DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

AUG 4 2014

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

RE: FDA-2013-P-0522

Dear Ms. Escher:

This letter responds to your citizen petition received on April 30, 2013 (Petition). You request that the U.S. Food and Drug Administration (FDA or the Agency):

(1) Revoke the March 2013 order approving Diclegis (doxylamine succinate and pyridoxine hydrochloride) as a Category A drug for pregnancy and require the drugmaker/applicant to conduct thorough safety testing regarding fetal germline impact of continuous gestational exposure to the drug prior to any subsequent FDA consideration of approval or labeling; or, at a minimum, recategorize Diclegis as a Category "C" pregnancy drug pending adequate testing; and

(2) Revise regulation of over-the-counter (OTC) and prescription drug labeling to expressly include potential for fetal germline perturbation among enumerated pregnancy medication risks. Pending appropriate testing of individual drugs, both individually and in combination with other drugs, a blanket warning should be added to all medications, as follows:

> *"Fetal Risk. A potential risk of taking a medication during pregnancy includes damage to the baby's vulnerable germ cells (egg or sperm precursors),* ***which may cause disease or developmental disorders in the next generation, your grandchildren****. This drug has not yet been tested for fetal germline impact. Because of potential for multigenerational impacts, you are advised to use caution before taking this drug in pregnancy."*[1]

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

I. BACKGROUND

A. Diclegis (doxylamine succinate and pyridoxine hydrochloride)

Doxylamine, one of the active ingredients in Diclegis, has been used as an active ingredient in both prescription and OTC medications in the United States since 1948.[2] Doxylamine is the active ingredient in prescription medications indicated for the treatment of nausea and vomiting during pregnancy and in

[1] Petition at 1–2.

[2] Doxylamine was first approved as safe by FDA on April 7, 1948, as Decapryn (doxylamine succinate 12.5 milligrams (mg) and 25 mg) tablets. See http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. The effectiveness of Decapryn was confirmed in the *Federal Register* on March 19, 1973 (38 FR 7265).

OTC antihistamines and nighttime sleep-aids. The Agency has confirmed on multiple occasions that doxylamine is safe and effective for its intended uses. In 1999, FDA determined that the prescription drug, Bendectin (doxylamine succinate and pyridoxine hydrochloride), was not withdrawn for reasons of safety and effectiveness.[3] When the Agency issued its determination, it publicly and carefully considered all of the available data regarding the safety and effectiveness of doxylamine. In addition, FDA approved Diclegis after reviewing the results of clinical trials and other data that showed the drug is safe and effective for its indicated use.[4] Doxylamine is also listed as an antihistamine active ingredient in the final monograph for Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over the Counter Human Use (OTC antihistamine final monograph), 21 CFR Part 341.[5] And, Doxylamine is approved and marketed as an OTC nighttime sleep-aid.[6]

B. Regulatory Framework

1. *Contraindications, Warnings and Precautions, and Boxed Warnings for Prescription Drugs*

FDA regulations state that the WARNINGS AND PRECAUTIONS section of prescription drug labeling (including the product's package insert) must describe clinically significant adverse reactions, other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur (21 CFR 201.57(c)(6)(i); see also 21 CFR 201.80(e) and (f)). For products described in 21 CFR 201.56(b)(1), a summary of the most clinically significant warnings and precautions information must be included in the HIGHLIGHTS OF PRESCRIBING INFORMATION (HIGHLIGHTS) for the product (§201.57(a)(10)).

---

[3] Bendectin was a prescription medication indicated for the treatment of nausea and vomiting during pregnancy. Bendectin (10 mg doxylamine succinate, 10 mg pyridoxine hydrochloride, and 10 mg dicyclomine hydrochloride) delayed-release tablets were approved originally on July 30, 1956, for the treatment of "nausea and vomiting of pregnancy which are unresponsive to conservative measures such as eating soda crackers or drinking hot and cold liquids, which interfere with normal eating habits or daily activities, and are sufficiently distressing to require drug intervention." In 1972, as part of the Agency's Drug Efficacy Study Implementation (DESI) review, FDA published its determination that Bendectin was possibly effective for the treatment of nausea and vomiting in pregnancy (37 FR 13489 (July 8, 1972)). In 1974, FDA published a *Federal Register* notice stating that "[i]n view of the fact that [Bendectin] is the only product on the market indicated for nausea and vomiting of pregnancy, the Commissioner concludes that it may remain available pending completion and review of the studies" being conducted to confirm its efficacy (39 FR 17343 (May 15, 1974)). After a thorough review of the data, on November 9, 1976, FDA approved a reformulated version of Bendectin containing only doxylamine and pyridoxine hydrochloride. In the *Federal Register* of January 28, 1977, FDA published its findings that a fixed-combination of doxylamine and pyridoxine hydrochloride was effective for the treatment of nausea and vomiting of pregnancy (42 FR 5422 (January 28, 1977)). Bendectin remained on the market until June 9, 1983, when it was voluntarily withdrawn by the manufacturer. After a thorough review, the Agency announced in a 1999 *Federal Register* notice its determination that Bendectin was not withdrawn from the market for reasons of safety or effectiveness (64 FR 43190 (August 9, 1999)).

[4] Efficacy and safety data for Diclegis were obtained from a single, randomized, double-blind, multicenter, placebo-controlled, parallel group clinical trial. The Agency also considered supportive safety and efficacy data from the 1976 approval of reformulated Bendectin (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride), the Agency's 1999 determination that Bendectin was not withdrawn for reasons of safety or effectiveness, and the safety data for Diclectin (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride), which is manufactured in Canada by the same sponsor as Diclegis.

[5] 59 FR 4216 (January 28, 1994).

[6] On October 18, 1978, FDA approved a New Drug Application for Unisom (doxylamine succinate, 25mg). See http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist.

FDA's *Guidance for Industry on Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (Warnings and Precautions Guidance) describes some factors that FDA may consider in assessing whether there is reasonable evidence of a causal relationship. These include: "(1) the frequency of reporting; (2) whether the adverse event rate in the drug treatment group exceeds the rate in the placebo and active-control group in controlled trials; (3) evidence of a dose-response relationship; (4) the extent to which the adverse event is consistent with the pharmacology of the drug; (5) the temporal association between drug administration and the event; (6) the existence of dechallenge and rechallenge experience; and (7) whether the adverse event is known to be caused by related drugs."[7]

2. *Warnings in Labeling for OTC Drugs*

All OTC drugs are subject to the labeling requirements set out in 21 CFR 201.66, "Format and content requirements for OTC drug product labeling." The warning requirements for OTC drug labeling are described in § 201.66(c)(5). OTC drugs, unlike prescription drugs, have a general set of warnings that are required by the regulations. These warnings are based on evidence related to use of specific classes of drugs, or are general warnings that FDA believes are necessary for all OTC products. For example, warnings such as "Ask a doctor before use…" or "Stop use and ask a doctor if…" are generally included on all OTC drug labels. In addition, specific warnings for pregnancy and breastfeeding to be included in OTC drug labeling are set out in 21 CFR 201.63. Unless an OTC drug is specifically exempted from the pregnancy warning under § 201.63(c) (i.e., it is intended to benefit the fetus or nursing infant, or it is indicated exclusively for pediatric use), it must bear the following warning: "**If pregnant or breast-feeding,** ask a health professional before use."[8] Under § 201.66(c)(5)(viii), FDA may require product-specific warnings for certain OTC drugs by regulation (see 21 CFR 201.300 Subpart G), by OTC monographs, or as a part of product approval. Warnings in OTC drug labeling also are designed to take into consideration that OTC drugs are intended for use by consumers for conditions appropriate for self-diagnosis and self-treatment.

3. *Pregnancy Categories*

For prescription drugs, FDA's regulations state that if a drug is absorbed systemically, the *Pregnancy* subsection of prescription drug product labeling must address the potential for teratogenic effects of the drug by inclusion of the appropriate pregnancy category, as well as the relevant required statements for that category (§§ 201.57(c)(9)(i) and 201.80(f)(6)(i)). The regulations specify the following criteria used to designate the appropriate category:[9]

---

[7] See *Guidance for Industry on Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf.

[8] 21 CFR 201.63(a).

[9] FDA has issued a proposed rule to amend its regulations concerning the requirements for pregnancy and lactation information in prescription drug and biological product labeling. See 73 FR 30831 (May 29, 2008). The proposed rule, if finalized, would reformat the information found under the Pregnancy subsection of labeling and would remove the pregnancy categories from prescription drug and biological product labeling. Under the proposed rule, labeling for prescription drugs and biological products would have new "Pregnancy" and "Lactation" subsections that include: (1) a summary of the risks of using a drug or biological product during pregnancy and lactation, (2) relevant clinical information to help health care providers make prescribing decisions and counsel women about the use of drugs and biological products during pregnancy and lactation, and (3) a discussion of the data supporting the risk summaries and clinical information.

- Pregnancy Category A: "adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)" (21 CFR 201.57(c)(9)(i)(A)(*1*) and 201.80(f)(6)(i)(*a*)).

- Pregnancy Category B: "animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women" or "animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)" (21 CFR 201.57(c)(9)(i)(A)(*2*) and 201.80(f)(6)(i)(*b*)).

- Pregnancy Category C: "animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks" or "there are no animal reproduction studies and no adequate and well-controlled studies in humans" (21 CFR 201.57(c)(9)(i)(A)(*3*) and 201.80(f)(6)(i)(*c*)).

- Pregnancy Category D: "there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective)" (21 CFR 201.57(c)(9)(i)(A)(*4*) and 201.80(f)(6)(i)(*d*)).

- Pregnancy Category X: "studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available)" (21 CFR 201.57(c)(9)(i)(A)(*5*) and 201.80(f)(6)(i)(*e*)).

4. Withdrawal of Approval

After an approved drug enters the marketplace, FDA may reassess its safety and consider whether changes in the available information concerning the product's risk-benefit profile call for regulatory action. FDA's assessment of postmarketing safety signals is governed by the same risk-benefit analysis and criteria as those used for drug approvals.[10] If FDA concludes that a product's risk-benefit profile is unfavorable, it may take steps to withdraw approval of that application.[11] Because the goal of

[10] FDA applies the same standards in both premarketing and postmarketing safety determinations because the underlying legal question in each case is the same: whether or not the drug product meets the statutory standard of safety. See, e.g., section 505-1(a)(1) – (2)(a) of the FD&C Act (21 U.S.C. 355-1(a)(1) – (2)(a)) (applying same risk-benefit analysis to unapproved and approved drug products); and compare FD&C Act sections 505(d) and 505(e) (applying similar requirements for refusing to approve an NDA and withdrawing an approved NDA on grounds of safety).

[11] See 21 CFR 314.105(c), which states in part that "FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness." The information required to satisfy this requirement includes not only comprehensive safety and efficacy data but also "an integrated summary of the

postmarketing safety surveillance is to identify and prevent or mitigate emerging safety concerns before they can cause significant harm to patients, FDA may consider a broad range of new information relevant to safety relating to a drug's potential serious risks or signals of serious risks (safety signals), including adverse event reports, peer-reviewed biomedical literature, and any other scientific data deemed appropriate by the FDA.[12]

Section 505(e)(2) of the FD&C Act[13] further authorizes FDA to withdraw the approval of a drug when consideration of new evidence of clinical experience, not contained in the NDA or not available until after the application was approved, or tests by new methods not deemed reasonably applicable when the application was approved, together with the evidence available to FDA when the application was approved, indicates that the drug "is not shown to be safe for use under the conditions of use upon the basis of which the application was approved."[14]

The criteria and procedures for withdrawing an approved application are detailed in FDA's regulations at 21 CFR part 314. In particular, § 314.150(b) permits FDA to initiate a formal withdrawal proceeding if it finds that new scientific data, clinical experience, or tests, evaluated together with the evidence available at the time of approval, reveal that the drug is not shown to be safe for use under the conditions upon the basis of which it was approved.[15] Alternatively, FDA has the option of notifying an applicant that it "believes a potential problem associated with a drug is sufficiently serious that the drug should be removed from the market" and asking the applicant to (1) permit FDA to withdraw approval of the product's NDA or ANDA, (2) waive its opportunity for a hearing under § 314.200,[16] and (3) voluntarily remove the product from the market.[17]

II. DISCUSSION

The Petition asks FDA to either withdraw approval of the application for Diclegis or, if withdrawal of approval is not appropriate, redesignate it as Pregnancy Category C. In addition, the Petition asks that

---

benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling" (21 CFR 314.50(d)(5)(viii)); see also Report to the FDA Commissioner, *Managing the Risks from Medical Product Use: Creating a Risk Management Framework*, May 1999 at 21 (available at http://www.fda.gov/Safety/SafetyofSpecificProducts/ucm180325.htm) ("After a thorough review of the data, FDA makes a decision to approve or not approve a product to treat a specific condition, based on a benefit-risk analysis for the intended population and use. . . . A safe product is one that has reasonable risks, given the magnitude of the benefit expected and the alternatives available").

[12] See section 505-1(b)(5) and (b)(6) of the FD&C Act (21 U.S.C. 355-1(b)(5) and (b)(6)) (separately defining "serious risk" and "signal of a serious risk"); section 505-1(b)(1) and (b)(6)(B) (distinguishing "adverse event" from a signal "derived from" adverse event information).

[13] Section 505(e)(1) of the FD&C Act authorizes withdrawal when evidence shows that the drug is unsafe.

[14] We note that the Petition relies on section 505-1(b)(5) of the FD&C Act as the basis for its request for FDA to withdraw approval of Diclegis. Section 505-1(b) of the FD&C Act gives definitions of key terms used in section 505-1, which pertains to Risk Evaluation and Mitigation Strategies. Thus, while the definitions in that section are informative as to what types of safety information FDA considers, they do not on their own constitute a basis for withdrawal of approval of an application. Rather, FDA uses the standard articulated in section 505(e)(2) of the FD&C Act to withdraw approval of a product based on new evidence of clinical experience.

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

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

[17] Section 314.150(d).

FDA add a blanket warning to *all* prescription and OTC drugs to warn against the potential for damage to germ cells. In support of these requests, the Petition cites 26 articles regarding epigenetics and germ cell perturbation.

A. Withdrawal of Approval of Diclegis

As explained in the Background section above, FDA will withdraw approval of a drug if new evidence shows that the drug is not safe, or not shown to be safe, for use under the conditions of use described in the approved labeling.[18] When FDA approves a drug, the Agency relies on "substantial evidence" derived from "adequate and well-controlled investigations" conducted by qualified experts, from which such experts could "fairly and responsibly" conclude that the drug is effective under the conditions of use suggested in its labeling.[19] To assess a drug's safety, FDA examines evidence from "all methods reasonably applicable to show whether or not such drug is safe,"[20] including "pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs."[21] As discussed in the Background section above, FDA would rely on similar information to withdraw approval of a drug.[22]

FDA's Division of Bone, Reproductive and Urologic Products (DBRUP) reviewed the 26 articles referenced in the Petition. In addition, DBRUP reviewed an additional 376 scientific publications to determine whether there is any available human data that demonstrates a causal link between Diclegis and perturbation of the epigenome.

With regard to the 26 articles submitted in the Petition, DBRUP did not find that they provide any new non-clinical or clinical safety findings or new analyses of existing information that would support withdrawal of approval of Diclegis. The articles do not provide any human or animal data for Diclegis which demonstrate or suggest that Diclegis disrupts the human fetal germ cell epigenome, as the Petition suggests.

Rather, the animal data presented in these articles discuss the role played by certain endocrine disrupting chemicals (EDCs), such as vinclozolin and other fungicides, bisphenol-A, dioxin, mono-(2-ethylhexyl)-phthalate, zearalerone, lindane, etc., in transgenerational inheritance of disease states or behaviors through alteration of the rodent fetal germ cell epigenome possibly through disruption of DNA methylation or histone modifications. There is no evidence presented in the referenced articles that doxylamine or pyridoxine, alone or in combination, act as EDCs or have any role in disruption of the human fetal germ

---

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

[19] Section 505(d) of the FD&C Act (21 U.S.C. 355(d)). The characteristics of adequate and well-controlled studies are set forth in FDA regulations at 21 CFR 314.126. As stated in the regulation, these criteria were developed over decades of scientific and regulatory experience and are recognized by the scientific community as the essential elements of well-controlled and credible investigations.

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

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

[22] See footnotes 10 – 17 above.

cell epigenome. In addition, the articles do not support the Petition's contention that doxylamine's ability to cross the placenta and its competitive agonistic effect at the histamine-1 (H1)[23] could be linked with transgenerational inheritance of the propensity for disease or defect.

DBRUP also conducted a search of the scientific literature in an attempt to identify articles that provide human or animal data for Diclegis that would support the Petition's claims that Diclegis disrupts the fetal germ cell epigenome and that FDA therefore should withdraw approval of the drug. Four articles were identified that specifically mention Diclegis; however, none of the articles provides any clinical safety data for Diclegis or clinical evidence that Diclegis poses a risk to the fetal germ cell epigenome.

DBRUP also conducted an extensive literature search and identified 376 articles containing key terms related to Diclegis. The majority of these articles provide information for Bendectin, but because Bendectin and Diclegis have the same active ingredients, the articles are still relevant to the question at hand. All of the articles address in utero and postnatal exposure in first generation (F_1) offspring with a focus on congenital abnormalities/fetal malformation (for example, limb defects) and other birth defects (for example, clefts of lip and palate). None of the articles provides information on the second generation [F_2 (grandchildren)]. DBRUP did not find any articles that demonstrated a risk to the fetal germline associated with the use of doxylamine and pyridoxine, alone or in combination, with resulting neurodevelopmental pathology in F_2 offspring.

Separate and apart from DBRUP's recent literature search, Bendectin has been deemed the most studied drug in pregnancy. It has been the subject of many cohort studies, case-control human studies, animal studies, commentaries, and meta-analyses that do not draw doxylamine's safety into question. In addition, as described above, FDA has reviewed the safety of doxylamine (as an active ingredient in both prescription and OTC drug products) multiple times.[24]

Two independent meta-analyses (pooled observational studies) of Bendectin and congenital birth defects, published subsequent to withdrawal of the product from the market, concluded that Bendectin is not a human teratogen. The first meta-analysis, by Einarson et al., incorporated 12 cohort and 5 case control studies published between 1963 and 1985. No statistically significant relationships were found between first trimester use of the combination of doxylamine and pyridoxine, with or without dicyclomine hydrochloride, and fetal abnormalities.[25] The second meta-analysis, by McKeigue, incorporated 16 cohort and 11 case-control studies published between 1963 and 1991 and concluded that "these meta-analyses of Bendectin exposures indicate that there is no measurable increase in the prevalence of congenital malformations in the population of exposed pregnant women, and it is very unlikely that the therapeutic use of Bendectin caused human birth defects."[26]

---

[23] Petition at 7.

[24] See also FDA's August 15, 2013, response to Citizen Petition FDA-1992-P-0494, discussing the history of FDA's determination that Bendectin is safe for use in the treatment of nausea and vomiting during pregnancy.

[25] Einarson TR et al. A method for meta-analysis of epidemiological studies. *Drug Intell Clin Pharm.* 1988; 22:8130824

[26] McKeigue PM et al. Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. *Teratology.* 1994;50:27-37.

A 1995 comprehensive scientific literature review by Robert Brent (178 articles between 1963 and 1993) of epidemiologic studies, animal studies, in vitro studies, basic science articles, review articles, meta-analyses, and case reports concluded that "the clinical use of Bendectin does not increase the risk of birth defects in populations of exposed pregnant women."[27]

In Canada, 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride are the ingredients in Diclectin delayed-release tablets, which are indicated for the management of nausea and vomiting of pregnancy. Diclectin has been marketed in Canada since 1983. Included in the New Drug Application for Diclegis were six Periodic Safety Update Reports (PSURs) for Diclectin, covering the reporting period 1983 to September 1, 2012, which includes administration of the drug to an estimated 2.7 million women in Canada. FDA examined these PSURs as part of its review of Diclegis, and based on the information available in the six PSURs, concluded that there was not an increased risk of having a child (F_1 generation) with a birth defect that exceeded the background rate of approximately 1% to 3%.

Finally, the Pediatric and Maternal Health Staff (PMHS) in FDA's Office of New Drugs performed a separate literature review of epigenetics in general. As part of this review, PMHS looked at the results of studies conducted at the Skinner laboratories at Washington State University. These studies focused on endocrine disruptors (i.e., bisphenol-A and vinclozolin) in animal models and have shown transgenerational epigenetic modifications in DNA methylation in males that can be detected in successive generations.[28] However, these studies also demonstrated that in addition to the potential for transmission of adverse effects across generations, there were also adverse effects in each generation. That is, outcomes from exposure in the parental F_0 animal will be reflected in the offspring (F_1). There may also be effects seen in subsequent generations (F_2 or F_3) but not without the offspring (F_1) generation also displaying some effects. These findings contradict the assertion in the Petition that "minute, invisible, latent birth defects . . . appear in greatly magnified form only many decades after the initial exposure."[29]

Thus, FDA's conclusion with respect to its review of available data and evidence, including the articles referenced in the Petition, is that no new evidence regarding the safety or effectiveness of Diclegis has been presented that changes the Agency's conclusion that the product is safe and effective under the conditions of use described in the product labeling. Your request that FDA withdraw approval of the application for Diclegis is denied.

B. Redesignation of Diclegis to Pregnancy Category C

---

[27] Brent RL. Bendectin: review of the medical literature of a comprehensively studied human nonteratogen and the most prevalent tortogen-litigen. *Reprod Toxicol.* 1995 Jul-Aug:9(4):337-334.

[28] Anway MD et al. Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science* 308:1466-1469 (2005); Anway MD et al. Endocrine disruptor vinclozolin induced epigenetic transgenerational adult-onset disease. *Endocrinology* 147:5515-5523 (2006); and Manikkam M et al. Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. *PLoS ONE* 8(1): e55387 (2013).

[29] Petition at 2.

The Petition also requests that, if FDA does not withdraw approval of the application for Diclegis, the Agency should "classify Diclegis as a Category C drug for pregnancy."[30] You state that Diclegis should be redesignated from Pregnancy Category A to Pregnancy Category C "owing to probable but yet unmeasured effects on germline. To risk permanent, life-long developmental derangement of even a small subset of grandchildren of Dicelgis consumers merely to address a woman's transient, normal, and harmless nausea and vomiting of pregnancy is unconscionable. *This is a risk-benefit tradeoff no reasonable person would make.*"[31]

Diclegis labeling designates the drug as Pregnancy Category A. FDA's current regulations specify that Pregnancy Category A be designated when "adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)" (21 CFR 201.57(c)(9)(i)(A)(*1*) and 201.80(f)(6)(i)(*a*)). As discussed above, Diclegis has been extensively studied and used in pregnant women and there is no evidence of a risk to the fetus from either adequate and well-controlled trials or epidemiological studies. Designation of a drug as Pregnancy Category C is assigned when "animal reproduction studies have shown an adverse effect on the fetus, … there are no adequate and well-controlled studies in humans, and … the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks" or "there are no animal reproduction studies and no adequate and well-controlled studies in humans" (§§ 201.57(c)(9)(i)(A)(*3*) and 201.80(f)(6)(i)(*c*)). Given the extent of the human studies done to support the approval of Diclegis (and Bendectin and Diclectin before that, as well as the clinical evidence that supports the OTC indications for doxylamine) that show no adverse effect on the fetus, we do not believe redesignation of Diclegis as Pregnancy Category C is appropriate.

C. Addition of a Warning to all Prescription and OTC Drugs Regarding Potential for Fetal Germline Perturbation

1. Addition of a Warning to Prescription Drug Labeling

The Petition requests that, "pending appropriate testing of individual drugs, both individually and in combination with other drugs," FDA should put a blanket warning against taking drugs during pregnancy in the absence of fetal germline impact assessment on all prescription and OTC products.[32]

As explained in the Background section above, FDA includes a warning on a prescription drug label if there is "reasonable evidence" of an association of a hazard with the product.[33] As explained in FDA's Warnings and Precautions Guidance, the WARNINGS AND PRECAUTIONS section of prescription drug labeling is "intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are *serious* or are *otherwise clinically significant.*"[34] The guidance defines "*serious* adverse reaction" as "any event or reaction that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a

[30] Petition at 7.
[31] Petition at 7–8 (emphasis in original).
[32] Petition at 8.
[33] See 21 CFR 201.80(e) and (f).
[34] Warnings and Precautions Guidance at 3 (emphasis in original).

congenital anomaly or birth defect." Thus, FDA will include (or add) a warning to a prescription drug's labeling if the Agency has reasonable evidence that the drug causes a serious adverse reaction.

In addition, FDA may include a warning in a prescription drug's label if an adverse reaction has not been observed with a drug but may be anticipated to occur because a drug with that particular pharmacology, chemistry, or class is likely to cause a specific adverse reaction.[35] Or, FDA may include a warning for an anticipated adverse event if animal data have demonstrated an adverse effect of the drug that raises concerns about a similar effect in humans.[36] In the context of contraindications, FDA distinguishes between anticipated adverse reactions and "theoretical possibilities." Anticipated adverse reactions are supported by data (e.g., from known pharmacologic effects, class effect, chemical relationships to other drugs known to cause reactions, or animal studies) while theoretical possibilities are based wholly on theory (e.g., not supported by data).[37] Theoretical possibilities are not included in labeling.

As FDA's literature reviews and the articles presented in the Petition confirm, cells that undergo alterations in their epigenome respond differently to environmental triggers. And, not all epigenetic changes result in an adverse phenotypic response in the cell. At the current time, it is still unclear which epigenetic changes are considered "normal, dynamic, or adaptive" and which are considered "adverse or pathologic."[38] Because our current understanding of epigenetic processes in normal cellular function is incomplete, it is not possible to reliably distinguish whether epigenetic changes are caused by or associated with a specific toxicity, adverse event, or outcome. Additionally, no one assay or test can capture all epigenetic events. The tests that are currently available to assess epigenetic effects are unvalidated and insufficiently reliable to be used to form the basis of a regulatory decision.[39]

Current evidence does not tie use of prescription drugs during pregnancy to "developmental disorders in the next generation." Without further evidence of a causal link to support the Petition's request to add a blanket warning about epigenetic risks to the labeling of all prescription drugs, such a warning would not be appropriate under FDA's regulations.

2. *Addition of a Warning to OTC Drug Labeling*

FDA imposes uniform labeling requirements, including warnings, on OTC products (see § 201.66) and sets specific labeling requirements for specific OTC drug products subject to an OTC monograph (see 21 CFR 201.63). Generally, warnings are included in OTC labeling when the Agency has reason to believe that it is important to warn consumers about a risk prior to taking the product. Warnings are also added to OTC drug labeling to account for the fact that consumers take OTC drugs without the supervision of a medical professional.

---

[35] Warnings and Precautions Guidance at 5.
[36] Id.
[37] Warnings and Precautions Guidance at 9.
[38] Alyea RA et al. Is the current product safety assessment paradigm protective for epigenetic mechanisms? *J. Pharmacol. and Toxicol. Methods* 66:202-214 (2012).
[39] LeBaron MJ et al. Epigenetics and chemical safety assessment. *Mutation Research* 705:83-95 (2010); Priestly CC et al. Epigenetics-relevance to drug safety science. *Toxicol. Res.*1:23-31 (2012).

FDA's regulations require that the labeling for all OTC drug products intended for systemic absorption contain a general warning stating, "**If pregnant or breast-feeding**, ask a health professional before use."[40] In other words, the labeling for all OTC products already contains a warning that informs pregnant women not to take the drug without first consulting a physician. In finalizing the regulations that require this warning, FDA considered other options submitted in public comments. One suggested warning stated: "A small number of drugs have been conclusively shown to a degree of scientific certainty to have adverse effects on the developing fetus. However, information of this type is not adequate to establish that this drug is safe for the developing fetus."[41] Regarding this suggested warning, FDA concluded that it is "not apt to be understood by the average consumer. Further, the message it is intended to convey can be more effectively obtained through consultation with a health professional."[42] Indeed, FDA adopted the pregnancy warning for OTC drugs because "a woman would be best advised on whether to use a particular OTC drug by a knowledgeable health professional who is either familiar with her medical history or readily available to her and capable of assessing her situation with respect to a particular drug."[43]

The warning proposed in the Petition is not appropriate for OTC drug labeling. It is too scientific in nature to be understood by the average consumer. Further, because the standard pregnancy warning in all OTC drug labeling directs a pregnant woman to ask a health professional before use, FDA believes it is sufficient to ensure that pregnant women learn of the potential risks of an OTC drug product prior to taking it. For these reasons, your request to add a warning regarding fetal germline impact to OTC drug labeling is denied.

III. CONCLUSION

After careful consideration, and, in light of the foregoing, your Petition is denied. FDA will continue to monitor available evidence concerning the epigenetic effects of the products it regulates, and, if warranted, will take appropriate regulatory action to protect the public health.

Sincerely,

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

[40] § 201.63(a).
[41] 47 FR 54751 (December 3, 1982).
[42] Id.
[43] Id.