SUMMARY FOR BASIS OF APPROVAL

Reference Number: 93-0395
Merck and Co.
Varicella Virus Vaccine Live
VARIVAX®

Varicella Virus Vaccine Live (Oka/Merck) is a preparation of the Oka/Merck strain of live, attenuated varicella zoster virus (VZV). The virus was obtained from a child in Japan with natural varicella and was attenuated by several passages in human embryonic lung cell cultures, followed by propagation in embryonic guinea pig cell cultures, and finally propagated in human diploid cell cultures.

I. Indications and Usage

VARIVAX® is indicated for vaccination against varicella zoster virus in individuals 12 months of age and older.

Revaccination

The duration of protection of VARIVAX® is unknown at present and the need for booster doses is not defined. However, a boost in antibody levels has been observed in vaccinees following exposure to natural varicella as well as following a booster dose of VARIVAX® administered four to six years post vaccination.

In a highly vaccinated population, immunity for some individuals may wane due to lack of exposure to natural varicella as a result of shifting epidemiology. Post-marketing surveillance studies are ongoing to evaluate the need and timing for booster vaccination.

Vaccination with VARIVAX® does not result in protection of all healthy susceptible children, adolescents, and adults.

II. Dosage and Administration

VARIVAX®, when reconstituted as directed, is a sterile preparation for subcutaneous administration. Each 0.5 ml dose contains the following: not less than 1500 PFU (plaque forming units) of Oka/Merck varicella virus at expiry; not less than 1350 PFU 30 minutes after reconstitution, sucrose, hydrolyzed gelatin, sodium chloride, monosodium-L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride, residual components of MRC-5 cells including DNA and protein, and trace quantities of sodium phosphate monobasic, EDTA, neomycin, and fetal bovine serum. The vaccine contains no preservative.

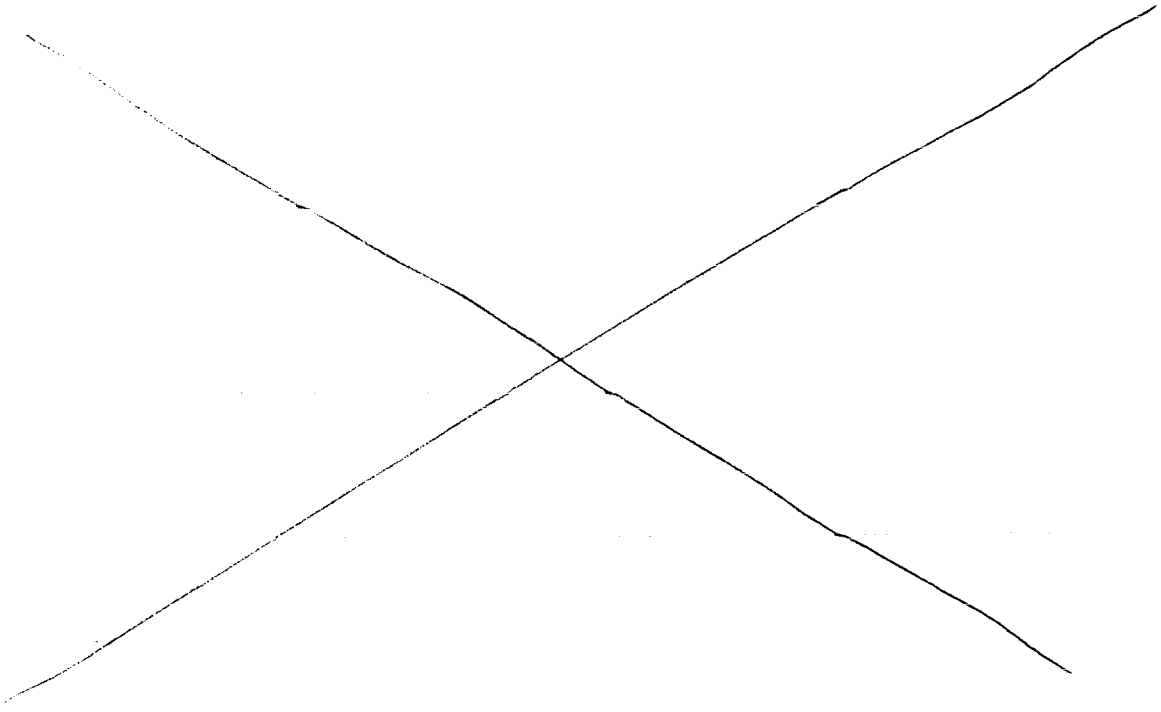
Vaccination in children 12 months to 12 years of age consists of one dose (0.5 ml) of VARIVAX® administered subcutaneously. Vaccination in adolescents and adults 13 years of age and older consists of two doses (0.5 ml, each) of VARIVAX® administered subcutaneously 4-8 weeks apart. Although VARIVAX® is recommended for subcutaneous administration (anterolateral thigh or upper arm), in clinical trials some children were given VARIVAX® intramuscularly. The seroconversion rates were similar to those observed in children who received the vaccine by the subcutaneous route. The vaccine should not be administered intravenously.

Reported adverse reactions were generally mild and included rash, soreness, and induration at the injection site, and generalized varicella-like rashes. Other reported complaints after immunization are summarized in Table 5.

III. Manufacturing Control

A. Manufacturing and Controls

The varicella-zoster virus was originally isolated from a three year old boy with typical chickenpox, by Dr. Michiaki Takahashi, et al. at the Research Institute for Microbial Diseases, Osaka University, Japan. This isolate was serially passaged through primary human embryonic lung culture, followed by guinea pig fibroblasts, and WI-38 cells. Subsequent passage of the virus is in MRC-5 cells.



Sterility of the pooled bulk vaccine is ensured by controlled aseptic processing

throughout the manufacturing process. Varicella Virus Vaccine Live (Oka/Merck) is manufactured using a robotic system which performs of manipulations and provides a high degree of aseptic processing and sterility assurance.

Control of viral adventitious agents is based on testing of the Master Seed, Stock Seeds, and Manufacturer's Working Cell Banks to ensure absence of other viral agents (including adenovirus-associated virus and retroviruses) as well as other microbial agents.

In addition, each batch of vaccine is tested to verify absence of viral adventitious agents using a testing approach appropriate for the varicella-zoster virus and MRC-5 host cell culture system used in the manufacture of this vaccine. Other than vaccine virus, no viral agents have been detected in any of the batches tested.

Karyological testing of the MRC-5 cell substrate used to produce Varicella Virus Vaccine Live revealed the presence of a clonal 7;12 translocation in cells derived from some manufacturer's working cell banks. In some flasks, at passages comparable to that used for vaccine manufacture, cells with this translocation comprised more than 5% of the cells. Additional experiments were performed to address the possibility that this anomalous DNA (or other cellular DNA in the vaccine) might integrate into and transform host cells. This translocation is not associated with any known genetic disease in humans. Further testing of these cells indicated no evidence for tumorigenicity in nude mice, and showed normal senescence in tissue culture. The approximately 2 µg of cellular DNA per dose of vaccine was determined to be unlikely to integrate into host cells and cause harm under the conditions of vaccination. The Vaccines and Related Biological Products Advisory Committee, with supplemental expert testimony, concluded on August 23, 1994 that this anomaly did not pose a safety risk which exceeded the known benefit of the vaccine.

Prior to filling into the final container, the clarified bulk is thawed and diluted to the target potency level. The final formulated bulk is tested for sterility. The filled vials are frozen and lyophilized to minimize potency loss. The vials are removed from the lyophilizer cabinet and stored at -20°C, or colder prior to labeling and packaging. Filled containers are tested for sterility, potency, identity, moisture, restoration, pH, and general safety. These tests have been determined to be appropriate for controlling the safety, freedom from contamination, and immunogenicity of the vaccine.

Varicella Virus Vaccine Live is a live virus vaccine which, due to the labile nature of the virus, does not undergo purification. Each 0.5 ml dose of the vaccine contains not less than 1500 PFU of Oka/Merck varicella-zoster virus (not less than 1350 PFU 30 minutes after reconstitution, sucrose, hydrolyzed gelatin, sodium chloride, monosodium-L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride, residual components of MRC-5 cells, and trace quantities of sodium phosphate monobasic, EDTA, neomycin, and fetal bovine

serum. The vaccine contains no preservative.

Lot release testing is performed on each lot of vaccine. In addition, new Master Seeds are evaluated for neurovirulence in monkeys.

B. Stability

The recommended storage temperature of the vaccine is -15°C or colder in a frost free freezer. Stability of the vaccine was monitored by the demonstration of potency in a plaque assay. Four lots of the vaccine were studied for 18-21 months. There was no statistically significant difference between the slopes of the five lots tested at any of the long term storage temperatures. The estimated loss in potency with storage at -15°C for 18 months is 18%. No loss in potency was observed at storage temperatures of -20°C or colder.

Stability testing of the reconstituted vaccine at 2-8°C shows potency losses of up to one half hour after reconstitution. Testing of the reconstituted vaccine at room temperature (20-25°C) showed similar losses. These data support holding the vaccine for up to 30 minutes at room temperature prior to administration. The package insert states that reconstituted product is to be used immediately and discarded if not used within 30 minutes.

The expiration dating for Varicella Virus Vaccine Live is 18 months at -15°C starting at the date of removal from -20°C for packaging. The package insert recommends storage at -15°C in a frost-free freezer. Prior to packaging, the product may be stored by the manufacturer for up to 24 months at -20°C or colder.

Varicella Virus Vaccine Live retains a potency level of 1500 PFU or higher per dose for at least 18 months in a frost-free freezer with an average temperature of -15°C or colder. The vaccine has a potency level of approximately 1350 PFU 30 minutes after reconstitution at room temperature (20°-25°C).

C. Validation

The major equipment systems and processes used in the manufacture and filling of the vaccine have been validated at the Merck & Co., Inc., West Point, PA, facilities. In addition, appropriate specifications have been established for monitoring environmental conditions and utilities for critical work areas in the manufacturing facility. Validation analyses for product potency and purity are performed at Merck & Co., Inc. The test methods were found to be suitable for control and regulatory purposes.

D. Labeling

The primary label used on the vials of Varicella Virus Vaccine Live states: the proper name and the trade name, VARIVAX®; vial size and volume; the caution

"STORE FROZEN"; the Durham-Humphrey statement; a space for adding the lot number and expiration date at the time of packaging; a space for the component number; the manufacturer's name and address "Dist. by: Merck & Co., Inc., West Point, PA 19486, USA; "and U.S. Govt. Lic. No 2.

The primary label used on the vials of Sterile Diluent for Merck & Co., Inc., Live Virus Vaccines (Sterile Water) states: the proper name, the vial size and volume; the product number; the statement "Contains No Preservatives"; the Durham-Humphrey statement; a space for adding the lot number and expiration at the time of packaging; and the manufacturer's name and address "Dist. by: Merck & Co., Inc., West Point, PA 19486, USA.

The carton containing 10 vials of diluent states: the proper name Sterile Diluent for Merck & Co., Inc., Live Virus Vaccines (Sterile Water) states: the proper name, the quantity of diluent vials and the volume of each, the product number, an ingredients and preservatives statement; directions for use; the letter code "B" identifying it as the diluent carton; the Durham-Humphrey statement; a warning to use only this diluent for reconstitution of the vaccine and to see the package circular for administration instructions; a storage statement; a space for the component number; a space for adding the lot number and expiration at the time of packaging; and the manufacturer's name and address "Dist. by: Merck & Co., Inc., West Point, PA 19486, USA."

The package insert (copy attached) is in compliance with the appropriate sections of 21 CFR, and contains statements regarding description, clinical pharmacology, indications and usage, contraindications, precautions, adverse reactions, dosage and administration, how supplied, and information on the stability and storage of the vaccine.

The trade name is not in conflict with the name of any other drug.

E. Establishment inspection

A pre-license inspection of the Merck biological production facilities in West Point, PA, was conducted by the Food and Drug Administration from February 28 through March 4, 1994. Compliance relative to all inspectional observations was demonstrated prior to licensure.

F. Environmental Impact Analysis Report

An environmental assessment for the manufacture and use of Varicella Virus Vaccine Live (Oka/Merck) was completed to address the environmental impact considerations of 21 CFR, Part 25. The information provided for this environmental assessment supports the finding of no significant environmental impact.

IV. Pharmacology

The safety and efficacy of VARIVAX® was evaluated in clinical trials which used lots of vaccine manufactured in 1982, 1984, 1987, and 1991. Over that period, the vaccine manufacturing process changed to increase the yield, viability and stability of live attenuated virus in the final product. Efforts to optimize vaccine dose coupled with changes in vaccine manufacture led to variability among clinical trials in the amount of live virus (PFU; plaque forming units) and the ratio of live:dead viral antigen administered to vaccine recipients. The decision to license VARIVAX® therefore required the review of information from studies conducted on vaccine manufactured in 1982, 1984, 1987 and 1991.

Preclinical testing also addressed the question of whether the vaccine lots produced in different years represented the same product. Virus strains from these campaigns produced similar quantities of glycoproteins, induced similar titers of antibodies, and retained restriction endonuclease cleavage sites and sequences in regions which are potentially variable among different strains of varicella-zoster virus.

An animal model does not exist to test the efficacy of varicella-zoster virus vaccines. The vaccine was tested for oncogenicity in newborn hamsters. There was no evidence for oncogenicity in these tests. In addition, cells used to manufacture the vaccine were tested for oncogenicity in nude mice and by observation of senescence in tissue culture, as described above. Thus, animal studies did not suggest any specific risks in humans.

The labeling is adequate from the standpoint of pharmacology.

V. Medical

A. General Information

Varicella is a common childhood infection in the United States. The disease has a seasonal occurrence with the peak incidence generally occurring between March and May. The estimated number of cases of varicella in the United States per annum is approximately 3,500,000. Over 90% of cases occur in children 1 to 14 years of age; 60% of these cases occur among children 5 to 9 years of age. The CDC estimates that between 8.3% and 9.1% of children ages 1-10 contract varicella each year (depending on age, Wharton et al., ICAAC 1991). Varicella is uncommon in infants less than 1 year of age and in adults over 20 years of age. Each of these latter two groups account for only 2 to 3% of all cases of varicella. However, the morbidity and mortality of the disease in these groups are much greater than in children 1-14 years of age.

Primary varicella infection is a generalized illness that has an incubation period of approximately 11 to 20 days, is highly contagious, and is characterized by a papulovesicular rash that usually resolves in 5 to 20 days with or without residual scarring. Although immunity following VZV infection is generally long-lasting,

the virus persists in latent form in the peripheral nerve tissue (ganglia). While chickenpox is generally a mild disease, it may be complicated by bacterial superinfection of skin lesions, pneumonia, encephalitis, Reye's syndrome, and congenital varicella syndrome. Over 9,000 hospitalizations and 50 - 100 deaths in the U.S. each year are attributed to chickenpox. Infection is more severe among adolescents, adults and the immunocompromised than normal children. Herpes zoster, the clinical disease characterized by a localized vesicular rash involving from one to three dermatomes, is due to the reactivation of latent VZV.

Preparations of immune globulin (varicella-zoster immune globulin-VZIG) given post-exposure to natural varicella have been shown to protect from clinical disease. A vaccine which induces both neutralizing antibody and cellular immunity would be expected to prevent natural disease. Clinical studies with VARIVAX® have shown production of varicella virus antibodies, cellular immunity, and protection from disease.

B. Adequately controlled studies supporting licensure

From 1981 to 1993, VARIVAX® was administered to 9454 healthy children (12 months to 12 years of age) and 1648 adolescents and adults (13 years of age and older) enrolled in clinical studies to assess immunogenicity, efficacy, and safety. The demographics of individuals included in the studies are summarized in table 1. The vaccine was usually administered as one dose in children 1-12 years of age and 2 doses (given 4-8 weeks apart) in adolescents and adults 13 years of age and older.

2. Efficacy

Table 2 provides clinical efficacy data from all vaccine studies submitted to support VARIVAX® licensure.

Over 2,000 children participated in clinical trials of the vaccine produced in 1982. Approximately half were enrolled in a placebo-controlled double-blind study designed to compare the effect of 17,430 PFU of Varicella Virus Vaccine Live to a placebo. No infections occurred among vaccine recipients during the first year of that trial while 0.6% of vaccinees developed breakthrough disease during the second year (Table 2). This compares with the 8.5% rate of chickenpox in the control group during the first year of study. These impressive levels of protection were obtained using a dose of attenuated varicella that was substantially higher than present in the current vaccine (0.5 ml of the licensed product contains an average of 3,500 PFU/dose at the time of manufacture and a minimum of 1,350 PFU 30 minutes after reconstitution at product expiry).

Additional studies of the 1982 vaccine were performed using a dose of 950 PFU. As shown in Table 2, the calculated efficacy of the vaccine at this lower dose ranged from 75% - 87% (1.2% and 2.1% of vaccinees developed breakthrough infections

during the first and second year following immunization, respectively, versus 8.3% - 9.1% wild-type infections among unvaccinated American children of the same age). Considering data from the subset of children who were actively followed in this study, the calculated efficacy two years after vaccination was 72%. It therefore appears that the amount of live virus per dose and the quality of clinical follow-up influenced the protective efficacy calculated for this vaccine.

The 1984 vaccine campaign included approximately 1,300 healthy vaccinees who received doses ranging from 2,460 - 14,000 PFU of attenuated virus. This and subsequent studies were not placebo controlled. In addition, only a subset of participants were actively followed so that the frequency of breakthrough chickenpox among vaccinees relied heavily on passive reporting of illness by parents. In the 1984 study, a protective efficacy of 93% during the first two years following immunization was calculated by i) assuming that all cases of breakthrough chickenpox were reported and ii) comparing this rate with the frequency of wild-type chickenpox in unvaccinated American children.

The 1987 campaign had an enrollment of 4,142 children and the best long-term follow-up of the clinical studies submitted to support vaccine licensure. Using the method described above, 1,000 - 1,625 PFU of vaccine was calculated to provide protective efficacy of 66% - 77% per year over the first two years of follow-up in these children. Among the subset of children on whom active follow-up was performed, protective efficacy over the first two years ranged from 61% - 67% (Table 2).

The 1991 immunization campaign involved 1,164 subjects who received 2,900 - 9,000 PFU of vaccine. The lots of vaccine used in that campaign and those currently manufactured by Merck are nearly identical. Three years of follow-up indicate that the vaccine is approximately 93% effective in preventing breakthrough infection when compared to chickenpox rates in historic controls (Table 2).

An additional method used to estimate vaccine efficacy involved vaccinees exposed to varicella in their home. Previous studies showed that 87% of unvaccinated children with household exposure to wild-type varicella contract disease (Ross et al, NEJM 1962). Combining data from the non-placebo controlled 1982, 1987 and 1991 campaigns, 20% of actively followed vaccinated children exposed to natural varicella in their homes developed breakthrough chickenpox. This represents a 77% decrease from the 87% rate of transmission reported in the literature for unvaccinated individuals. In adolescents and adults who received two doses of vaccine, 17 of 64 (or 27%) reported breakthrough chickenpox following household exposure.

Vaccinated children who contracted varicella usually developed a milder form of breakthrough chickenpox than did unvaccinated controls. In a blinded trial, breakthrough chickenpox was characterized by a 3-fold lower incidence of fever, a 6-fold decrease in the number of chickenpox lesions, and a one day shorter illness than disease in unimmunized controls. Milder illness was also observed in vaccinated adolescents and adults - a population otherwise at high risk for severe

disease.

There have been too few cases of breakthrough chickenpox reported to determine the absolute rate at which the serious but rare complications of varicella infection (such as pneumonitis, encephalitis, hepatitis and congenital varicella syndrome) might occur. However, there is no evidence to suggest that vaccination is associated with an increase in the frequency of the serious complications of chickenpox.

C. Additional data supportive of licensure

1. Immunogenicity

Studies designed to monitor the serum anti-varicella antibody response induced by VARIVAX® immunization were conducted on a subset of vaccinees participating in the efficacy trials. Serological studies to detect and quantify specific antibodies to VZV (anti-VZV) have been performed on vaccinees by several methods. Antisera from vaccinees recognize a spectrum of VZV proteins, especially glycoproteins. The majority of serological data have been generated using a highly sensitive and specific ELISA based on reactivity with an enriched mixture of glycoproteins (gp) isolated from VZV-infected cells (gpELISA). Data from this gpELISA show good concordance with the other serological assays, consistent with the finding that viral glycoproteins are targets of neutralizing antibodies. In vaccinated children, neutralizing antibody titers rise concomitant with gpELISA titer. Children with no history of varicella infection generally had titers below 0.3 "units" by this assay whereas wild-type varicella infection induced titers >1,000.

Seroconversion was not always associated with protection from breakthrough disease. Rather, the higher the gpELISA titer, the greater the likelihood of protection from breakthrough chickenpox. In general, children with gpELISA titers below 2.5 were no better protected from infection than those with no detectable serum antibody. Statistically significant protection from disease ($p < .05$) correlated with gpELISA titers >5. Table 3 provides data on the distribution of gpELISA titers in children immunized with lots of VARIVAX® produced in 1982, 1987 and 1991. As the dose of virus administered rose from 950 to 17,430 PFU, the fraction of children with protective gpELISA titers rose from 60% to 97% (Table 3).

Clinical studies have demonstrated that VARIVAX® induces detectable varicella antibody in 97% of children as measured by gpELISA 6 weeks after one dose. Using a cutoff of ≥ 0.3 units, anti-varicella antibodies were induced in >99% of children vaccinated with 17,430 PFU of virus in 1982, >95% of children vaccinated with 950 - 1,600 PFU of virus in 1982 and 1987 and >99% vaccinated with >2,900 PFU of virus 1991 (Table 3). Studies of seroconversion kinetics in children show that 36%, 100%, and 99% had seroconverted by 2, 4, and 6 weeks post-vaccination, respectively. Seventy-four percent (74%) of children who received between 905 to 9000 PFUs of varicella virus in the vaccine developed titers ≥ 5 U by gpELISA (Table 3), a titer

which correlates with more complete protection from disease. Limited studies of the cellular immune response in vaccinees indicate that VARIVAX® induces a proliferative T-cell response in children, adolescents and adults when measured 4-6 weeks post-vaccination.

In adolescents and adults, 75-94% developed detectable antibody as measured by the gpELISA 4-6 weeks post-vaccination. Seroconversion by the gpELISA was 99% 4-6 weeks after a second dose of vaccine in adolescents and adults. After one dose, only 32% of these subjects developed titers ≥ 5 U by gpELISA (Table 3). More vaccinees developed antibody levels ≥5 U when the two doses of VARIVAX® were administered 8 rather than 4 weeks apart.

In clinical studies involving healthy children who had received 1 dose of vaccine, anti-VZV was present in 98.89% at 1 year, 98.9% at 2 years, 97.5% at 3 years, and 99.5% at 4 years post-vaccination. In addition, limited follow-up data on vaccinees showed that 100% of vaccinees were seropositive at least 7 years post-vaccination. Antibody levels were present at least 1 year in 97.2% of healthy adolescents and adults who had received 2 doses of Varicella Virus Vaccine Live separated by 4-8 weeks.

D. Additional data on clinical issues.

1. Safety & Communicability

VARIVAX® has been generally well tolerated. The type and incidence of complaints which were reported within 42 days post-vaccination in ~8900 children are summarized in Table 3. Injection site complaints and non-injection site rashes (varicella-like, generalized were reported in 19.3% and 3.8% of children, respectively). Oral temperatures ≥102°F (39°C) were reported in 14.7% of children over the 42 day follow-up period. The most common systemic complaint in children was upper respiratory illness (62.4%). In a placebo-controlled efficacy trial with VARIVAX®, 16% of children who received placebo reported an oral temperature ≥102°F during 56 days of follow-up. Comparable rates of other systemic reactions were observed in the vaccine and placebo groups.

The types and incidence of complaints which were reported within 28 or 42 days post-dose 1 and dose 2 in ~1600 adolescents and adults are summarized in Table 4. Injection site complaints were reported in 24.4% and 32.5% of vaccinees post-dose 1 and dose 2, respectively, Non-injection site rashes (varicella-like, generalized) were reported in 5.5% and 9.5% of vaccinees post-dose 1 and dose 2, respectively. The most common systemic complaint in adolescents and adults was upper respiratory illness (43.4% post-dose 1 and 39.7% post-dose 2).

Reye's syndrome has occurred in children and adolescents following natural varicella infection, the majority of whom had received salicylates. In clinical studies in healthy children and adolescents in the United States, physicians advised

varicella vaccine recipients not to use salicylates for six weeks after vaccination. There were no reports of Reye's syndrome in varicella vaccine recipients during these studies.

The potential exists for vaccinees to transmit the Oka strain of varicella to household contacts. Six of 446 unvaccinated children seroconverted while three additional children developed chickenpox after household exposure to siblings immunized with VARIVAX (Weibel, et al. NEJM 1984). Nine unvaccinated controls developed 'chickenpox-like rashes' but did not seroconvert, although the IAHA assay used to detect serum anti-varicella antibodies in that study was less sensitive than the gpELISA. These data suggest that vaccine recipients may transmit the attenuated strain of varicella virus to close contacts. The labeling appropriately suggests that vaccinees should avoid contact with susceptible high-risk individuals or non-immune pregnant women for several weeks after receiving VARIVAX® (package insert). The relative risk of a vaccinee transmitting the attenuated strain of varicella to an immunocompromised family member must be weighed against the risk of wild-type infection in the absence of vaccination.

2. Herpes zoster

Eight cases of herpes zoster have been reported in children during 44, 994 person years of follow-up in clinical trials resulting in a calculated incidence of 18 cases per 100,000 person-years. These were, for the most part, milder than typical cases of zoster caused by wild-type virus. One case of herpes zoster has been reported in the adolescent and adult age group during 7826 person-years of follow-up, resulting in a calculated incidence of 12.8 cases per 100,000 person years. All nine cases were mild and without sequelae. Two of the cultures (one child and one adult) obtained from vesicles were positive for wild-type VZV as confirmed by restriction endonuclease analysis. The long-term effect of VARIVAX® and the influence of exposure to wild-type varicella among vaccinees studied so far on the incidence of herpes zoster is unknown at present.

There is an additional concern that universal vaccination might result in increased rates of zoster in vaccinated and unvaccinated individuals. Evidence suggests that re-exposure to natural chickenpox boosts cellular immunity and potentially reduces an individual's likelihood of developing zoster. Since vaccine-induced herd immunity will reduce exposure to wild-type varicella, mathematical modelling indicates that the frequency of zoster in adults could increase. Careful monitoring of zoster rates over time will facilitate the detection of such an effect.

3. Simultaneous administration with other childhood vaccines

VARIVAX® can be administered concomitantly with M-M-R-II® using separate syringes at separate injection sites. Limited data in studies using an investigational vaccine, a formulation combining live attenuated measles, mumps, rubella, and varicella vaccines in one syringe, suggest that the varicella vaccine can be

administered concomitantly with booster doses of DTaP (diphtheria, tetanus, acellular pertussis) and PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] using separate sites and syringes. However, anti-varicella levels were decreased when the investigational vaccine containing varicella was administered concomitantly with DTaP or PedvaxHIB. Additional studies are ongoing to assess concomitant use of VARIVAX® with other pediatric vaccines.

4. Duration of efficacy

The duration of the immune response induced following vaccination with VARIVAX® is an issue of considerable importance. It is unknown whether children who are immunized with varicella vaccine develop lifelong immunity. If the protective effect of immunization wanes, a program of universal immunization may create a population of adults who are at risk of serious illness.

Several factors complicated the assessment of long-term varicella vaccine efficacy. First, most of the clinical trials conducted by Merck were designed to monitor short-term rather than long-term efficacy. Second, many patients in these trials were followed passively and their participation in the trial waned as time following vaccination increased. Table 2 documents this effect and shows that the calculated frequency of breakthrough disease varied among actively versus passively followed children. Third, subjects vaccinated during the 1987 campaign who did not produce serum antibodies against varicella were generally re-immunized with vaccine one year later. Thus, the effect of a single vaccination in this trial was obscured.

The 1987 study contained the largest number of children actively followed for more than three years. Results from that study indicate that the highest level of protection was obtained during the first two years post immunization (Table 2). There was an approximate 32% decrease in protective efficacy from the first to fifth year post immunization ($p. <.01$). However, breakthrough rates were relatively stable from 3 - 5 years post vaccination, suggesting that immunity was maintained over that period (Table 2). Only three years of follow-up data were available from the 1991 campaign, but protective efficacy exceeded 90% throughout that trial (Table 2). While there was little active long-term follow-up of subjects participating in the 1982 and 1984 trials, passive follow-up suggests that immunity persisted during those trials as well.

Serologic studies of children immunized with VARIVAX® showed that anti-varicella titers not only persisted but actually increased with time post immunization (Fig 1). This seemingly paradoxical finding highlights an important limitation to the long-term analysis of vaccine efficacy. Wild-type varicella is endemic in the U.S, so some children participating in efficacy trials were undoubtedly re-exposed to chickenpox when their friends or siblings became infected. Such inadvertent exposure could have boosted the vaccinee's immune response, resulting in increased serum antibody titers and potentially extending the

subject's immunity to varicella. Only after most children are immunized with VARIVAX® will this booster effect diminish and an unequivocal analysis of the vaccine's long-term efficacy become possible.

To monitor the effect of vaccine use, Merck has agreed to conduct phase IV (post-licensure) studies. These include trials in which a cohort of i) 25,000 immunized children will be followed over the short term to detect rare adverse events, ii) 7,000 children will be actively followed for at least 15 years to monitor changes in varicella rates and iii) five sets of 8,000 children will be studied over 15 years to determine whether varicella incidence changes following wide-spread vaccine use. In addition, Merck will conduct case-control studies of vaccine effectiveness over a 15 year period, monitor varicella epidemiology among children enrolled in certain day care centers, monitor the persistence of antibody in children and adults immunized with VARIVAX®, and examine whether the anamnestic response induced by re-vaccination varies over time. These studies will be supplemented by epidemiological surveys conducted by the CDC designed to assess the frequency of varicella infection following widespread use of VARIVAX®.

5. Immunotoxicology

As noted above, human MRC-5 cells are the substrate upon which the Oka strain of varicella is grown. In the process of isolating virus from these cells, MRC-5 derived proteins and DNA are also obtained. The nearly 2 μg of unmodified mammalian DNA present in each dose of VARIVAX® exceeds that present in any other approved childhood vaccine.

To assess whether these impurities could induce a harmful anti-DNA autoimmune response, serum IgG anti-DNA antibody levels were monitored in a cohort of 293 subjects who were immunized and boosted with VARIVAX®. A comparison of anti-DNA titers before immunization and at 6 weeks and 1 year after boost showed no significant change in either the average anti-DNA antibody titer or the frequency of elevated anti-DNA titers in immunized subjects.

E. Labeling

The labeling is adequate from the perspective of the clinical studies.

VI. Advisory Panel Consideration

Data concerning the safety and efficacy of VARIVAX® for the prevention of varicella disease (chickenpox) were discussed in open public hearings at the Vaccines and Related Biological Products Advisory Committee meetings on the following dates: January 14, 1985, January 24, 1986, July 22, 1986, June 17, 1987, January 25, 1990, January 28, 1994, and January 27, 1995. Data concerning manufacturing issues of VARIVAX® were discussed in closed session at the

Vaccines and Related Biological Products Advisory Committee meetings on June 7, 1994, and August 23, 1994.

Philip R. Krause, M.D., Chairman

Dennis Klinman, M.D., Ph.D.

Norman Baylor, Ph.D.

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TABLE 1
Demographics of persons included in clinical studies of VARIVAX®

	Healthy children (Ages 1-12 years)	Healthy Adolescents & Adults (≥13 years)
Male	4895 (51.8%)	636 (38.6%)
Mean age (years)	3.94	25.88
Female	4559 (48.2%)	1012 (61.4%)
Mean age (years)	4.03	27.39
Total	9454 (100%)	1648 (100%)
Mean age (years)	3.98	26.81

Table 2. Long-term clinical follow-up of VARIVAX® Recipients

A. Active and passive follow-up combined

Annual Breakthrough Incidence and (Number of Vaccinees Studied)

Interval after immunization	Vaccine Manufacturing Campaign 1982#	1982±	1984	1987	1991
1	0.2% (487)	0.4% (908)	0.3% (1154)	2.1% (3537)	0.2% (1011)
2	0.0% (543)	1.2% (1021)	0.9% (1294)	2.9% (3842)	0.8% (1134)
3	0.6% (534)	2.1% (1004)	0.6% (1279)	3.3% (3713)	1.0% (682)
4	1.3% (528)	1.2% (989)	0.7% (1271)	3.6% (3563)	
5	1.9% (518)	2.1% (971)	0.8% (1261)	3.3% (3371)	
6	1.0% (513)	0.9% (956)	0.9% (1247)	3.0% (2831)	
7	0.6% (508)	0.3% (951)	0.3% (1076)		
8	0.0% (506)	0.4% (943)			
9	0.2% (505)	0.5% (938)			
10	0.0% (504)	0.0% (917)			
PFU	17,430	950	2,460 - 14,000	1000 - 1625	2900 - 9000

B. Active follow-up alone

Breakthrough Incidence and (Number of Vaccinees Studied) per Year

Interval after immunization	Vaccine Manufacturing Campaign 1982#	1982±	1984	1987	1991
1	0.2% (401)	0.8% (615)		3.0% (2994)	0.6% (955)
2	*	1.2% (417)		3.3% (2415)	0.8% (717)
3	*	2.4% (123)		4.4% (911)	*
4	*	1.8% (111)		4.3% (538)	
5	*	1.9% (108)		4.5% (376)	
6	*	*			
7	*	*			
8	*	*			
9	*	*			
10	*	*			

*Fewer than 100 subjects actively followed during preceding 12 month interval.
+Trial participants in 1982 received either 17,430 PFU (#) or 950 PFU (+) of virus.
For each follow-up interval, the annual incidence of breakthrough varicella (%) and the number of children included in the study population are shown. In part A, calculations assume that all breakthrough cases that occurred in vaccinated individuals were reported. The 12 month follow-up intervals started 6 weeks after initial vaccination in this population. In part B, only those subjects contacted for information on breakthrough disease within the previous interval were included. Individuals re-immunized with vaccine were excluded from further analysis. The 12 month follow-up intervals for these individuals started 6 months after initial vaccination. See Table II for information on vaccine dose. The FDA was not provided with data concerning subjects actively followed in the 1984 trial.

Table 3. Distribution of gpELISA titers among subjects vaccinated with different lots of VARIVAX®

	Percent of trial participants			
gpELISA Titer (OD)	1982#	1982+	1987	1991
≤ 0.3	0.2	4.6	4.6	0.5
>0.3 - 5	2.8	35.4	23.1	9.3
5 - 10*	10.7	28.6	18.8	16.6
>10*	86.2	31.4	53.6	73.6
N	457	714	3603	2625
PFU	17,430	950	1000 - 1625	2900 - 9000

Serum anti-varicella antibody titers were measured 6 weeks following vaccination by gpELISA.

* gpELISA titers correlating with significantly increased protection against subsequent varicella infection.

\+ Trial participants in 1982 received either 17,430 PFU (#) or 950 PFU (+) of live virus.

Table 4

Antibody responses among healthy individuals+ who received VARIVAX®

Population	Seroconversion*	%≥5 gpELISA Titer
Healthy Children 1-12 years		
Dose 1**	97%	74%
Healthy Adolescents & Adults ≥13 years		
Dose 1 ***	79%	32%
Dose 2	99%	82%

+ Includes only subjects who received between 905-9000 PFUs

* Seroconversion= detectable antibody levels by gpELISA (assay not commercially available)

**6 weeks post-vaccination

***4-6 weeks post-vaccination

Table 4

Frequency of clinical complaints (without regard to causality), occurring at a frequency >1% within 42 days following administration of VARIVAX® in healthy children (N=9230*).

Clinical Complaints	Frequency (%)
Injection Site	
Injection site complaints (pain/soreness, swelling and/or erythema, varicella-like rash, pruritus)	19.3
Body as a whole	
Fatigue	27.4
Fever (≥102°F)	14.7
Headache	11.1
Malaise	9.2
Chills	4.8
Digestive System	
Diarrhea	22.8
Loss of appetite	19.8
Vomiting	15.7
Abdominal pain	8.2
Teething	9.7
Nausea	7.1
Constipation	1.1
Respiratory system	
Upper respiratory illness	62.4
Cough	40.4
Lower respiratory illness	3.0
Psychiatric/Behavioral	
Irritability, nervousness	31.4
Disturbed sleep	24.1

Table 4 (continued)

Special Senses	
Otitis	14.9
Eye complaints	6.2
Integumentary System	
Diaper rash/contact rash	11.9
Other rash	8.0
Varicella-like rash	3.8
Allergy/allergic rash/hives	2.1
Heat rash/prickly heat	1.6
Insect bites	1.6
Eczema/dry skin/dermatitis	1.2
Itching	1.1
Hematologic/Lymphatic system	
Lymphadenopathy	3.1
Musculoskeletal system	
Myalgia	3.1
Stiff Neck	1.7
Arthralgia	1.5

*No data on 314 subjects

Table 5
Frequency of clinical complaints (without regard to causality) occurring at a frequency >1% within either 28 or 42 days following administration of VARIVAX® in healthy adolescents and adults.

Clinical Complaint	Frequency (%) Dose 1* N=1639	Dose 2** N=984
Injection Site		
Injection site complaints (pain/soreness, swelling and/or erythema, varicella-like rash, pruritus, hematoma, induration, stiffness)	24.4	32.5
Body as a whole		
Headache	35.4	27.9
Fatigue	29.0	24.4
Malaise	12.0	10.4
Fever (≥100°F)	10.2	9.5
Chills	8.7	7.7
Digestive System		
Diarrhea	11.3	10.7
Abdominal pain	7.7	7.4
Loss of appetite	7.4	6.2
Vomiting	4.4	3.0
Constipation	2.3	1.9
Nausea	13.4	11.3
Respiratory system		
Upper respiratory illness	43.4	39.7
Cough	17.6	19.9
Lower respiratory illness	1.7	2.4
Psychiatric/Behavioral		
Disturbed sleep	15.6	12.4
Irritability/Nervousness	11.1	6.4

Table 5 (continued)

Clinical Complaint	Frequency (%)	
	Dose 1*	Dose 2**
Special Senses		
Eye complaints	8.5	5.9
Otitis	5.2	3.8
Integumentary system		
Varicella-like rash	5.5	0.9
Itching	4.5	0.8
Other rash	3.3	1.9
Allergy/allergic rash/hives	1.4	1.7
Contact rash	1.2	0.6
Cold/canker sores	1.1	1.2
Hemic/Lympthatic system		
Lymphadenopathy	8.8	7.0
Musculoskeletal System		
Myalgia	16.9	13.7
Stiff neck	11.3	7.9
Arthralgia	6.1	4.4

* No data on 33 subjects
** No data on 29 subjects