

**Citizen's Petition**

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**August 2, 2002**

Dockets Management Branch  
Food and Drug Administration  
Department of Health and Human Services  
Room 10-61  
5630 Fishers Lane  
Rockville, MD 20857

The undersigned submits this petition pursuant to 21 C.F.R. 10.20, 10.30, 201.57, 314.80, 314.81, 601.2 and any and all other applicable regulations or statutes to request the Commissioner of Food and Drugs to amend the product insert and/or label for Hemophilus vaccines manufactured by several different companies.

**A. Action requested**

The under signed request the following actions:

\* The product insert of the hemophilus vaccines should have a "black box" warning that the hemophilus vaccine causes diabetes and the risk of vaccine induced diabetes exceeds the benefit of preventing hemophilus, for the general public.

\* The product insert should recommend restricting use of hemophilus vaccines to those at highest risk for complications from hemophilus. Such users may include those which are immune compromised. The insert should state that the risk may still exceed the benefit in these individuals.

\* Warning letters should be sent to physicians informing them that the risk of diabetes caused by the hemophilus vaccine exceeds the benefit of preventing hemophilus in the general public.

\* Warning letters should be sent to state health departments informing them that the risk of diabetes caused by the hemophilus vaccine exceeds the benefit of preventing hemophilus in the general public and explicitly stating that mandatory immunization of the general public with hemophilus vaccines will cause more children to be harmed than benefit.

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\* Any manufacturer wishing to market any vaccine should be required to perform proper prospective, randomized, blinded clinical trials to prove a vaccine causes a benefit in health, not just a reduction in infections or infectious complications.

\* Manufacturers should be restricted from promoting any vaccine products for general use or lobbying for mandatory immunization either directly, or indirectly by financially subsidizing those who are, until it has been proven the vaccine causes a long term benefit in health.

\* The manufacturers should alert prescribers, through label changes and warning letters, that the risk of vaccine induced diabetes is not limited to hemophilus vaccine and the risk of vaccine induced diabetes may exceed the benefit with other vaccines as well. Prescribers should be aware that safety testing of vaccines in the past was so severely compromised that the value of the vaccine is in doubt. Prescribers should also be told other autoimmune diseases, beside diabetes, may also result from vaccination.

**B. Statement of Grounds**

The hemophilus vaccine has been proven to cause type 1 diabetes, insulin dependent, (IDDM) (1). Causation was established based on a large prospective randomized clinical trial and confirmed with data from at least 3 smaller epidemiology studies, referenced in the paper, as well as animal toxicity data. Most of the cases of diabetes caused by the hemophilus vaccine occur between 3-4 years after immunization. This is consistent with earlier papers showing a 2-4 year delay between mumps infections and the development of IDDM (2-5). The mechanisms of vaccine induced IDDM has been extensively reviewed and are not limited to the hemophilus vaccine (6). The timing of immunization with several different vaccines has been associated with different risks of IDDM (7). An independent group in Sweden has confirmed an association between immunization and pancreatic beta cell autoimmunity (8). Extensive immunization with multiple vaccines, as occurs in children and the military, is associated with a 3 fold or more rise in the risk of IDDM (9).

The data (1) shows the hemophilus vaccine causes more children to develop IDDM than would suffer chronic complications from hemophilus infections if unvaccinated, 58 cases of IDDM/100,000 versus 7 deaths and 7 to 26 cases of severe disability/100,000 from infection with hemophilus (10) respectively. Children who develop diabetes before the age of ten, as occurred in this study, are most likely going to die from the chronic complications of diabetes. The problem is more serious than this data shows because the newer more potent hemophilus vaccines are associated with an even greater incidence of IDDM in Finland. Furthermore this study only looked at children with type 1 diabetes, an autoimmune disease. There is currently an epidemic of type II diabetes in the US (11) and many of these diabetics suffer from decreased secretion of insulin. Recent data shows that many children diagnosed with type II diabetes, 30% or more, (12) have autoantibodies against pancreatic islet cells indicating an autoimmune

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diabetes and have a high risk of developing insulin dependent diabetes (13) . It is certain that the hemophilus vaccine is causing islet cell damage to many more children than 58/100,000 detected in the study, with many of these children eventually being diagnosed with type II diabetes. Furthermore the vaccine is also causing other children to develop autoimmune diseases besides diabetes as discussed in a paper describing the mechanisms of vaccine induced diabetes (6).

The health of Americans has been threatened because the public has been misled by vaccine manufacturers and individuals funded by manufacturers. These individuals have published and or disseminated erroneous reports on the safety of vaccines. A review of several flawed studies is included (**Appendix A**). Manufacturers are not only falsely promoting their products as safe but in many cases lobbying to have mandatory immunization with their vaccines.

Public safety is at jeopardy because the manufacturers are not in compliance with US regulation such as 21 CFR 601.2 and other statues governing the proper testing and labeling of pharmaceuticals. The FDA has failed to:

- \* Require manufacturers to perform proper safety studies
- \* Require manufacturers put proper warnings on their products
- \* Prevent manufacturers from making false statements about the safety of their vaccines

### **C. Environmental impact**

There is no environmental impact imposed by the relief requested in this petition.

### **D. Economic impact**

Not applicable at this time.

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**E. Certification**

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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.

Please feel free to contact me if you have any questions or desire to meet to discuss how to improve the safety of vaccines.

Sincerely,



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Appendix

Paper entitled "Study Design Flaws Hide Association between Vaccines and IDDM"

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## **Study Design Flaws Hide Association between Vaccines and IDDM.**

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## **Introduction**

We recently published data from a prospective randomized clinical trial that proved the Hemophilus vaccine causes IDDM (1). This data is supported by several additional epidemiology studies (2). Several authors have performed studies and have been unable to duplicate our findings. Recently the Institute of Medicine reviewed the published data and erroneously concluded that “the epidemiological evidence favors rejection of a causal relationship between multiple immunization and an increased risk for type 1 diabetes” (3). The failure of several studies to show an association between vaccines and IDDM can be explained by study design flaws. Common study design issues affecting the ability to detect an association between immunization and IDDM are discussed below.

### **Lack of statistical power**

Graves et al (4) published a paper which questioned the ability of the hemophilus and other vaccines to cause IDDM. She employed a case control study and concluded “results of this and other studies do not suggest that any change in the immunization schedule would prevent the development of B-cell autoimmunity or lower the risk of developing type 1 diabetes.” Graves relied on a single autoantibody to predict the development of IDDM and it is well known that a single autoantibody has very low specificity for predicting the development of IDDM (5). She studied only 25 individuals with an autoantibody and 292 controls. Only 5 antibody positive children in Grave's study group developed diabetes. Graves' found the hemophilus vaccine associated with an odds ratio of 1.64 which is even greater than the relative risk of 1.17 found with the hemophilus vaccinated children by age 10 in Finland (1). Therefore, her data actually supported an association between the hemophilus vaccine and IDDM in contrast to what she states (6). Several case control studies (7, 8) found similar or higher odds ratios associated with the hemophilus vaccine, than found in Finland. However all were not powered to reach statistical significance and they authors concluded their findings do not support an association between the hemophilus vaccine and IDDM.

### **Erroneous data, calculations and incomplete analysis**

Tuomilehto and others (9) published a preliminary analysis of clinical trial data pertaining to the effect of the Hemophilus vaccine on IDDM in Finland. They concluded that the hemophilus vaccine was unlikely to cause IDDM. However their analysis was severely flawed (10). The study involved groups receiving 4 doses, 1 dose and 0 doses of hemophilus vaccine. The cumulative incidence of IDDM/100,000 in the 3 groups were 261, 237, 207 at 7 years and 398, 376, 340 at 10 years of age respectively. Tuomilehto compared groups receiving 4 doses to 1 dose and groups receiving 1 dose to 0 doses. This analysis minimizes the difference. Most researchers would compare the group receiving 4 doses to the group receiving 0 doses. Alternatively they would compare the combined vaccinated groups to the group receiving 0 doses. Both reach statistical significance. The authors failed to perform a cluster analysis which

showed most of the extra cases of IDDM occurred in clusters starting approximately 3 years after immunization and lasting approximately 6-8 months. The paper passed peer review in part because the data that was submitted was erroneous and actually showed an higher incidence of IDDM in unvaccinated controls than in the vaccinated groups. The calculations of relative risk in the final manuscript were erroneously low as well.

Karen Poutasi, the Minister of Health in New Zealand, published two letters (11) (12) trying to refute an association between the hepatitis B vaccine and a rise in the incidence of IDDM in the South Island of New Zealand, Canterbury (13, 14). She stated a reasons for believing that the hepatitis B vaccine does not cause IDDM "The Auckland registry (North Island) did not exhibit any epidemic increase after December 1989 when hepatitis immunization was recommended at age 6 weeks (12). She states "Classen fails to explain why the Auckland diabetes registry did not show any increase following the introduction of the Hepatitis B vaccine." However a later publication from New Zealand admitted a rise in IDDM did occur in the North Island (15).

Willis and Scott (16), question the published association (13) between the hepatitis b vaccine and the development of IDDM in New Zealand. They compared the incidence of IDDM in children born before February 1988 to the incidence in children born after this time. They concluded the data does not support an association between Hepatitis B immunization and IDDM. The analysis was flawed for two reasons. First it assumed those born prior to 1988 did not receive hepatitis B vaccine. In fact there was a massive catch-up program in New Zealand with the hepatitis B vaccine originally given to all preschool children (17) but was soon expanded so that all the children under the age of 16 received the hepatitis B vaccine, not just those born after 1988. The acceptance rates were estimated to be above 70% (Personal communications, Dr. Harry Nicholls, Senior Advisor for Communicable Diseases, Ministry of Health, Wellington, NZ). Thus children born in the 1970s and early 1980s received the hepatitis B vaccine. Second the incidence of IDDM differs depending on the age of the child in most countries including New Zealand, with fewer cases of IDDM occurring in ages 1-5 versus 10-14 (18). Willis' analysis only proves that the incidence of IDDM is higher in older children, those born before 1988, than the very young children, those born after 1988.

### **Timing of immunization**

A paper from Montreal (19) was published on an association between the BCG vaccine and the incidence of IDDM in Quebec. The Montreal paper contains two separate case control studies, series A and B. Series B analyzed cases of IDDM in 0-18 year olds occurring between 1982 and 1986. Series A pertains to a population of children 7 or older. The authors concluded that there was no effect of the BCG vaccine on the development of IDDM. The analysis was flawed however because it did not consider the effect of timing of the first dose of BCG vaccine on the development of IDDM. Immunization with BCG at birth is associated with a decreased risk of IDDM while immunization starting at school age is associated with an increased risk of IDDM (2).

Sufficient data was not available from this paper to determine how many children immunized in the first year of life were actually immunized in the first month of life. However analysis of cases and controls indicates the BCG vaccine is associated with an increased risk of IDDM when given starting after 1 year of life. Series B contained 249 cases of IDDM and 431 prospectively collected matched controls age 0 through 18. The authors found 14 of 249 diabetics had received BCG immunization after 1 year of life versus 12 of 431 controls, odds ratio 2. This is consistent with ecological data from Europe (20). Data from Series A that was incomplete and not easily analyzable.

### **Inadequate follow up time**

Hyoty (21) studied the effect of the measles mumps rubella vaccine on the development of IDDM. Their analysis found an statistical significant rise in the incidence of IDDM in children under 5 who received a MMR vaccine at age 1 but only a small rise in the incidence of IDDM in children immunized at 6 years of age. The analysis was flawed (20). The MMR vaccine was given to children 6 years of age in Finland however the authors only studied the effect on IDDM in children age 7 and older (21), thus potentially missing the rise in the incidence of IDDM in 6 year olds who received the vaccine. Another reason why Hyoty's calculation resulted in a low relative risk of the MMR vaccine in the children age 7-9 can be explained in part by the short follow up time in the study. Hyoty did not follow the children for a total of 4 years after immunization and thus likely missed a large number of cases of vaccine induced IDDM. Studies have shown that vaccine induced cases of IDDM often do not occur until 3 to 4 years after immunization (1). The children born in December of 1981, and immunized with MMR at age 6, were followed through the end of 1990 for the development of diabetes. Therefore they would have barely reached age 9 by the end of the study and would have been followed for less than 3 years after receiving the MMR vaccine.

### **Confounding effect of multiple vaccines and other factors**

Sweden stopped the BCG (1975), smallpox (1976), pertussis (1979) and started the MMR (1982) vaccines in a close temporal fashion (22) making it difficult to study the effect of a single vaccine on the development of IDDM. The confounding effect of the changes of the different vaccines on IDDM had the ability to influence the outcome of several studies performed in Sweden looking at the association between vaccines and IDDM.

The effect of the DTP vaccine on IDDM was studied in Sweden (23). The study involved comparing the incidence of IDDM in birth cohorts that received a DTP vaccine lacking an aluminum adjuvant, 1977 and 1978 birth cohorts to birth cohorts receiving a DT vaccine containing an aluminum adjuvant, birth cohorts 1980 and 1981. Both groups appeared to have similar rates of IDDM. The analysis was flawed because the MMR vaccine was started at about the same time that the pertussis vaccine was discontinued in Sweden. The 1977 and 1978 birth

cohorts received the pertussis vaccine but did not receive the MMR vaccine at age 18 months. The 1980 and 1981 birth cohorts did not receive the pertussis vaccines but did receive the MMR vaccine at age 18 month. Thus the results indicate the pertussis vaccine had an effect similar to the MMR vaccine. Based on the study it is not possible to distinguish the effect of the aluminum adjuvant from the pertussis vaccine. Therefore one can not make a conclusion on the effect of the pertussis vaccine on IDDM. It is likely that both the aluminum adjuvant and the pertussis vaccine increase the risk of diabetes because both are immune stimulants.

Bloom et al (22) presented data that the measles mumps rubella (MMR) vaccine may be associated with a protective effect on IDDM, odds ratio 0.69 with confidence interval between 0.48-0.98. The presumed mechanism is that immunization with the live attenuated virus protected children from natural infections with the virulent natural viruses. The authors did not look specifically at those that were not immunized and did not get infected since these people may be at an increased risk of developing IDDM. The study is extremely difficult to interpret because it did not evaluate the confounding effects of other vaccines. For example 86% of diabetics who were asked to participate entered the study where as only 67% of controls asked to participate did so. The result is that the actual controls that entered the study may not have been well matched to the actual group of diabetics that entered the study.

Dahlquist and Gothefors (24) published Swedish data and concluded that the BCG vaccine does not alter the incidence of IDDM. Their analysis was flawed (2, 25) and reanalysis of the data indicates that immunization at birth with BCG is associated with a clinically significant reduction in IDDM. The concern with the Dahlquist and Gothefors' analysis is that it fails to acknowledge that the smallpox vaccine was discontinued in 1976 in Sweden, while the BCG vaccine was discontinued in 1975. The smallpox vaccine was administered in Sweden primarily at 2 months or 9 months of age (26) (27) as compared to the BCG vaccine which was administered at birth. Data from rodent and human studies (1) show that vaccines administered starting after 2 months of life increase the incidence of IDDM thus having the opposite effect of administering vaccines at birth (2). The Swedish BCG data needs to be analyzed in a way to compensate for the confounding effect of the smallpox vaccine.

### **Improper definition of unimmunized**

A seven center collaborative study looked for an association between vaccines and the development of IDDM (8). The study involved 900 diabetic children and 2,302 controls. Data from one center, Austria, (28) was published separately. The vaccinated group in the Austrian center was comprised of those with complete immunization while the unimmunized group comprised of people who did not complete the recommended number of shots for a given vaccine. Data on the hemophilus vaccine from Finland (10) indicates that there is likely to be little difference expected in the incidence of IDDM between those receiving 3 and those receiving 4 doses of the HiB vaccine since the majority of the effect on IDDM occurs with the first shot. Furthermore, prediabetics may experience more severe acute adverse events following immunization because of their hyperactive macrophages (29, 30) thus they may be less likely to

complete immunization than people who do not have a propensity for IDDM. Using a case control design similar to that used by the Austrians would give the erroneous interpretation that vaccines are protective against IDDM.

### **Insufficient data**

A US case control study (7) found the acellular pertussis vaccine associated with a odds ratio of .92 or 1.12 depending on the which regression analysis they used. The whole cell pertussis vaccine was associated with odds ratios of 0.23 and 0.28 depending on which regression analysis they used. About 30 % of children received both the whole cell pertussis vaccine and the acellular pertussis vaccine. Very few children received the acellular pertussis vaccine alone. The data was incomplete however since the authors did not show the rates for pertussis immunized versus not pertussis immunized, only the subgroup analysis described above. The study also had the short comings of several of the papers above, insufficient power, no adjustment for confounding vaccines, and the possibility of biases due to the likelihood that diabetes prone children could have more severe acute vaccine reactions.

### **Improper controls and endpoints**

A German group (31) performed an almost identical study to that performed by Graves (4). The case control study involved 29 patients with a single autoantibody associated with the development of IDDM, and 251 controls. Only 4 children actually developed diabetes. It is well known that a single autoantibody has very low specificity for predicting the development of IDDM (5). Patients were followed for as little as two years after birth. The controls were not well matched by age to the cases. The controls appear to be older, thus likely to have received more vaccines solely because they are older. The study thus contains some of the same flaws as Grave's study.

### **Conclusion**

We have proven that the hemophilus vaccine causes IDDM in humans (1). Additional data indicates several other vaccines cause IDDM as well (2). Several studies have been performed but have been unable to repeat our findings. Analysis of these studies reveals several study design issues that prevented the authors from duplicating our findings. Knowledge of these study design issues will hopeful allow others to repeat our findings.

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