued an Approvable Letter to the applicant indicating that before NDA 21945 for hydroxyprogesterone could be approved, the following deficiencies, among others, needed to be addressed:

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[46] Food and Drug Administration. Summary minutes of the Advisory Committee for Reproductive Health Drugs. August 29, 2006. https://wayback.archive-it.org/7993/20170404053134/https://www.fda.gov/ohrms/dockets/ac/06/minutes/2006-4227M1.pdf. Accessed October 4, 2019. PDF page 5.
[47] *Ibid*. PDF page 6.
[48] *Ibid*. PDF page 6.
[49] *Ibid*. PDF page 7.
[50] *Ibid.* PDF page 7.
[51] *Ibid.* PDF page 7.
[52] *Ibid.* PDF page 8.

Clinical

1. Further study is needed to provide confirmatory evidence of the drug's efficacy in terms of a benefit on neonatal morbidity and mortality either directly, or through a well-established surrogate, such as the rate of preterm birth prior to 35 and 32 weeks of gestation.
2. There are insufficient data to evaluate a potential association of hydroxyprogesterone caproate…with increased risk of early fetal loss (second trimester miscarriage and stillbirth).

Information needed to address the clinical deficiencies

1. Submit a draft protocol and evidence of the feasibility of conducting an additional multicenter, well-controlled trial to verify and describe further the observed clinical benefit of [hydroxyprogesterone] for the prevention of recurrent preterm birth, as stated in Subpart H 21 CFR 314.510. If a placebo-controlled trial is determined not to be feasible, provide alternative study design proposals.

2. Provide a draft protocol to evaluate the potential association of [hydroxyprogesterone] with increased risk of second trimester miscarriage and stillbirth. This could be assessed as a part of the confirmatory efficacy study referred to in Item No. 1 above.[53]

Disturbingly, the FDA indicated that the additional clinical trial to establish the safety and effectiveness of hydroxyprogesterone could be conducted postapproval.

4. Second NDA submission

a. Applicant's first Complete Response

In April 2008, the applicant (now Cytec Corporation) submitted a Complete Response to the FDA in response to the agency's October 2006 Approvable Letter. The proposed brand name for hydroxyprogesterone under the NDA remained Gestiva. The response included, among other things, the following:

- A draft clinical protocol (Study 17-ES-003) to confirm and expand upon the efficacy and safety findings from Study 17P-CT-002
- A draft protocol (Study 17-FU-004) for a follow-up study of the children whose mothers had participated in Study 17-ES-003

[53] Food and Drug Administration. Approvable letter to Adeza Biomedical regarding NDA 21945. October 20, 2006. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000OtherActionLtrs.pdf. Accessed October 4, 2019.

- A final report from a nonclinical multigenerational reproductive toxicology study in rats[54]

b. FDA reviewers' assessment of the applicant's Complete Response

i. Pharmacology review

The Complete Response included data from a single multigenerational reproductive toxicity study of hydroxyprogesterone in rats. The pharmacology reviewer reported that the study did not show any adverse effects of the drug on the health of dams, fetuses, offspring, or second-generation offspring.[55] Based on this data, the reviewer recommended approval of NDA 21945.[56]

However, given the other information available in the published literature that had been cited in the pharmacology review during the first review cycle, the data from the single multigenerational reproductive toxicity study in a single rodent species failed to adequately address the prior observation that high doses of hydroxyprogesterone were associated with increased embryo lethality in several species and the fact that the nonclinical data was insufficient to calculate a NOAEL in animals.

ii. Statistical review

The statistical reviewer who reviewed the first NDA submission also conducted the statistical review of the applicant's Complete Response. The statistical reviewer highlighted the fact that the Complete Response did not contain "any additional efficacy data" to obviate the concerns and deficiencies noted during the review of the first NDA submission [57] and again voiced the following comments that signaled strong opposition to approval of the drug based on the existing data:

> However, from a statistical perspective, the effect of 17 α-hydroxyprogesterone, caproate injection on preterm births has not been established by adequate and well-controlled clinical trials -- a requirement of Subpart H approval. Although Study 17P-CT[-]002 demonstrated statistically significantly [sic] reductions in preterm deliveries, **it is my position that the level of evidence from this single study is not sufficient to support the effectiveness of 17 α-hydroxyprogesterone, caproate injection and, therefore, does not support the requirements for Subpart H**; see Statistical Review of NDA 21-945, dated 10/19/2006.[58] [Emphasis added]

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[54] Food and Drug Administration. Summary review of NDA 21945. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000SumR.pdf. Accessed October 4, 2019. PDF page 19.

[55] Food and Drug Administation. Pharmacology review(s) for NDA 21945. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000PharmR.pdf. Accessed October 4, 2019. PDF page 9.

[56] *Ibid*. PDF page 31.

[57] Food and Administration. Statistical review(s) of NDA 21945. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf. Accessed October 4, 2019. PDF page 59.

[58] *Ibid.* PDF page 49.

The statistical reviewer believed that a clinical trial that confirmed efficacy in reducing preterm birth should have been required *prior to approval*, as reflected in the following comment:

> The proposed study, with some modifications, **could be employed to develop the evidence for an alternative path to Subpart H approval**. After a sufficient number of subjects have delivered, the results of the effect of 17 α-hydroxyprogesterone, caproate injection on preterm births could be submitted to us for review. **If the data were sufficient to establish efficacy on preterm births, the application could be given Subpart H approval at that time. The ongoing study would need to be completed in order for us to review the effects on fetal and neonatal losses and on neonatal morbidity – the clinical endpoints of interest.**[59] [Emphasis added]

iii. Clinical review

The primary clinical reviewer made the following recommendation regarding the Complete Response from the applicant:

> **This reviewer recommends a complete response (approvable) action for Gestiva (17α-hydroxyprogesterone caproate…for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth**. This recommendation is based on one multicenter clinical trial that showed statistically significant reductions in preterm birth (PTB) at <35 and < 32 weeks [of] gestation, both surrogate endpoints acknowledged by an Advisory Committee to predict reduction in neonatal mortality and morbidity. **However, the findings from this single study alone are not sufficiently persuasive to support approval alone. Additionally, data from the literature do not consistently demonstrate a decrease in PTB when women with a history of previous PTB are treated with [hydroxyprogesterone].**[60] [Emphasis added]

Although agreeing with the submitted draft protocol for the postmarket clinical trial requested in the FDA's October 2006 Approvable Letter, the clinical reviewer expressed concern about whether the proposed confirmatory trial was feasible and likely to be completed successfully given the following 2008 opinion issued by the American College of Obstetricians and Gynecologists, despite a lack of additional evidence for the efficacy of hydroxyprogesterone or any other progesterone in preventing preterm birth:

> Progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and a prior spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes.[61]

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[59] *Ibid*. PDF page 60.
[60] Food and Drug Administration. Medical review(s) of NDA 21945. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000MedR.pdf. Accessed October 4, 2019. PDF page 83.
[61] *Ibid*. PDF page 84.

The clinical reviewer worried that physicians and institutional review boards (IRBs), particularly in the U.S., would be reluctant to conduct a randomized, placebo-controlled trial of hydroxyprogesterone for the prevention of preterm birth.[62] In order to address these feasibility concerns, the clinical reviewer recommended that the applicant accomplish the following initial steps in implementing the postmarket clinical trial *prior to approval*:

- Obtain IRB approval from approximately 15 research centers (both U.S. and non-U.S.) to enroll the target number of 1,707 subjects.
- Enroll a minimum of 5% of planned subjects (85 subjects); a minimum of 15 subjects should be enrolled from U.S. sites. No site should ultimately enroll more than 15% of all subjects.
- All sites (U.S. and non-U.S.) must use the same predefined definitions of neonatal morbidity.[63]

c. Final FDA regulatory action regarding the applicant's Complete Response

The FDA concluded that the applicant had adequately addressed the nonclinical toxicology deficiencies but had failed to adequately address clinical deficiencies documented in the review of the initial NDA submission.[64] In particular, the applicant had failed to establish the feasibility of conducting and successfully completing the required postmarket confirmatory clinical trial in the U.S.

5. Third NDA submission

a. Applicant's second Complete Response

On July 10, 2010, the applicant (now Hologic, Inc.) submitted a second Complete Response to the FDA, which included the following:

- An update on the status of ongoing confirmatory clinical trial (Study 17P-ES-003)
- A Safety update that included blinded safety data from Study 17P-ES-003
- An update on the publications not previously submitted to the agency regarding the use of hydroxyprogesterone for the prevention of preterm birth
- Proposed product labeling[65]

The proposed brand name under this third NDA submission was changed to Makena.

[62] *Ibid*. PDF page 84.
[63] *Ibid*. PDF page 174.
[64] Food and Drug Administration. Summary review of NDA 21945. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000SumR.pdf. Accessed October 4, 2019. PDF pages 5-6.
[65] *Ibid*. PDF page 20.

b. FDA reviewers' assessment of the applicant's second Complete Response

i. Statistical review

The statistical reviewer reaffirmed her prior view that the data from the single premarket clinical trial testing hydroxyprogesterone submitted by the applicant failed to demonstrate the efficacy of the drug for the prevention of preterm delivery, as reflected in the following conclusion:

> From a statistical perspective, the information and data submitted by the Applicant **do not provide convincing evidence regarding the effectiveness of 17 α-hydroxyprogesterone**, caproate injection (17P) for the prevention of preterm deliveries among women with a history of at least one spontaneous preterm delivery.[66] [Emphasis added]

The statistical reviewer noted that the FDA's medical division had changed course and was recommending approval of the drug based on a statistically significant treatment effect for the surrogate endpoint of preterm delivery prior to 37 weeks of gestation (see medical reviewer discussion below), which was a departure from the first two review cycles that focused on surrogate endpoints of preterm delivery before 35 weeks of gestation and before 32 weeks of gestation[67] and which, as previously noted, a large majority of the Advisory Committee for Reproductive Health Drugs had concluded was *not* an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity.

The statistical reviewer noted that the prior statistical analyses had not sufficiently addressed the data from the NICHD clinical trial regarding the primary endpoint of preterm delivery prior to 37 weeks of gestation because of the focus on the surrogate endpoints of preterm delivery before 35 weeks of gestation and before 32 weeks of gestation.[68] The reviewer therefore conducted additional analyses exploring the effect of race on the efficacy results related to the primary endpoint of preterm delivery prior to 37 weeks of gestation and concluded that the results of these new analyses did not support the efficacy of hydroxyprogesterone based on a single trial given the following:

- **The treatment effect at 37 weeks [of gestation] does not appear to be consistent among groups defined by gestational age at randomization. This finding may be confounded with race and study center.**
- **Lack of consistency of efficacy results among subgroups defined by race.**
  - For subjects who were black, the benefit of [hydroxyprogesterone] compared with Placebo appears to emerge at around 24 weeks [of gestation].
  - For subjects who were non-blacks, a treatment benefit does not emerge until 35 weeks [of] gestation.

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[66] Food and Drug Administration. Statistical review(s) of NDA 21945. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf. Accessed October 4, 2019. PDF page 6.
[67] *Ibid*. PDF page 6.
[68] *Ibid*. PDF page 6.

- **Lack of consistency of safety results at Week 24 [of gestation] among subgroups defined by race.**
  - Among subjects who were black, the estimated rate of fetal and neonatal losses was 6% for subjects, regardless of treatment assignment.
  - Among subjects who were non-black, subjects randomized to Placebo did not have any fetal or neonatal losses compared with an estimated rate of 9% among those randomized to [hydroxyprogesterone].
- The doubling of the treatment effect from <35 weeks [of gestation] to <37 weeks [of gestation] is likely due to the increased number of deliveries among non-black subjects randomized to Placebo.[69]

[Emphasis added]

ii. Clinical review

The primary clinical reviewer noted that the applicant had "provided the requested documentation the confirmatory safety and efficacy trial (Study 17P-ES-003) [had] been initiated at both US and non-US sites and [had] enrolled more than 5% of the planned 1,700 subjects."[70]

The clinical reviewer therefore recommended approval of Makena under Subpart H of 21 C.F.R. 314.510:

> As the primary reviewing Medical Officer for this application, I recommend an *approval action* under the Subpart H regulation (21 CFR 314.510)… for 17α-hydroxyprogesterone caproate…for the reduction of the risk of preterm birth (PTB) in women with a singleton pregnancy who have a history of a singleton spontaneous preterm birth. I make this recommendation because the Applicant has fully addressed the clinical deficiencies that are listed in the January 23, 2009 Complete Response letter to my satisfaction.[71]

However, in a remarkable reversal of course, the primary medical reviewer based this approval recommendation on the reduction of preterm births prior to 37 weeks in the NICHD clinical trial, rather than on the results of the post hoc analyses of the secondary surrogate endpoints of preterm delivery before 35 weeks of gestation and before 32 weeks of gestation, as reflected in the following statement:

> The Applicant submitted a single phase 3 clinical trial which demonstrated a statistically strong (p<.001) reduction in the incidence of preterm births prior to 37 weeks [of] gestation, the protocol pre-specified primary endpoint. There is recent evidence that "late preterm births" (births between $34^{0/7}$ and $36^{6/7}$), which comprise 71.3% of all preterm

[69] *Ibid*. PDF page 7.
[70] Food and Drug Administration. Medical review(s) of NDA 21945. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000MedR.pdf. Accessed October 4, 2019. PDF page 16.
[71] *Ibid*. PDF page 6.

> births, are increasing, and suffer greater neonatal and childhood morbidity and mortality than previously thought (Adams-Chapman 2006, Tomashek 2007, McIntire 2008, Martin 2009, The Consortium on Safe Labor 2010). These data indicate that "preterm birth prior to 37 weeks" is "a surrogate endpoint that is reasonably likely to predict clinical benefit." As such, I find the evidence of benefit on this surrogate endpoint sufficient to support approval on the basis of a single clinical trial,…[72]

This represented a tacit acknowledgment that the deficiences regarding the secondary surrogate endpoints of preterm delivery before 35 weeks of gestation and before 32 weeks of gestation that had been identified by the statistical reviewer during the first and second review cycles were legitimate and could not be refuted by the available data.

Despite the detailed and well-reasoned concerns documented by the primary statistical reviewer regarding the deficiencies of the data from the NICHD clinical trial, the primary clinical reviewer, cross-disciplinary team leader, and DRUP director did not concur with with the statistical reviewer's overall assessment that the data from the NICHD clinical trial did not adequately support the efficacy of hydroxyprogesterone for reducing the risk of preterm birth.[73] The DRUP director even acknowledged that the statistical reviewer's concerns regarding the effect of race on hydroxyprogesterone treatement outcomes had not been fully addressed during the third review cycle.[74]

c. Approval of Makena

On February 3, 2011, the FDA approved Makena under the accelerated approval pathway for the following indication:[75]

> Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.[76]

Under the accelerated approval, the applicant was required to complete the already initiated clinical trial of hydroxyprogesterone in women with a singleton pregnancy who had a previous

[72] *Ibid*. PDF page 6.
[73] Food and Drug Administration. Summary review of NDA 21945. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000SumR.pdf. Accessed October 4, 2019. PDF page 31.
[74] *Ibid*. PDF page 31.
[75] Food and Drug Administration. Accelerated approval letter for NDA 021945. February 3, 2011. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/021945s000ltr.pdf. Accessed October 4, 2019.
[76] Ther-Rx Corporation. Label: hydroxyprogesterone caproate injection (MAKENA). February 2011. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021945s000lbl.pdf. Accessed October 4, 2019.

spontaneous preterm birth (Protocol #17P-ES-003) and the clinical follow-up study (Protocol #17P-FU-004) of children born to women who participated in Protocol #17P-ES-003.[77]

6. Protocol #17P-ES-003, the PROLONG trial

a. Trial design[78,79]

Study 17P-ES-003, also called the PROLONG trial, was a multicenter, randomized, double-blind, placebo-controlled clinical trial in women aged 18 or older with a singleton pregnancy and a history of previous singleton spontaneous preterm delivery. To be eligible for enrollment, the women had to be at a minimum of 16 weeks, 0 days of gestation and no more than 20 weeks, 6 days of gestation at the time of randomization, based on clinical information and evaluation of the first ultrasound.

Subjects received intramuscular injections of hydroxyprogesterone at a dose of 250 mg or vehicle (castor oil) every week until 36 weeks, 6 days of gestation or delivery. Planned subject enrollment was 1,707 subjects, and 1,710 subjects were enrolled.

The prespecified co-primary efficacy endpoints were:

- Preterm birth before 35 weeks, 0 days of gestation (as determined by projected gestational age). All deliveries occurring from randomization until 35 weeks, 0 days of gestation, including miscarriages occurring from 16 weeks, 0 days through 19 weeks, 0 days of gestation and elective abortions, were to be included.
- Composite neonatal morbidity and mortality index. The composite index includes neonatal mortality and the following morbidity components occurring in liveborn infants at any time during the birth hospitalization up through discharge from the neonatal intensive care unit or the first 28 days of life:
    - Grade 3 or 4 Intraventricular Hemorrhage
    - Respiratory Distress Syndrome
    - Bronchopulmonary Dysplasia
    - Necrotizing Enterocolitis
    - Proven sepsis

The key prespecified secondary outcome of the study was as follows:

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[77] Food and Drug Administration. Accelerated approval letter for NDA 021945. February 3, 2011. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/021945s000ltr.pdf. Accessed October 4, 2019.
[78] Food and Drug Administration. Medical review(s) of NDA 21945. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000MedR.pdf. Accessed October 4, 2019. PDF pages 37-48.
[79] ClinicalTrials.gov. Confirmatory study of 17P versus vehicle for the prevention of preterm birth in women with a previous singleton spontaneous preterm delivery (PROLONG). https://clinicaltrials.gov/ct2/show/record/NCT01004029. Accessed October 4, 2019.

- Exclude a doubling of the risk in the hydroxyprogesterone group compared with the placebo group of the composite of:
    - Fetal/early infant death, defined as:
        - Spontaneous abortion/miscarriage (delivery from 16 weeks, 0 days of gestation through 19 weeks, 6 days of gestation); or
        - Death (from minutes after birth until 28 days of life) occurring in liveborns born at less than 24 weeks of gestation.
    - Stillbirth (antepartum or intrapartum death from 20 weeks of gestation through term).

Other prespecified secondary outcomes included the following:

- Preterm birth before 32 weeks of gestation
- Preterm birth before 37 weeks of gestation

b. AMAG Pharmaceuticals report on topline results of Study 17P-ES-003, the PROLONG trial

On March 8, 2019, AMAG Pharmaceuticals, the current sponsor of NDA 21945, announced that the topline results of the PROLONG trial failed to demonstrate statistically significant differences between the hydroxyprogesterone group and the placebo group for the two co-primary endpoints of delivery before 35 weeks of gestation (hydroxyprogesterone group 11.0% vs. placebo group 11.5%, p=0.72) and the percentage of liveborn infants who met the composite neonatal morbidity and mortality index (hydroxyprogesterone group 5.4% vs. placebo group 5.2%, p=0.84).[80]

The company also reported that the adverse event profile, which included miscarriage and stillbirth, was comparable between the two trial groups.

In a desperate attempt to salvage its ineffective drug, AMAG Pharmaceuticals also announced that it would carry out additional post hoc subgroup analyses of the data. However, given the clear failure of the trial to show statistically significant differences between the groups for the two prespecified co-primary efficacy endpoints, such post hoc analyses would be insufficient and inappropriate to support the efficacy of hydroxyprogesterone for reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

7. Conclusion

In summary, hydroxyprogesterone (Makena) never should have been approved by the FDA under the accelerated approval pathway (21 C.F.R. Part 314, Subpart H) for reducing the risk of

[80] AMAG Pharmaceuticals. AMAG Pharmaceuticals announces topline results from the PROLONG trial evaluating Makena (hydroxyprogesterone caproate injection). *AMAG Pharma*. March 8, 2019. https://www.amagpharma.com/news/amag-pharmaceuticals-announces-topline-results-from-the-prolong-trial-evaluating-makena-hydroxyprogesterone-caproate-injection/. Accessed October 4, 2019.

preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth because:

> (1) The approval was based on a single efficacy trial (the NICHD trial) and a primary efficacy endpoint (reduction in the rate of preterm birth before 37 weeks of gestation) that the FDA's Advisory Committee for Reproductive Health Drugs had found was *not* an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity, the key meaningful clinical outcome related to preterm birth.
>
> (2) As explained in careful detail by the FDA's statistical reviewer, the NICHD trial was not designed to support the marketing approval of hydroxyprogesterone and the data from the trial — including the analyses of the prespecified primary efficacy endpoint as well as post hoc analyses of the secondary efficacy endpoints of reductions in preterm birth before 35 weeks of gestation and before 32 weeks of gestation, which may have been adequate surrogates for a reduction in fetal and neonatal mortality or morbidity — did not provide convincing evidence that the drug was effective.
>
> (3) As a result of (1) and (2), there were not data from an adequate and well-controlled clinical trial that established that the drug had an effect on a surrogate endpoint that was reasonably likely to predict clinical benefit.
>
> (4) From a safety standpoint, important concerns were raised by the clinical data that suggested increased early fetal loss in women treated with hydroxyprogesterone, a finding that mirrored nonclinical data showing that high doses of the drug were associated with increased embryolethality in mice, rats, and monkeys. These safety concerns were not adequately addressed by the data from the single multigenerational rat reproductive toxicity study.

Nevertheless, having approved hydroxyprogesterone, the FDA appropriately required that the sponsor complete a postmarket clinical trial to verify hydroxyprogesterone's clinical benefit. That trial was recently completed, and AMAG Pharmaceuticals has reported that the trial failed to demonstrate statistically significant differences between the hydroxyprogesterone group and the placebo group for the two prespecified co-primary endpoints of delivery before 35 weeks of gestation and the percentage of liveborn infants who met the composite neonatal morbidity and mortality index. Thus, the postmarket trial failed to verify the drug's clinical benefit.

It is inconceivable that the FDA would have approved NDA 21945 for hydroxyprogesterone if the efficacy data from the postmarket trial showing no benefit had been available prior to approval, and the only appropriate course of action now is obvious: The drug must be taken off the market. We therefore request that the FDA immediately (1) withdraw the approval of all medications containing hydroxyprogesterone caproate and (2) place hydroxyprogesterone caproate 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 FDCA.

C. ENVIRONMENTAL IMPACT STATEMENT

We claim categorical exclusion under 21 C.F.R. § 25.31(a) from the environmental assessment requirement. An assessment is not required because the requested action would not increase the use of the active moiety that is the subject of this petition.

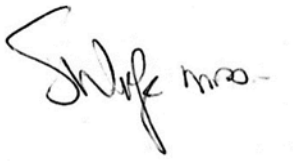
D. ECONOMIC IMPACT

Will be submitted upon request.

E. CERTIFICATION

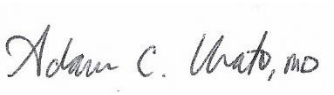
We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Meena Aladdin, M.S., Ph.D.
Health Researcher
Public Citizen's Health Research Group



Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen's Health Research Group

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



Adam C. Urato, M.D.
Chief, Maternal-Fetal Medicine
MetroWest Medical Center
Framingham, Massachusetts