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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, rm. 1061
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April 26, 2013

Re: Citizen Petition to: (1) Revoke Approval for Diclegis (doxylamine succinate and pyridoxine hydrochloride) Pending Fetal Germline Safety Assessment; and (2) Revise Pregnancy Drug Labeling Rules to Alert Consumers to Potential for Fetal Germ Cell Perturbation

To the Commissioner of the Food and Drug Administration:

The undersigned respectfully submits this petition in accordance with 21 C.F.R. 10.30, and pursuant to the written suggestion of Nancy Hayes, Acting Director, Office of Regulatory Policy, Center for Drug Evaluation and Research (letter to Escher dated April 16, 2013), to request that the Commissioner of Food and Drugs revoke approval for the drug Diclegis (doxylamine succinate and pyridoxine hydrochloride) pending fetal germline impact assessment, and to issue additional pregnancy label warnings for all drugs regarding potential for fetal germ cell perturbation.

A. Action requested

This petition requests that the Commissioner take the following actions:

(1) Revoke the March 2013 order approving Diclegis 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, re-categorize Diclegis as a category "C" pregnancy drug pending adequate testing; and

(2) Revise regulation of 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:

FDA-2013-P-0522 CP

"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."*

B. Statement of grounds

This petition is made pursuant to 21 U.S.C. Sec. 355-1(b)(3) to present to the FDA "new safety information" regarding both a particular drug and a class of drugs in general. Under that statute, new safety information may include "scientific data deemed appropriate by the Secretary about a serious risk or an unexpected serious risk associated with use of the drug that the Secretary has become aware of (that may be based on a new analysis of existing information) since the drug was approved."

The term "serious risk" means a risk of a serious adverse drug experience. 21 U.S.C. Sec. 355-1(b)(5). A "serious adverse drug experience" is defined an adverse drug experience that results in, among other things, "a congenital anomaly or birth defect." 21 U.S.C. Sec. 355-1(b)(4).

This petition presents a new analysis of existing information that calls out the increased risks of serious birth defects caused by exposure to Diclegis and other gestational drugs in the form of impaired development of fetal germline, the delicate and submicroscopic genetic and epigenetic material within germ cells (egg and sperm precursors) that gives rise to the subsequent generation. Impairment of the molecular programming of a baby's germline represents a harrowing paradox: minute, invisible, latent birth defects, but with potentially catastrophic consequences that appear in greatly magnified form only many decades after the initial exposure, and in separate and distinct organisms, that is, the children of exposed fetuses.

1. Overview: environmentally induced fetal germline impairment

Comprehension of the petitioner's request must begin with the understanding that gestational drug exposures affect three generations at once: the mother, her fetus (child), and the fetal germ cells (child's future children). The fetal germ cells, sometimes called stem cells, are the precursors to the baby's egg or sperm, containing both the genetic and epigenetic material, together providing the complicated instruction book for the development of the next generation. Although it is textbook knowledge that prenatal exogenous exposures can permanently perturb the epigenetic programming of the germline, to date the FDA has not made any attempt to ascertain fetal germline impacts of any drug taken by pregnant women or to warn women and their partners, or even their medical providers, of this vast dimension of profound risk.

Complicating matters, and therefore the relevant adverse drug effect information that tends to reach FDA staff, people who have been exposed *in utero* to gestational drugs lack access to the medical or other records showing the nature and extent of their prenatal exposures, leaving them without knowledge of silent insults which may have triggered lifelong consequences for themselves and/or their children. Lack of information does not equate to lack of impact, however; and most assuredly many mysterious and increasingly prevalent pathologies suffered today are at least in part the result of germline havoc wreaked by long-forgotten prenatal drug exposures of a previous era.

It is well known that fetal germline epigenetic reprogramming is vulnerable to damage by exogenous compounds, particularly man-made, synthetic "Franken-molecules" that mimic natural biochemistry and hormones, but disrupt the very precise biochemical process of germline development which was forged over millions of years of mammalian evolution. The germ cells are not only the most vulnerable of all human tissues during early embryonic development, and they are of course also the most important in the child's body, assuming that child desires to reproduce upon reaching maturity. Submicroscopic molecular disturbance of the germline, whether considered mutation or epimutation, could, during development of the resulting child, become magnified as a subtle, moderate or severe developmental abnormality or disease. This is owing to abnormal gene expression caused by permanent *de novo* aberrations affixed during germline construction.

2. Scientific support for fetal germline impairment and pathology in successive generation

Far from being inert marbles of immutable DNA sequences, our germ cells are highly vulnerable to environmental interference, particularly during susceptible periods of development. The epigenome of the germ cell is known to be susceptible to environmental influences. (Skinner, Birth Defects Research (Part C) 93:51–55 (2011).) Indeed, because of the inherent lability of the epigenome, this represents a primary target for environmentally induced disruption. (See, eg, McCarrey, The epigenome as a target for heritable environmental disruptions of cellular function, Molecular and Cellular Endocrinology, Volume 354, Issues 1–2, 9-15, 2012.) Petitioner will briefly address three points relevant to *in utero* exposures of the fetal germline: (1) the particular vulnerability of the fetal germline; (2) sources of germline epigenetic perturbation; and (3) evidence for resulting neurodevelopmental pathologies.

But first, a note. While some may protest, "most germline impairment research examines effects of ambient environmental chemicals, not pharmaceutical drugs," the biochemistry of the body and its component cells does not distinguish between chemicals marketed as therapeutic agents and other chemicals marketed for other purposes, such as the killing of vermin or the softening of plastics. What matters is the timing, dose and nature of compound, its chemistry and metabolites, and not how it is packaged and marketed to the public. Indeed, for the vast majority of people, their most

acutely toxic, high-dose abnormal, xenobiotic and/or endocrine-disrupting environmental exposures come in the form of drugs and pharmaceuticals, not pesticides, fungicides, smog, smoking or water pollution. This is especially true for fetuses.

a. The germline reprogramming window of susceptibility

It is well established that the epigenome is inherently more susceptible to environmental disruption than the genome. (See McCarrey 2012.) The idea that the human germline epigenome is particularly sensitive to derangement by exogenous exposures during certain windows of susceptibility, including early fetal development, is, likewise, non-controversial. (Skinner, Birth Defects Research 2011.) The timeframe of greatest concern is the period of gonadal development during early gestation, approximately weeks 6-18 in humans. Ibid.

The vulnerability stems from the fact the fetal germline epigenome is denuded of most existing epigenetic tags and dynamically remodeled in a sex-specific manner during that timeframe. In human fetuses of both genders, primordial germ cells enter genital ridges, and then enter a premeiotic stage and undergo rapid DNA demethylation followed by sex-specific de novo methylation. (Durcova- Hills et al., Influence of sex chromosome constitution on the genomic imprinting of germ cells, PNAS 2006 Jul 25;103(30); Anway et al., Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 308:1466–1469 2005; Guerrero-Bosagna C et al., Epigenetic transgenerational actions of vinclozolin on promoter regions of the sperm epigenome. PLoS ONE 5:e13100 (2010).; Anway et al., Endocrine disruptor vinclozolin induced epigenetic transgenerational adult-onset disease. Endocrinology 147:5515–5523 2006; Anway et al., Transgenerational effect of the endocrine disruptor vinclozolin on male spermatogenesis, J Androl 27:868–879 2006; Anway and Skinner, Transgenerational effects of the endocrine disruptor vinclozolin on the prostate transcriptome and adult onset disease. Prostate 68:517–529 2008; Chamorro-Garcia, Transgenerational inheritance of increased fat depot size, stem cell reprogramming, and hepatic steatosis elicited by prenatal obesogen tributyltin in mice, Environ Health Perspect (2013): .doi: 10.1289/ehp.1205701 (2013).) Methylation is only one of the epigenetic processes affected by *in utero* exposures. Histone modification, among other molecular modifications to DNA, can also be affected. (Walker and Gore, Transgenerational neuroendocrine disruption of reproduction, Nature Reviews Endocrinology 7, 197-207 2011.)

In the female fetus, germ cells mature before birth, whereas in males these cells develop after the onset of puberty, allowing for additional susceptibility to environmental insults. Prenatal exposures have been demonstrated to impact fetal oogenesis at the onset of meiosis in the fetal ovary and the formation of follicles in the perinatal ovary. (Bisphenol A alters early oogenesis and follicle formation in the fetal ovary of the rhesus monkey Hunt et al., doi: 10.1073/pnas.1207854109 PNAS September 24, 2012.) Transmission of DNA methylation occurs mainly through maternal gametes. (De Assis, High-fat or ethinyl-oestradiol intake during pregnancy increases mammary cancer risk in

several generations of offspring, Nat Commun. 2012; 3: 1053.) In theory, this means that dysregulation of a female fetus's germ cells may cause greater impairment in subsequent offspring than *in utero* insults to the male.

As the embryonic stem cell epigenome is altered due to this germ line transmission, all the resulting organism's cell populations and tissues will have an altered epigenome and corresponding transcriptome. (Anway et al., 2008; Skinner et al., 2010.) Although not all cell types or tissues will develop a disease state, those tissues that have a sufficiently altered transcriptome will have a greater susceptibility to abnormal development. (Skinner et al., 2010. Furrow et al, Environment-sensitive epigenetics and the heritability of complex diseases. Genetics 189:1377–87 (2011).) Normal epigenetic gene regulation is essential for normal development, and consequently, environmentally induced dysregulation of the epigenome will promote abnormal development. Epigenetic changes to somatic cells, such as those triggering various forms of cancer, are often reversible, but altered epigenetic markers of germline are not; they are fixed through the development of the organism and are irreversible.

b. Sources of epigenetic perturbation

The character, dose, and duration of the *in utero* exposures will affect the extent of epigenetic disfigurement of the fetal germline. Endocrine disrupting compounds, for example, have repeatedly been shown to induce epimutations and impact gene expression profiles of germ cells, at both low and high doses. (See, eg, Manikkam 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. doi:10.1371/journal.pone.0055387 (2013); Crews, Epigenetic transgenerational inheritance of altered stress responses, PNAS USA. 2012 doi: 10.1073/pnas.1118514109; Susiarjo et al 2013, Bisphenol A Exposure Disrupts Genomic Imprinting in the Mouse, PLoS Genet 9(4): e1003401. doi:10.1371/journal.pgen.1003401; Walker and Gore, Transgenerational neuroendocrine disruption of reproduction, Nature Reviews Endocrinology 7, 197-207 2011. Doyle et al. (2013), Transgenerational Effects of Phthalate on Male Germ Cells, BOR Papers in Press Published on March 27, 2013 as DOI:10.1095/biolreprod.112.106104; Manikkam et al, Dioxin (TCDD) induces epigenetic transgenerational inheritance of adult onset disease and sperm epimutations, PLoS ONE 7(9): e46249. doi:10.1371/journal.pone.0046249 (2012); Del Mazo et al, The effects of different endocrine disruptors defining compound specific alterations of gene expression profiles in the developing testis, Reproductive Toxicology 33:1, 106–115 (2012).)

However, EDCs are not the only exposures that impair germline development. For example, a recent study has revealed that fetal exposure to nicotine due to maternal smoking has multigenerational effects on rat offspring. (Rehan et al, Perinatal nicotine exposure induces asthma in second generation offspring, BMC Medicine 2012, 10:129; See also Linschooten, et al., Paternal lifestyle as a potential source of germline mutations transmitted to offspring, FASEB J. 2013 Mar 28. (paternal smoking can affect

the chance of heritable mutations in unstable repetitive DNA sequences in sperm). Hydrocarbons also have been shown to have germline effects. (Tracey et al 2013, Hydrocarbons (jet fuel JP-8) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations.) These are just examples of the many environmental factors that manipulate or influence germline development.

c. Resulting neurodevelopmental pathology in germline offspring

As we have seen, a transient *in utero* exposure to a xenobiotic compound may permanently alter the epigenetic programming of the germline, resulting in pathologies in offspring. While many pathologies related to compromised robustness of the human germline have been demonstrated, including metabolic disorders, infertility, follicle loss and polycystic ovary disease, kidney disease, pubertal abnormalities in females, and several forms of cancer, a particular concern is impaired neurodevelopment of resulting offspring. (See Walker and Gore 2011.) Studies have shown neurodevelopmental and behavioral abnormalities connected to impaired germline synthesis. (See, eg, Rissman et al., Gestational Exposure to Bisphenol A Produces Transgenerational Changes in Behaviors and Gene Expression, Endocrinology 1195 (2012); Skinner et al., Transgenerational epigenetic programming of the brain transcriptome and anxiety behavior, PLoS ONE 3(11): e3745. doi:10.1371/journal.pone.0003745 2008.)

Exposure even to common chemicals, such as a common fungicide, has been show to promote an epigenetic reprogramming of the male fetal germline, causing changes in the brain transcriptome of subsequent offspring. (Skinner et al. 2008.) Several brain signaling pathways were influenced including those involved in axon guidance and long-term potentiation. (Ibid.) In a separate study, a *single* exposure to the fungicide, vinclozolin, three generations removed altered the physiology, behavior, metabolic activity, and transcriptome in discrete brain nuclei in descendant males, causing them to respond differently to chronic restraint stress. (Crews et al. 2012.) This alteration of baseline brain development promotes a change in neural genomic activity that correlates with changes in physiology and behavior, revealing the interaction of genetics, environment, and epigenetic transgenerational inheritance in the shaping of the adult phenotype. Ibid.

Also alarming is that an accumulation of epimutations can ultimately influence the genome itself. Epigenetic alterations such as methylation deserts or increased retrotransposition can influence genetics (mutations) via weakening of the epigenome, which may increase the risk for copy number variations, including duplications and deletions. (LaSalle, A genomic point-of-view on environmental factors influencing the human brain methylome, Epigenetics 2011;6:862-869.) Human neurodevelopment appears to be particularly sensitive to alterations in epigenetic pathways; neuronal development and functioning may be particularly impacted by even subtle alterations to DNA methylation. Ibid.

3. Because of the timing of administration and the receptor-blocking nature of the drug, Diclegis may pose a significant risk to the epigenetic synthesis and integrity of fetal germline

In March of 2013, the FDA approved the drug Diclegis for nausea and vomiting of pregnancy (NVP). While testing of Diclegis revealed no increase in obvious somatic birth defects caused by fetal exposure to the drug, neither the FDA nor the drugmaker made any attempts to ascertain whether continuous, daily fetal exposure during the first half of pregnancy (as per dosing instructions) can compromise the synthesis and integrity of the delicate fetal germline.

The process of fetal germline reprogramming occurs during precisely the time period of morning sickness experienced by most pregnant women. Indeed, it is likely that morning sickness — wherein a pregnant woman becomes exceedingly sensitive to her environment — evolved at least in part as a mechanism to protect the exposed and sensitive germline from potentially harmful exposures. Yet, administration of Diclegis is expressly targeted at this known window of epigenetic susceptibility.

Doxylamine, the medicinal ingredient in Diclegis, is a synthetic molecule invented in the 1950s. It crosses the placenta and enters fetal tissues. It is a competitive agonist of the histamine-1 (H1) receptors, and by design interferes with the normal binding of cellular receptors and intracellular signaling. The action of H1 receptors are implicated in neurogenesis, learning, and memory. Doxylamine is a CNS depressant.

Per the dosing instructions, 10mg of the antihistamine may be taken up to 4 times daily, for 40 mg daily. It is reasonably foreseeable that many consumers will continue use for about three months, or 90 days, for a total of 3600 mg of foreseeable fetal germline exposure to a synthetic molecule that interferes with receptor activity and intracellular signaling. It is reasonable to assume this exposure could therefore interfere with normal synthesis of the germline epigenome. This does not even take into account the synergistic, cumulative effects of other drugs also taken by the patient, which may include fertility treatment hormones, antidepressant drugs, antihypertensives, diabetes drugs, PPIs and others.

What is the effect of this massive quantity of receptor-disrupting "Franken-molecules" on the cellular receptors of the germ cell, which provide direction to the epigenome under development? Given what evolutionary biology now teaches us about the epigenetic susceptibilities of the early germline, it is shocking that the FDA has never even asked the question.

If the FDA is unwilling to revoke approval of Diclegis pending adequate testing, it should at a minimum classify Diclegis as a Category C drug for pregnancy owing to probable but yet unmeasured effects on germline. To risk permanent, life-long developmental derangement of even a small subset of grandchildren of Diclegis consumers merely to

address a woman's transient, normal, and harmless NVP is unconscionable. *This is a risk-benefit tradeoff no reasonable person would make.*

C. The time has come to revise regulation of OTC and prescription drug labeling to expressly include potential for fetal germline perturbation among enumerated pregnancy medication risks

The FDA's outdated approach to evaluating adverse consequences of pregnancy drug exposures, which ignores the existence and vulnerability of the fetal germline, has misled the medical establishment and American public. The time has come to revise regulation of 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 pregnancy label warning should be added to 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."*

Pregnant women and their partners have the right to know all, not just some, of the risks involved in ingesting pharmaceutical drugs, particularly to the developmental integrity of their descendants.

C. Environmental impact

The requested action has no environmental impact, the petitioner claims categorical exclusion.

D. Economic impact

The requested action has no economic impact.

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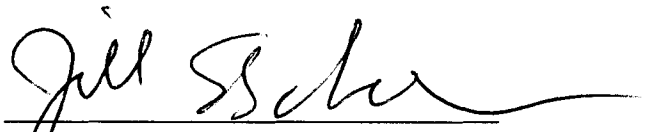
E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

I wish to thank the FDA staff for its consideration of this petition.

Very truly yours,



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