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Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
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UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES AND THE FOOD AND DRUG ADMINISTRATION

PETITION FOR ADMINISTRATIVE ACTION TO REQUIRE CLINICAL TRIAL OF ENGERIX-B AND RECOMBIVAX-HB TO ASSESS THE SAFETY OF THESE PRODUCTS	**:**	**Docket No. _____**

CITIZEN PETITION

This petition is being submitted pursuant to 21 C.F.R. § 10.30 and related relevant provisions of the Federal Food, Drug, and Cosmetic Act and Public Health Service Act, the Public Health and Welfare at, *inter alia*, 42 U.S.C. § 262(a)(2)(A)-(C) and 42 U.S.C. § 262(j), and 42 U.S.C. § 300aa-10 *et seq.*, to request that the Commissioner of Food and Drugs (the "**Commissioner**") withdraw or suspend the approval granted by the Food and Drug Administration ("**FDA**") for Engerix-B and Recombivax HB for infants[1] and toddlers until a properly controlled and adequately powered double-blind trial of sufficient duration is conducted to assess the safety of these products as required pursuant to applicable federal statutes and regulations for licensing these products.

The clinical trials relied upon to license these products only assessed safety for up to five days after injection. Therefore, these trials did not comply with the applicable federal statutory and

[1] Excluding infants born to mothers who test positive for HBsAg during pregnancy.

regulatory requirements necessary to prove they were "safe" prior to licensure. *See, e.g.*, 21 U.S.C. § 393 (The FDA "shall promote the public health by … reviewing clinical research and taking appropriate action … [to] protect the public health by ensuring that …. drugs are safe and effective."). Consequently, the FDA must either withdraw or suspend the approval of these products until an appropriate clinical trial is conducted, as required by law, to determine their safety for licensure.

A. Action Requested

1. That the FDA withdraw or suspend the approval for Engerix-B and Recombivax HB for infants[2] and toddlers until a double-blind placebo-controlled trial of sufficient duration[3] is conducted to assess the safety of these products.

B. Statement of Grounds

2. The Centers for Disease Control and Prevention ("**CDC**") Recommended Child and Adolescent Immunization Schedule recommends universal vaccination of all infants with a Hepatitis B vaccine at birth, 1-month of age, and 6-months of age.[4] There are only two Hepatitis B vaccines licensed for administration to newborns: Engerix-B and Recombivax HB.

3. The Informed Consent Action Network ("**ICAN**") is a non-profit organization that advocates for informed consent and disseminates information necessary for same with regard to all medical interventions. In 2017, a supporter of ICAN advised the organization that the clinical trial relied upon by the FDA to license each of the two Hepatitis-B vaccines on the market only reviewed safety for a few days after injection. ICAN found this claim incredible. It assumed the claim was likely false.

4. Indeed, the importance of capturing all potential health issues for a material duration during a clinical trial is reflected in the trials of, for example, the drugs Enbrel[5], Lipitor[6], and Botox,[7] which had safety review periods of 6.6 years, 4.8 years and 51 weeks respectively, each with a placebo control group. As another example, the weight loss drug Belviq, indicated only for adult use, was safety tested in a placebo-controlled trial for two years before being licensed by the FDA.[8]

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[2] *Id*.

[3] As discussed below, safety should be assessed until the infants and toddlers are at least six years of age so that the rates of autoimmune and neurological disorders, many of which are not diagnosed until childhood, can be assessed.

[4] *See* https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html#note-hepb (last visited Sept. 3, 2020).

[5] https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103795s5503lbl.pdf (last visited Sept. 3, 2020).

[6] https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf (last visited Sept. 3, 2020).

[7] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103000s5302lbl.pdf (last visited Sept. 3, 2020).

[8] https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022529lbl.pdf (last visited Sept. 3, 2020). In February 2020 the drug was voluntarily removed from the US market at the request of the FDA due to emerging data showing that people who had taken the drug as part of a large clinical trial had an increased occurrence of cancer five years later. *See also* https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-weight-loss-drug-

5. As the FDA explains in its guidance materials: the clinical trial relied upon for licensure is typically "1 to 4 years"[9] and the duration of a clinical trial should "reflect the product and target condition."[10] The time frame for the safety review should be longer for minors, and in particular for babies and toddlers, since autoimmune, neurological, and developmental disorders will often not be diagnosed until after babies are at least a few years old.[11] Indeed, a 2019 review of 306 pediatric studies, authored by researchers at the FDA and Duke University, explained that, compared to licensing a drug for adults, "data on drug efficacy and safety in children may require an additional 6 years."[12]

6. Moreover, Congress mandated that the FDA only license a drug if its sponsor has proven it to be "safe and effective." *See, e.g.*, 21 U.S.C. § 393. The FDA relies upon clinical trial reports provided by the sponsor of the drug to make this determination. The clinical trial information submitted must be sufficient to demonstrate the product is "safe." *Id*. While there are many ways to demonstrate that a product is safe, five days of post-administration safety data for a product that will be injected into babies is patently insufficient to demonstrate safety.

7. Hence, the claim that Engerix-B and Recombivax HB were licensed by the FDA based on only a few days of safety data after each injection sounded like science fiction. ICAN simply found the claim not credible. That was until ICAN reviewed the package insert for each of these two products issued by their manufacturer and subsequently approved by the FDA, which each described their pre-licensure clinical trials. To ICAN's amazement, they appeared to indicate that safety in these clinical trials was only reviewed for a few days after the injection of each into babies.

8. Hence, on October 12, 2017, ICAN sent a letter[13] to the FDA's parent department, HHS, with the following request:

> All drugs licensed by the FDA undergo long-term double-blind pre-licensure clinical trials during which the rate of adverse reactions in

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belviq-belviq-xr-lorcaserin-market (last visited Sept. 3, 2020); https://www.health.harvard.edu/blog/weight-loss-drug-belviq-recalled-2020040919439 (last visited Sept. 3, 2020).

[9] https://www.fda.gov/patients/drug-development-process/step-3-clinical-research (last visited Sept. 3, 2020).

[10] https://www.fda.gov/media/102332/download (last visited Sept. 3, 2020).

[11] For example, according to the CDC, even for a common neurological disorder such as ADHD, "5 years of age was the average age of diagnosis for children reported as having severe ADHD." https://www.cdc.gov/ncbddd/adhd/features/key-findings-adhd72013.html (last visited Sept. 3, 2020). As another example, learning disabilities, a group of common developmental issues, are often "identified once a child is in school." https://www.nichd.nih.gov/health/topics/learning/conditioninfo/diagnosed (last visited Sept. 3, 2020). Even for asthma, a very common autoimmune condition, whose symptoms are obvious, diagnosis can be difficult for children under 5 years of age because lung function tests aren't accurate before 5 years of age and "[s]ometimes a diagnosis can't be made until later, after months or even years of observing symptoms." https://www.mayoclinic.org/diseases-conditions/childhood-asthma/diagnosis-treatment/drc-20351513 (last visited Sept. 3, 2020).

[12] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6526087/ (last visited Sept. 3, 2020).

[13] https://www.icandecide.org/wp-content/uploads/2019/09/ICAN-HHS-Notice-1.pdf (last visited Sept. 3, 2020).

> the group receiving the drug under review is compared to the rate of adverse reactions in a group receiving an inert placebo, such as a sugar pill or saline injection. … And even with these long-term studies, drugs are still often recalled. …
>
> [Nonetheless], of the two Hepatitis B vaccines licensed by the FDA for injection into one-day-old babies, Merck's was licensed after trials that solicited adverse reactions for *only five days* after vaccination and GlaxoSmithKline's was licensed after trials that solicited adverse reactions for *only four days* after vaccination.[14] …
>
> The 1986 Act expressly requires that you, as the Secretary, "shall make or assure improvements in … the licensing … and research on vaccines, in order to reduce the risks of adverse reactions to vaccines." (42 U.S.C. § 300aa-27(a)(2).) Given this statutory obligation: … **Please list and provide the safety data relied upon when recommending babies receive the Hepatitis B vaccine on the first day of life?**[15]

9. HHS, in a response reviewed and approved by the FDA,[16] responded by letter,[17] dated January 18, 2018, to the foregoing question as follows:

> Data relied upon in licensing infant use of hepatitis B vaccines is summarized in the respective package inserts. Furthermore, pediatric data from other countries and in the literature, support the safety of these vaccines in infants. The recommendation for all children to receive these vaccines was made by the Advisory Committee for Immunization Practices. Their reasoning is summarized in a *Morbidity and Mortality Weekly Report* at https://www.cdc.gov/mmwr/preview/mmwrhtml/00033405.htm. Follow-up studies support the safety of infant vaccination with hepatitis B vaccines.[18]

10. After a careful review of HHS and the FDA's response, ICAN responded by letter, dated December 31, 2018,[19] which provided, in relevant part, as follows:

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[14] https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110114.pdf (last visited Sept. 3, 2020); https://www.fda.gov/media/119403/download (last visited Sept. 3, 2020).

[15] *See* n. 13, *supra.*

[16] https://www.icandecide.org/wp-content/uploads/2020/08/Review-Copy.pdf (last visited Sept. 3, 2020).

[17] https://www.icandecide.org/wp-content/uploads/2019/09/HHS-Response-1.pdf (last visited Sept. 3, 2020).

[18] *Id.*

[19] https://www.icandecide.org/wp-content/uploads/2019/09/ICAN-Reply-1.pdf (last visited Sept. 3, 2020).

In our opening letter, we asked that HHS "Please list and provide the safety data relied upon when recommending babies receive the Hepatitis B vaccine on the first day of life."[20]

A. Safety Data for Hepatitis B Licensure is Plainly Deficient

HHS begins its response by stating: "Data relied upon in licensing infant use of hepatitis B vaccine is summarized in the respective package insert."[21] It is troubling that HHS responds to the above request by citing the package inserts when our opening letter explained that these precise package inserts provide that their safety was not monitored for longer than five days after injection.[22] As a result, HHS's response merely affirms the concerns we expressed in our original letter that the Hepatitis B vaccine was inadequately tested for safety prior to licensure.

Recombivax HB's package insert asserts it was deemed safe for children based on a clinical trial in which 147 infants and children (up to 10 years of age) were monitored for five days after vaccination.[23] This trial is useless for assessing the safety of this vaccine for pediatric use (let alone for babies on the first day of life) because the sample size is too small, the safety review period is too short, and there is no placebo control. The safety information in the package insert for Engerix-B is just as inadequate since the clinical trial for this vaccine also had no placebo control and only monitored safety for four days after vaccination.[24]

These package inserts plainly do not support the safety of administering these products to babies. Hence, HHS's assertion that the "Data relied upon in licensing infant use of hepatitis B vaccine is summarized in the respective package insert" is very troubling.

B. Safety of Hepatitis B Recommendation for Babies Plainly Deficient

Aside from the package inserts, HHS's response points to only one other identifiable document to support its claim that the Hepatitis B vaccine is safe for babies – a report from the Advisory Committee on Immunization Practices (**ACIP**) that HHS asserts it relied upon

[20] *See* n. 13, *supra.*

[21] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf (last visited Sept. 3, 2020).

[22] *See* n. 17, *supra*.

[23] *See* n. 17, *supra.*

[24] *Id*.

for its "recommendation for all children to receive these vaccines."[25] Sadly, as with the package inserts, this ACIP report does not support the safety of these vaccines for babies or children. A copy of the report is cited in a footnote to this sentence.[26]

The ACIP report cites seven studies to support its recommendation that every baby in this country receive Hepatitis B vaccine injections at 1-day, 1-month, and 6-months of life.[27] Two of the cited studies only included adult[s] … and therefore provide no useful data to evaluate the safety of injecting newborns.[28] The third was a retrospective study that did not use either of the Hepatitis B vaccines licensed for infants in the United States, excluded children that did not complete the vaccine series and lacked a placebo control.[29] The fourth was a retrospective study of potential neurological events from the Hepatitis B vaccine based on reports submitted to a passive surveillance system … "[in which] underreporting is a well-recognized problem" … [and which] involved "virtually all" adults and did not provide any separate results for infants or children.[30] …

The three remaining studies … were clinical trials. But none … are useful for understanding the safety of injecting Hepatitis B vaccine into babies.[31] First, none of them had a placebo control.[32] Second, none … assessed safety for longer than seven days after vaccination.[33]

Indeed, one study had 122 infants and monitored safety for only 7 days.[34] Another study had 79 children monitored for 5 days.[35] Remarkably, in this study 18 percent of the children experienced a systemic or serious adverse reaction … but, absent a placebo

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[25] http://icandecide.org/hhs/vaccine-safety-1-29-18.pdf (last visited Sept. 3, 2020).

[26] https://www.cdc.gov/mmwr/preview/mmwrhtml/00033405.htm (last visited Sept. 3, 2020).

[27] *Id.*

[28] https://www.ncbi.nlm.nih.gov/pubmed/6810736 (last visited Sept. 3, 2020); https://pubmed.ncbi.nlm.nih.gov/6997738/ (last visited Sept. 3, 2020).

[29] Chen D-S. Control of hepatitis B in Asia: mass immunization program in Taiwan. In: Hollinger FB, Lemon SM, Margolis HS, eds. Viral hepatitis and liver disease. Baltimore: Williams & Wilkins, 1991:716-9.

[30] https://www.ncbi.nlm.nih.gov/pubmed/2962488 (last visited Sept. 3, 2020).

[31] https://www.ncbi.nlm.nih.gov/pubmed/2952812 (last visited Sept. 3, 2020); *see also* https://pubmed.ncbi.nlm.nih.gov/2943814/ (last visited Sept. 3, 2020); https://www.ncbi.nlm.nih.gov/pubmed/2528292 (last visited Sept. 3, 2020).

[32] *Id.*

[33] *Id.*

[34] https://www.ncbi.nlm.nih.gov/pubmed/2952812 (last visited Sept. 3, 2020).

[35] https://www.ncbi.nlm.nih.gov/pubmed/2943814 (last visited Sept. 3, 2020).

control, the pharmaceutical company paid researchers were left to decide [if they] were related to the vaccine.[36] The final study had 3,000 infants and children but *only* monitored safety on the day of and the third day after vaccination.[37] …

As this shows, even though we asked for the science to support the safety of injecting every newborn with the Hepatitis B vaccine starting on the first day of life, the studies HHS has provided do not support such safety and would not be sufficient to license these products for veterinary use in farm animals. For example, prior to licensure of a vaccine for use in chickens, "Daily observation records are required for at least 21 days after vaccination."[38]

C. Urgent Need for Placebo-Controlled Trial of Hepatitis B Vaccine

The need to assess the safety of each Hepatitis B vaccine in robust clinical trials is manifest. The following is a list of the reported post-marketing adverse reactions added to the package insert for Engerix-B because Merck had a "basis to believe there is a causal relationship between the drug and the occurrence of the adverse event"[39]:

> Abnormal Liver Function Tests; Allergic Reaction; Alopecia; Anaphylactoid Reaction; Anaphylaxis; Angioedema; Apnea; Arthralgia; Arthritis; Asthma-Like Symptoms; Bell's Palsy; Bronchospasm; Conjunctivitis; Dermatologic Reactions; Dyspepsia; Earache; Eczema; Ecchymoses; Encephalitis; Encephalopathy; Erythema Multiforme; Erythema Nodosum; Guillain-Barré Syndrome; Hypersensitivity Syndrome (serum sickness-like with onset days to weeks after vaccination); Hypoesthesia; Keratitis; Lichen Planus; Meningitis; Migraine; Multiple Sclerosis; Myelitis; Neuritis; Neuropathy; Optic Neuritis; Palpitations; Paralysis; Paresis; Paresthesia; Purpura; Seizures; Stevens-Johnson Syndrome; Syncope; Tachycardia; Tinnitus;

[36] *Id*.

[37] https://www.ncbi.nlm.nih.gov/pubmed/2528292 (last visited Sept. 3, 2020).

[38] https://www.aphis.usda.gov/animal_health/vet_biologics/publications/memo_800_204.pdf (last visited Sept. 3, 2020).

[39] 21 C.F.R. 201.57

> Transverse Muscular Weakness; Thrombocytopenia; Urticaria; Vasculitis; Vertigo; Visual Disturbances.[40]

And these are the reported post-marketing adverse reactions for Recombivax HB added to its package insert because GSK had a basis to conclude each has a causal relationship with that vaccine:

> Agitation; Alopecia; Anaphylactic/Anaphylactoid Reactions; Arthralgia; Arthritis; Arthritis Pain In Extremity; Autoimmune Diseases; Bell's Palsy; Bronchospasm; Constipation; Conjunctivitis; Dermatologic Reactions; Ecchymoses; Eczema; Elevation Of Liver Enzymes; Encephalitis; Erythema Multiforme; Erythema Nodosum; Exacerbation Of Multiple Sclerosis; Febrile Seizure; Guillain-Barré Syndrome; Herpes Zoster; Hypersensitivity Reactions; Hypersensitivity Syndrome (serum sickness-like with onset days to weeks after vaccination); Hypesthesia; Increased Erythrocyte Sedimentation Rate; Irritability; Lupus-Like Syndrome; Migraine; Multiple Sclerosis; Muscle Weakness; Myelitis Including Transverse Myelitis; Optic Neuritis; Peripheral Neuropathy; Petechiae; Polyarteritis Nodosa; Radiculopathy; Seizure; Stevens-Johnson Syndrome; Somnolence; Syncope; Systemic Lupus Erythematosus (SLE); Tachycardia; Thrombocytopenia; Tinnitus; Urticaria; Urticaria; Uveitis; Vasculitis; Visual Disturbances.[41]

These post-marketing reactions reveal a consistent pattern of autoimmune, neurological and other chronic disorders that would appear or only be diagnosed years after vaccinating a baby. Nevertheless, … HHS responds to these post-marketing reports of chronic life-long injuries by saying that "causation has not been proven," knowing … that causation is highly unlikely to be proven, one way or another, until a placebo-controlled trial of sufficient duration is conducted.

By approving, recommending and aggressively promoting use of the Hepatitis B vaccine for all infants, HHS created a liability-free captive market for Merck and GSK by ensuring millions of babies every year will be injected with their Hepatitis B products. Since HHS's recommendation in 1991 for the universal pediatric use of these products, these companies have generated over $10 billion in

[40] *See* n. 17, *supra.*

[41] *Id*.

> sales from this vaccine. Yet, HHS's response makes clear that it lacked the clinical trial safety data necessary to support its licensure and aggressive marketing of this product for use in all babies.
>
> It is deeply troubling that, despite repeated assurances by HHS that the safety science for this vaccine is robust and complete, when we demanded to actually see this science, HHS was unable to produce it because it apparently does not exist. …
>
> Please identify and provide a copy of any placebo-controlled trial with a safety review period longer than one week that HHS relied upon when it recommended that every baby in this country receive either Recombivax HB or Engerix-B on the first day of life.[42]

11. HHS has not responded or provided any information in response to the foregoing request. No response was received even after ICAN sent a follow-up letter to HHS, dated March 10, 2020, stating that "It has now been over 13 months since ICAN submitted these follow-up questions and concerns regarding vaccine safety. Nonetheless, HHS has failed to respond to the questions posed in our letter of December 31, 2018, nor to any of the substance in that letter."[43]

12. In the summer of 2019, ICAN submitted FOIA requests directly to the FDA requesting the clinical trials relied upon by the FDA to license Engerix-B and Recombivax HB which reviewed safety for more than one week after administration.[44] The FDA has failed to produce any such clinical trials. In sum, neither the FDA nor HHS, despite repeated demands, have been able to produce any clinical trials that would support the safety of these products such that the FDA could have fulfilled its statutory duty to ensure their safety prior to licensing them for injection into newborns, infants and toddlers.

C. Environmental Impact

13. ICAN hereby states that the relief requested in this petition will have no environmental impact and therefore an environmental assessment is not required under 21 C.F.R. Sections 25.30 and 25.31.

D. Economic Impact

14. Economic impact information will be submitted upon request of the commissioner.

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[42] *See* n. 25, *supra*.

[43] https://www.icandecide.org/wp-content/uploads/2020/08/ICAN-Follow-Up-Final.pdf (last visited Sept. 3, 2020).

[44] https://www.icandecide.org/wp-content/uploads/2020/08/Binder1.pdf (last visited Sept. 3, 2020).

E. Certification

15. 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.

16. ICAN therefore respectfully urges that the action requested above be adopted forthwith.

Respectfully submitted,

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