(Document 1 of 2)

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Merck Research Laboratories
Worldwide Product Safety & Epidemiology

PERIODIC SAFETY UPDATE REPORT FOR:
Measles, Mumps, and Rubella Virus Vaccine Live, MSD

01-Jan-2001 to 31-Dec-2005

International Birth Date: 01-Apr-1978 (Ireland)

Date of this Report: 17-Jan-2006

C

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MERCK

TO: SEE ATTACHED LIST

FROM: [redacted]

DATE: 22-Feb-2006

SUBJECT: Measles, Mumps, Rubella Virus Vaccine Live Periodic Safety Update Report

The attached document represents the 5-year Periodic Safety Update Report (PSUR) for M-M-R II™ (measles, mumps, rubella virus vaccine live). This report is in the format proposed by the International Conference on Harmonisation (ICH), Topic E2C. This is a worldwide document that summarizes safety data received by Merck & Co., Inc. from worldwide sources and updates to the Company Core Data Sheet (CCDS) between 01-Jan-2001 to 31-Dec-2005.

As with all Merck & Co., Inc. products, the safety profile measles, mumps, rubella virus vaccine live is monitored on a continuous basis.

Please submit this PSUR to your regulatory agency only if they require the document. When submitting this PSUR, please submit the full and complete report, as provided.

[redacted]

(484) [redacted]

C

Distribution List – M-M-R®II
Periodic Safety Update Report

TO: SEE ATTACHED LIST

C

CC: [redacted]

FROM: [redacted]

SUBJECT: 5-Year Periodic Safety Update Report for measles, mumps, rubella virus vaccine live, MSD: Reporting Period 01-Jan-2001 to 31-Dec-2005

Please acknowledge the receipt of this Periodic Safety Update Report by completing this form and returning this form to [redacted], or **fax to (484)** [redacted] Thank you in advance for your cooperation.

Sincerely,

[redacted]
Merck & Co., Inc., [redacted]
West Point, PA 19486 USA
☎(484) [redacted]

Name_____Country_____
(Please print clearly)

Did you send this Periodic Safety Update Report to your regulatory agency? Yes/No

Date report sent _____(Day/Month/Year)

If not sent, do you intend to send it? Yes/No

Estimated date to be sent_____(Day/Month/Year)

I hereby acknowledge receipt of this 5-year Periodic Safety Update Report.

_____ _____
(Signature) (Date)

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Merck Research Laboratories
Worldwide Product Safety & Epidemiology

PERIODIC SAFETY UPDATE REPORT FOR:
Measles, Mumps, and Rubella Virus Vaccine Live, MSD

01-Jan-2001 to 31-Dec-2005

International Birth Date: 01-Apr-1978 (Ireland)

Date of this Report: 17-Jan-2006

MERCK

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MEASLES, MUMPS, AND RUBELLA VIRUS VACCINE LIVE
EXECUTIVE SUMMARY
01-Jan-2001 TO 31-Dec-2005

The attached document represents a 5-year Periodic Safety Update Report (PSUR) for measles, mumps, and rubella virus vaccine live, MSD. This report is in the format proposed by the International Conference on Harmonisation Harmonised Tripartite Guideline E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, November 6, 1996 (ICH E2C). This is a worldwide document that summarizes safety data received by Merck & Co., Inc., from worldwide sources, between 01-Jan-2001 to 31-Dec-2005.

Measles, mumps, and rubella virus vaccine live (MSD) is indicated for simultaneous vaccination against measles, mumps, and rubella in individuals 12 months of age or older.

Measles, mumps, and rubella virus vaccine live, MSD, was first approved in Ireland on 01-Apr-1978 and is currently registered and approved in 56 countries. Measles, mumps, and rubella virus vaccine live (MSD) is a live virus vaccine for vaccination against measles (rubeola), mumps and rubella (German measles). Measles, mumps, and rubella virus vaccine live (MSD) is a sterile lyophilized preparation of (1) ATTENUVAX™ (Measles Virus Vaccine Live, MSD), a more attenuated line of measles virus derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; (2) MUMPSVAX™ (Mumps Virus Vaccine Live, MSD), the Jeryl Lynn™ (B level) strain of mumps virus propagated in chick embryo cell culture; and (3) MERUVAX II™ (Rubella Virus Vaccine Live, MSD), the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts.

During the reporting period of this PSUR, the estimated number of marketed measles, mumps, and rubella virus vaccine live doses distributed worldwide between 01-Jan-2001 and 31-Dec-2005 was approximately [redacted] Approximately [redacted] patients are estimated to have been vaccinated, based on the assumption that each patient received one dose. There were approximately [redacted] patients exposed to measles, mumps, and rubella virus vaccine live in [redacted]-sponsored clinical trials during the reporting period of this PSUR.

Overall, 5,149 spontaneous reports were received from healthcare providers and 23 reports were identified from studies.

There were no new major findings that alter the established overall safety profile of measles, mumps, and rubella virus vaccine live and the overall positive benefit over risk for the product.

During the reporting period of this PSUR, safety-related updates made to the Company Core Data Sheet (CCDS) are discussed in Section 4. Changes to Reference Safety Information). There are no pending safety-related updates.

As with all Merck & Co., Inc. products, the safety profile of measles, mumps, and rubella virus vaccine live is monitored on a continuing basis.

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1. Introduction

This PSUR on measles, mumps, and rubella virus vaccine live, (Merck Sharp & Dohme-MSD) is in the format proposed by the ICH E2C. It summarizes the safety data received by Merck & Co., Inc., from worldwide sources, between 01-Jan-2001 and 31-Dec-2005.

Measles, mumps, and rubella virus vaccine live (MSD) is a live virus vaccine for vaccination against measles (rubeola), mumps and rubella (German measles). Measles, mumps, and rubella virus vaccine live (MSD) is a sterile lyophilized preparation of (1) ATTENUVAX™ (Measles Virus Vaccine Live, MSD), a more attenuated line of measles virus derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; (2) MUMPSVAX™ (Mumps Virus Vaccine Live, MSD), the Jeryl Lynn™ (B level) strain of mumps virus propagated in chick embryo cell culture; and (3) MERUVAX II™ (Rubella Virus Vaccine Live, MSD), the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts.

Measles, mumps, and rubella virus vaccine live (MSD) is indicated for simultaneous vaccination against measles, mumps, and rubella in individuals 12 months of age or older.

2. Worldwide Market Authorization Status

B

At the time of this report, measles, mumps, and rubella virus vaccine live (under the Worldwide Tradename of M-M-R II™) had been registered and approved in 56 countries (see Appendix 1). An application is pending in [redacted] There are no records of any registration being revoked or withdrawn for safety reasons.

3. Update on Regulatory or Manufacturer Actions Taken for Safety Reasons

There have been no regulatory or manufacturer actions related to measles, mumps, and rubella virus vaccine live that resulted in marketing authorization withdrawal or suspension, failure to obtain marketing authorization renewal, restriction on distribution, clinical trial suspension, dosage modification, change in target population, or pharmaceutical changes for safety reasons.

4. Changes to Reference Safety Information

The International Physicians Circular (IPC) is the Company Core Data Sheet (CCDS) which contains the Company Core Safety Information (CCSI), indications, dosage, pharmacology, and other product information. The CCDS for measles, mumps, and rubella virus vaccine live that was current at the end of the cut-off date is included in Appendix 2.

4.1 Changes to Reference Safety Information During the PSUR Reporting Period

During the reporting period of this PSUR (01-Jan-2001 to 31-Dec-2005), the following safety-related updates were added to the CCDS for measles, mumps, and rubella virus vaccine live [Changes in **BOLD**]. New sections or subsections that were added are also indicated in **BOLD**.

The updates made in June 2004 included the update of "human albumin" to "**recombinant** human albumin" based on revisions to the manufacturing process. Also "natural" was revised to "wild-type" when describing measles, mumps, or rubella infection/disease for both clarity and specificity. This identifies the infection/disease as being caused by non-vaccine-type measles, mumps, or rubella virus. These two updates were made throughout the CCDS.

23-Feb-2001

SIDE EFFECTS

RARE

Hypersensitivity

Allergic reactions such as wheal and flare at injection site, anaphylaxis and anaphylactoid reactions, as well as related phenomena such as angioneurotic edema (including peripheral or facial edema) and bronchial spasm, urticaria **in individuals with or without an allergic history**.

03-Apr-2002

DOSAGE AND ADMINISTRATION

RECOMMENDED VACCINATION SCHEDULE

Individuals first vaccinated at 12 **to 15 months** of age or older**, in order to avoid maternal antibody interference,** should be revaccinated at 4-6 years of age **since increased risk of exposure typically occurs around elementary school entry.** Revaccination is intended to seroconvert those who do not respond to the first dose.

11-Jun-2004

INTRODUCTION

The reconstituted vaccine is for subcutaneous administration. When reconstituted as directed, the dose for injection is 0.5 mL and contains not less than 1,000 $CCID_{50}$ (50% cell culture **infectious** dose) of measles virus; **12,500** $CCID_{50}$ of mumps virus; and 1,000 $CCID_{50}$ of rubella virus. Each

dose of the vaccine is calculated to contain sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), **recombinant** human albumin (≤0.3 mg), fetal bovine serum (<1 ppm), other buffer and media ingredients and approximately 25 mcg of neomycin. The product contains no preservative.

INDICATIONS

Infants who are less than **12** months of age may fail to respond to the measles component of the vaccine due to presence in the circulation of residual measles antibody of maternal origin; the younger the infant, the lower the likelihood of seroconversion. In geographically isolated or other relatively inaccessible populations for whom immunization programs are logistically difficult, and in population groups in which **wild-type** measles infection may occur in a significant proportion of infants before 15 months of age, it may be desirable to give the vaccine to infants at an earlier age. Infants vaccinated under these conditions at less than 12 months of age should be revaccinated after reaching **12 to** 15 months of age.

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION *Do not inject* ***intravascularly***.

PRECAUTIONS

OTHER

~~This product contains albumin, a derivative of human blood. Although there is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), no cases of transmission of CJD or viral diseases have ever been identified that were associated with the use of albumin.~~

SIDE EFFECTS

OCCASIONAL

Skin

Rash, **or measles-like rash**, usually minimal but may be generalized

Generally, fever, rash, or both appear between the 5th and the 12th days.

RARE

Nervous/Psychiatric

Febrile convulsions in children, afebrile convulsions or seizures, headache, dizziness, paresthesia, polyneuritis, polyneuropathy, Guillain-Barre syndrome, ataxia, **aseptic meningitis (see below)**, measles inclusion body encephalitis (MIBE) (see CONTRAINDICATIONS). Encephalitis/encephalopathy have been reported approximately once for every 3 million doses. In no case has it been shown that reactions were actually caused by vaccine. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with **wild-type** measles (one per two thousand reported cases).

Other

Death from various, and in some cases unknown, causes has been reported rarely following vaccination with measles, mumps, and rubella vaccines; however, a causal relationship has not been established **in healthy individuals (see CONTRAINDICATIONS)**. No deaths or permanent sequelae were reported in a published post-marketing surveillance study in Finland involving 1.5 million children and adults who were vaccinated with M-M-R II during 1982 to 1993.

Cases of aseptic meningitis have been reported following measles, mumps, and rubella vaccination. Although a causal relationship between the Urabe strain of mumps vaccine and aseptic meningitis has been shown, there is no evidence to link Jeryl Lynn™ mumps vaccine to aseptic meningitis.

5. Patient Exposure

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5.1 Clinical Trials

The [redacted] of patients who were enrolled in [redacted]-sponsored clinical trials between 01-Jan-2001 to 31-Dec-2005 and who were treated with measles, mumps, and rubella virus vaccine live was approximately [redacted]

Additionally, there were approximately [redacted] patients who were treated with measles, mumps, and rubella virus vaccine live in a study sponsored by MedImmune entitled "Safety and Immunogenicity of Concurrent LAIV (FluMist®) with Measles-Mumps-Rubella (MMR®II) and Varicella (VARIVAX®) Vaccines in Infants 12 to 15 Months of Age."

5.2 Market Experience

The estimated number of marketed measles, mumps, and rubella virus vaccine live doses distributed worldwide between 01-Jan-2001 and 31-Dec-2005 was approximately [redacted] Approximately [redacted] patients are estimated to have been vaccinated, based on the assumption that each patient received one dose.

6. Presentation of Individual Case Histories

Description of the Data Presented

This PSUR covers the period from 01-Jan-2001 to 31-Dec-2005. Individual case reports (ICRs) included in this PSUR include spontaneous reports received by Merck & Co., Inc., published individual case reports of suspected adverse drug reactions (ADRs) identified by the Company during the period covered by this PSUR, and reports of serious adverse events occurring in clinical studies and considered possibly, probably, or definitely drug-related by the reporting study physician. In keeping with the ICH E2C, throughout this report, these reports are referred to as ADR reports. The use of this term, however, does not imply, necessarily, that the reported events occurred due to an effect of measles, mumps, and rubella virus vaccine live, MSD, either in the opinion of the Company, or in the opinion of the reporter, or in fact. The data described in this document include reports in which measles, mumps, and rubella virus vaccine live, MSD was considered the primary suspect therapy.

References for the published individual patient case reports are included in Appendix 9.

The ADR terminology used in this PSUR reflects the diagnosis or terminology used by the reporter. The reporter terminology has been mapped to a Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) and an autoencoder developed by Merck. On 08-Apr-2002, the Company implemented use of MedDRA for ADR reports. All prior reports in the database have been mapped to MedDRA, version 4.1. The terminology displayed in the line listings and summary tabulations of this PSUR is based on version 8.1 of MedDRA, which was the version of MedDRA that was in use at the time the PSUR line listings and summary tabulations were generated. Due to the mapping of the historic data, changes in MedDRA versions, and evolving coding guidelines and conventions, it is possible that, over time, different Preferred Terms may have been used to identify synonymous reactions. With the transition to MedDRA, the Preferred Terms are now organized into 26 System Organ Class (SOC) groups versus the 15 Body Systems into which Preferred Terms were previously organized. Therefore, with the transition to MedDRA, the summary tabulations supplied in this PSUR may not be able to be compared with those in prior PSURs. In addition, the ADR Preferred Terms tabulated in the line listings and summary tabulations of this PSUR use British spellings. However, American spellings of ADR Preferred Terms are used throughout the discussions in Sections 1 through 10 of this PSUR.

For new spontaneous reports and follow-up information entered into the Worldwide Adverse Experience System (WAES) database on or after 18-Apr-2003 all medical events with onset or worsening after initiation of the primary suspect therapy which did not prompt the contact with the Company and for which there is no implicit or explicit expression of possible drug causality by the reporter, are captured as abstracted events. Abstracted events are adverse events that are not related to the spontaneously reported adverse experience. Previously, these events were described in ADR narratives as "incidental findings." If a subject/patient experiences a medical event while on therapy with a Merck product and this event is mentioned in a report, the event is considered an abstracted event if the following conditions are met:

- The event is not the focus of the report.
- The reporter does not link the event with the current/suspect therapy or any other Merck product; i.e., there is no implication of association with a Merck product.

Abstracted Events are coded and included as adverse experiences in tabulations, but are referred to as abstracted ADRs throughout this PSUR. The numbers of events in these tabulations, therefore, may be larger than comparable numbers in similar reporting periods in prior PSURs because of this change in coding procedures.

For purposes of this report, a serious reaction is defined as one that: results in death, or is life-threatening, or results in a persistent or significant disability/incapacity, or results in or prolongs hospitalization, or is a congenital anomaly, or is a cancer, or is the result of an overdose (accidental or intentional). Since 01-Apr-1998, a serious report could also include any report with an "important medical event" (i.e., requires medical or surgical intervention to prevent one of the aforementioned outcomes).

Spontaneous Reports

Reports on marketed products that were reported spontaneously are presented separately from study reports. Per the general principles of ICH E2C, all adverse experiences from spontaneous reports are assumed to be ADRs unless indicated otherwise by the reporting healthcare provider. Spontaneous reports also include reports from the literature and from government agencies. Only those reports in which a healthcare provider was identified as a reporting source are included in the line listings and summary tabulations in Appendices 3, 4, and 5. These reports may have been reported by healthcare providers or they may have initially been reported by consumers and follow-up was received from healthcare providers. Spontaneous reports in which the only information provided was from consumers, are attached as an addendum and are not further discussed.

The line listings that describe spontaneous reports in which a healthcare provider has been identified are listed in the SOC of the most important ADR term as determined by a Merck reviewer and are separated as follows:

Appendix 3, Table 1 - Line listing of reports that have at least one serious ADR term

Appendix 3, Table 2 - Line listing of reports that have only non-serious ADR terms including one that is unlisted

Reports that have only non-serious, listed ADRs do not appear in the line listings.

The period summary tabulations for spontaneous reports are organized by ADR term and categorized by SOC. The tabulations are separated as follows:

Appendix 4, Table 1 - Period summary tabulation of ADR terms that are unlisted with the number of serious and non-serious reactions for each term

Appendix 4, Table 2 - Period summary tabulation of ADR terms that are listed with the number of serious and non-serious reactions for each term

In addition, a cumulative summary tabulation (Appendix 5) is provided and includes ADR terms that are serious and unlisted.

It is important to emphasize that the spontaneous reporting system is a voluntary system of reporting. Therefore, despite attempts to obtain follow-up information per Standard Operating Procedures, the data are not necessarily complete and may include reports with unsubstantiated diagnoses and incomplete information, irrespective of whether the reports originated from a healthcare provider or consumer.

Study Reports

Study reports include cases from Merck-sponsored investigational clinical trials, from postmarketing clinical trials, compassionate use programs, and from postmarketing surveillance (PMS) studies conducted anywhere in the world. Cases from retrospective and prospective studies that are described in the literature are classified as PMS studies.

The line listings that describe study reports (Appendix 6) include any report that had at least one serious, drug-related ADR term. Reports are also included if drug relationships were unknown or not provided. Drug relationships are those provided by the reporting investigators. The line listings are in the SOC of the most important ADR term as determined by a Merck reviewer.

The period summary tabulations for study reports are organized by ADR term and categorized by SOC. The tabulations are separated as follows:

Appendix 7, Table 1 Period summary tabulation of ADR terms that are serious, unlisted, and drug-related

Appendix 7, Table 2 Period summary tabulation of ADR terms that are serious, listed and drug-related

In addition, cumulative summary tabulations are provided and include study reports that have a serious, unlisted, drug-related ADR term (Appendix 8).

Description of Data Tables

Line Listings

The line listings of reports from spontaneous notifications, from studies or compassionate use, from literature, and from regulatory authorities are in order of SOC. A report that contains more than one ADR term is assigned to the primary SOC, i.e., SOC of the most clinically significant ADR term as determined by a Merck reviewer. Other ADR terms in the report are listed with it. The listings include the following information:

-the Merck identification number of the report (WAES NO)

-the primary reporting source (SOURCE)

-Physician
-Other healthcare provider (HCP) i.e., physician's assistant, nurse, dentist, veterinarian
-Pharmacist
-Consumer
-Lawyer

-Company representative
-Agency

-the country from which the report originated (COUNTRY)

-patient age and sex (AGE, SEX)

-patient's total daily dose of drug at the time of the initial ADR (DOSE)

-the start date of therapy (THER START)

-the stop date of therapy (THER STOP)

-the date of onset of the ADR (ONSET)

-drug relationship provided by the investigator for study reports (DR)

-(Y) yes (definite, probable, possible)
-(N) no (probably not, definitely not)
-(U) unknown or blank

-serious (SER)-(Y) yes, -(N) no

-ADR term (with the notation # for any that are a worsening of a pre-existing condition)

-outcome from the ADR (RECOVERED/RESOLVED, RECOVERED/RESOLVED WITH SEQUELAE, RECOVERING/RESOLVING, NOT RECOVERED/NOT RESOLVED, FATAL, UNKNOWN)

All cases submitted individually on an expedited basis to one or more regulatory authorities have been marked with an asterisk beside the Merck reference number.

Period and Cumulative Summary Tabulations

Summary tabulations, if applicable, may be generated from the database at different times subsequent to the data-lock point of the PSUR compared with the generation of Appendix Summary Tabulations; therefore, the number of reports in these summary tables may differ slightly from those presented in the appendix as PSUR line listings.

A single patient report may include serious and non-serious, listed and unlisted ADRs in one or more SOCs. Therefore, the sum of reports (or ADRs) from all SOCs, or the sum of serious and non-serious, listed and unlisted reports (or ADRs), can be greater than the total distinct number of reports received.

Likewise, the combined summation of each serious and non-serious or listed and unlisted total number of reports (or ADRs) presented in separate tables can be greater than the total distinct number of reports received.

A single patient report may be updated after the data-lock point of the previous PSUR. Therefore, the summation of the cumulative number of reports (or ADRs) in the prior PSUR with the period number of reports (or ADRs) in this PSUR reporting period, may not equal the current cumulative number of reports (or ADRs).

If an ADR is reported more than one time in the same report, the ADR is counted once; however, if this ADR is presented as serious/non-serious or listed/unlisted and the reported causal association (yes, no, or unknown) differs for the individual occurrences of this ADR, then the ADR is counted for each unique occurrence.

Percentages are the number of reports in the SOC per total number of distinct reports.

7. Studies

7.1 Newly Analyzed Studies

During the reporting period of this PSUR, there were 6 newly analyzed studies that contained important, new safety information for measles, mumps, and rubella virus vaccine live. These 6 protocols are briefly summarized below.

7.1.1 Protocol 006

Title: A Randomized Double-Blind Comparison Of M-M-R™ II And Priorix™ In Infants 12 To 24 Months Of Age

Objectives: The primary objective of this study was to examine the differences in mumps virus strain specificity of virus neutralizing antibody responses elicited by immunization with M-M-R™ II (Trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.) and PRIORIX™ (Trademark of GlaxoSmithKline, Rixensart, Belgium). Secondary objectives were: (1) To compare the safety and tolerability of M-M-R™ II and PRIORIX™. (2) To summarize the geometric mean titers and seroconversion rates (as measured by ELISA) for measles, mumps, and rubella for both M-M-R™ II and PRIORIX™. (3) If differences in neutralization of JL-2 are observed in M-M-R™ II and PRIORIX™ sera, to explore whether these differences are reproducible using wild-type mumps isolates that are genotypically similar to JL-2. (4) To compare the mumps virus neutralization titers induced against the Merck Jeryl Lynn™ strain by M-M-R™ II and PRIORIX™. (5) To identify any mumps strains that are less susceptible to PRIORIX™ sera, purify them, grow them out in culture, and probe them to identify regions of difference, particularly regions in the HN gene segments.

Safety Findings: The following table is a summary of clinical adverse experiences. Laboratory data were not collected in this study; therefore, no laboratory adverse experiences were reported.

A total of 5 subjects (3 recipients of M-M-R™ II and 2 recipients of PRIORIX™) reported non-vaccine-related serious adverse experiences. No subject reported vaccine-related serious adverse experiences. No enrolled subjects died during the study period. Overall, the safety profiles for recipients of M-M-R™ II and PRIORIX™ were found to be comparable. The proportion of subjects with vaccine-related injection-site adverse experiences were 4.7 and 4.8% in the 2 treatment groups, respectively. The total proportions of injection-site adverse experiences, including non-vaccine-related incidents, were 5.9 and 4.8% for the 2 treatment groups, respectively. The 95% confidence interval on the risk difference included zero, indicating no evidence of an overall difference in injection-site adverse experiences between the groups. The incidence rates of measles/rubella-like rash were 2.4 and 4.8% for the 2 treatment groups, respectively. The 95% confidence interval on the risk difference included zero, suggesting no evidence of a difference in rash rates. No incidents of mumps-like symptoms were reported during the study period. The percentages of subjects with elevated temperatures (≥102°F [≥38.9°] rectal equivalent or abnormal) within 6 weeks postvaccination were 51.8 and 56.0% for the 2 treatment groups, respectively. These differences were not statistically significant. There was one report of febrile seizure in a recipient of M-M-R™ II that was determined to be not vaccine related.

Clinical Adverse Experience Summary

	M-M-R™ II N=85		PRIORIX™ N=84	
Number (%) of subjects:	n	(%)	n	(%)
With no adverse experience	15	(17.6)	16	(19.0)
With one or more adverse experiences	70	(82.4)	68	(81.0)
Injection-site adverse experiences	5	(5.9)	4	(4.8)
Systemic adverse experiences	69	(81.2)	66	(78.6)
With rash	8	(9.4)	7	(8.3)
With maximum temperatures, rectal equivalent, ≥102°F (38.9°C) or abnormal	44	(51.8)	47	(56.0)
With vaccine-related adverse experiences†	23	(27.1)	22	(26.2)
Injection-site adverse experiences	4	(4.7)	4	(4.8)
Systemic adverse experiences	19	(22.4)	18	(21.4)
With serious adverse experiences	3	(3.5)	2	(2.4)
With serious vaccine-related adverse experiences‡	0	(0.0)	0	(0.0)
Who died‡	0	(0.0)	0	(0.0)
Discontinued due to an adverse experience‡	0	(0.0)	0	(0.0)
Discontinued due to a vaccine-related adverse experience‡	0	(0.0)	0	(0.0)
Discontinued due to a serious adverse experience‡	0	(0.0)	0	(0.0)
Discontinued due to a serious vaccine-related adverse experience‡	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely related to the study vaccine.

‡ At any time during study.

Percentages are calculated based on the number of subjects with follow-up after any visit.

Risk differences planned for injection-site adverse experiences, systemic clinical adverse experiences, and occurrence of any adverse experience.

Conclusion: In healthy children, 12 to 24 months of age, vaccinated with M-M-R™ II or PRIORIX™: (1) M-M-R™ II and PRIORIX™ induce similar levels of mumps-specific neutralizing antibodies to various mumps strains (wild-type strains Lo-1, Merck Jeryl Lynn™, Tennessee, and Barnes, as well as vaccine virus substrain Jeryl Lynn™ JL-2), in terms of geometric mean titers (GMTs) and seroconversion rates (SCRs) at 42 days postvaccination. Although differences were not statistically significant, neutralizing antibody titers tended to be consistently numerically higher in subjects vaccinated with M-M-R™II than in those immunized with PRIORIX™ with respect to GMTs; (2) M-M-R™ II and PRIORIX™ elicit comparable SCRs and GMTs for measles, mumps, and rubella by ELISA; (3) M-M-R™ II and PRIORIX™ are generally well tolerated and display similar safety and tolerability profiles.

7.1.2 Protocol 007-02

Title: A Study of M-M-R™II at Mumps Expiry Potency in Healthy Children 12 to 18 Months of Age

Objectives: (1) To demonstrate a similar immune response to mumps virus by neutralization among subjects receiving M-M-R™II containing an expiry dose of mumps virus concomitantly with VARIVAX™ in comparison to subjects receiving M-M-R™II containing a release dose of mumps virus concomitantly with VARIVAX™ and (2) To demonstrate an adequate immune response by mumps virus neutralization among subjects receiving M-M-R™II containing an expiry dose of mumps concomitantly with VARIVAX™.

Safety Findings: The following table is a summary of clinical adverse experiences. Safety data based on laboratory adverse experiences were not collected in this study; therefore, no laboratory

adverse experiences were reported. A total of 25 subjects reported serious adverse experiences during the 42 days postvaccination safety follow-up. Only 1 subject reported a vaccine-related serious adverse experience. The incident was reported as a febrile seizure occurring 19 days postvaccination and lasting 1 day with no sequelae noted. No enrolled subjects died during the study period or were discontinued from the study due to an adverse experience. No subjects reported a vaccine-related serious adverse experience during the 1-year persistence follow-up period. In general, the safety profiles of M-M-R™II containing a mumps virus potency of no more than □□ $\log_{10}$ $TCID_{50}$ mumps virus potency and M-M-R™II containing a mumps virus potency of no more than □1 $\log_{10}$ $TCID_{50}$ mumps virus potency were comparable to the safety profile of M-M-R™II containing a dose of mumps virus (4.8 $\log_{10}$ $TCID_{50}$ mumps virus potency) within the current release range. Incidence rates of injection-site adverse experiences and systemic adverse experiences were comparable among the 3 treatment groups. The proportion of subjects with elevated temperatures (defined as maximum temperature [oral equivalent] ≥102°F [38.9°C] or abnormal) between Days 0 to 42 postvaccination were 30.3%, 30.5%, and 31.2% for the □□, □1, and 4.8 $\log_{10}$ $TCID_{50}$ Mumps-Virus-Potency groups, respectively.

Clinical Adverse Experience Summary

	Treatment Groups of M-M-R™II					
	3.8 $\log_{10}$ $TCID_{50}$/dose Mumps Virus Potency† (N=663)		4.1 $\log_{10}$ $TCID_{50}$/dose Mumps Virus Potency† (N=662)		4.8 $\log_{10}$ $TCID_{50}$/dose Mumps Virus Potency‡ (N=672)	
	n	(%)	n	(%)	n	(%)
Number of subjects	663		662		672	
Subjects without follow-up	32		26		29	
Subjects with follow-up	631		636		643	
Number (%) of subjects:						
with no adverse experience	91	(14.4)	105	(16.5)	92	(14.3)
with one or more adverse experiences	540	(85.6)	531	(83.5)	551	(85.7)
injection-site adverse experiences	253	(40.1)	239	(37.6)	260	(40.4)
systemic adverse experiences	489	(77.5)	488	(76.7)	497	(77.3)
with vaccine-related§ adverse experiences	347	(55.0)	313	(49.2)	337	(52.4)
injection-site adverse experiences	251	(39.8)	237	(37.3)	258	(40.1)
systemic adverse experiences	181	(28.7)	148	(23.3)	150	(23.3)
with serious adverse experiences	10	(1.6)	6	(0.9)	9	(1.4)
with serious vaccine-related adverse experiences	0	(0.0)	1	(0.2)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to an adverse experience	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a vaccine-related adverse experience	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)	0	(0.0)

† Two sublots of M-M-R™II derived from the same parent lot as the control lot of M-M-R™II were aged to target mumps virus potencies with a 95% upper confidence bound of no more than 3.7 and 4.0 $\log_{10}$ $TCID_{50}$/dose. After reassignment of the mumps house standard (HS) potency to 4.3 $\log_{10}$ $TCID_{50}$/0.1mL, the 95% upper confidence bound values were no more than 3.8 and 4.1 $\log_{10}$ $TCID_{50}$, respectively. Final mumps virus potencies (95% upper confidence bound) were 3.76 (3.79) and 4.04 (4.08) $\log_{10}$ $TCID_{50}$, respectively.

‡ The mumps virus potency of 4.8 $\log_{10}$ $TCID_{50}$/dose is the point estimate for the control group and is representative of a mumps potency within the release range for M-M-R™II.

§ Determined by the investigator to be possibly, probably, or definitely related to the vaccine.

Conclusion:

A safety and immunogenicity study was conducted in healthy children 12 to 18 months of age. From this study, one can conclude that the expiry dose of mumps virus in M-M-R™II is no less than 4.1 $\log_{10}$ $TCID_{50}$ based on the following study results: (1) M-M-R™II with a mumps expiry dose of 4.1 $\log_{10}$ $TCID_{50}$ is highly immunogenic and induces an acceptable mumps-specific neutralizing antibody SCR that is comparable to that induced by M-M-R™II containing a release

mumps virus potency of 4.8 $\log_{10}$ $TCID_{50}$. M-M-R™II with a mumps expiry dose of 3.8 $\log_{10}$ $TCID_{50}$ does not induce an acceptable mumps-specific neutralizing antibody SCR nor is it comparable to that induced by M-M-R™II containing a release mumps virus potency of 4.8 $\log_{10}$ $TCID_{50}$. (2) M-M-R™II with a mumps expiry dose of 4.1 $\log_{10}$ $TCID_{50}$ induces comparable SCRs for measles-, mumps-, and rubella-specific antibodies by ELISA as M-M-R™II containing a release mumps virus potency of 4.8 $\log_{10}$ $TCID_{50}$. Comparable SCRs to measles and rubella by ELISA were demonstrated for M-M-R™II with a mumps expiry dose of 3.8 $\log_{10}$ $TCID_{50}$ when compared with the current release mumps virus potency of 4.8 $\log_{10}$ $TCID_{50}$, but was not achieved for mumps. (3) Among subjects who seroconverted by ELISA, antibody to measles, mumps, and rubella persists for at least 1 year (the maximum time period evaluated in this study) with any of the 3 formulations of M-M-R™II evaluated. (4) M-M-R™II with a mumps expiry dose of 3.8 $\log_{10}$ $TCID_{50}$ or 4.1 $\log_{10}$ $TCID_{50}$, or M-M-R™II with a release dose of 4.8 $\log_{10}$ $TCID_{50}$ is generally well tolerated.

7.1.3 Protocol 009

Title: A Comparison Of The Safety, Tolerability, And Immunogenicity Of M-M-R™$_{II}$ Manufactured With Recombinant Human Albumin (rHA) Versus M-M-R™$_{II}$ Manufactured With Pooled-Donor Human Serum Albumin (HSA) In Healthy Children 12 To 18 Months Of Age

Objectives: (1) To demonstrate that the antibody response rates to measles, mumps, and rubella among children who receive M-M-R™$_{II}$[†] (Measles, Mumps, and Rubella Virus Vaccine Live) manufactured with rHA will be similar to the antibody response rates among children who receive M-M-R™$_{II}$ manufactured with HSA. (2) To demonstrate that M-M-R™$_{II}$ manufactured with rHA will induce acceptable antibody response rates to measles, mumps, and rubella. (3) To demonstrate that M-M-R™$_{II}$ manufactured with rHA will be generally well tolerated.

Safety Findings: Clinical adverse experiences reported during the 42 days postvaccination are summarized in the following table. The 2 treatment groups were generally comparable in terms of the incidence rates of serious adverse experiences, systemic adverse experiences, and adverse experiences of special interest. Although injection-site reactions were reported by a significantly greater proportion of subjects who received M-M-R™$_{II}$ with rHA (35.8%) than subjects who received M-M-R™$_{II}$ with HSA (29.7%), the incidence rates were within the range observed in previous clinical trials in which M-M-R™$_{II}$ had been administered. The majority of local reactions were reported as pain at the injection site and were mostly of mild intensity and short duration (<48 hours). The 6.1% difference in incidence rates of injection-site reactions could be attributable, at least in part, to variability between vaccine lots, which has been observed in recipients of M-M-R™$_{II}$ in previous clinical trials. A total of 8 subjects (3 recipients of M-M-R™$_{II}$ with rHA and 5 recipients of M-M-R™$_{II}$ with HSA) experienced serious adverse experiences, but none was assessed to be related to the study vaccine. No subjects were discontinued from the study because of an adverse experience.

[†] M-M-R $_{II}$ is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

Summary of Overall Clinical Adverse Experiences and Adverse Experiences of Special Interest (Days 1 to 42 Following Vaccination)

	M-M-R™$_{II}$ With rHA (N=641)		M-M-R™$_{II}$ With HSA (N=638)		Risk Difference ([M-M-R™$_{II}$ With rHA] - [M-M-R™$_{II}$ With HSA]) Percentage Points (95% Confidence Interval)[†]
	n	(%)	n	(%)	
Number of subjects:	641		638		
without follow-up	7		6		
with follow-up	634		632		
Number (%) of subjects:					
with no adverse experience	114	(18.0)	126	(20.0)	-2.0 (-6.4, 2.3)
with one or more adverse experiences	520	(82.0)	504	(80.0)	2.0 (-2.3, 6.4)
injection-site adverse experiences	227	(35.8)	187	(29.7)	6.1 (0.9, 11.3)
systemic adverse experiences	469	(74.0)	463	(73.5)	0.5 (-4.4, 5.3)
with vaccine-related adverse experiences[‡]	308	(48.6)	274	(43.5)	5.1 (-0.4, 10.6)
injection-site adverse experiences	226	(35.6)	186	(29.5)	6.1 (1.0, 11.3)
systemic adverse experiences	139	(21.9)	147	(23.3)	-1.4 (-6.0, 3.2)
with serious adverse experiences	3	(0.5)	5	(0.8)	-0.3 (-1.4, 0.7)
with serious vaccine-related adverse experiences[‡]	0	(0.0)	0	(0.0)	0.0 (-0.6, 0.6)
discontinuations due to adverse experiences	0	(0.0)	0	(0.0)	
with no adverse experiences of special interest[§]	547	(86.3)	545	(86.2)	0.1 (-3.7, 3.9)
with one or more adverse experiences of special interest[§]	87	(13.7)	87	(13.8)	0.0 (-3.9, 3.8)
urticaria	8	(1.3)	8	(1.3)	-0.0 (-1.4, 1.4)
angioedema	1	(0.2)	0	(0.0)	0.2 (-0.4, 0.9)
non-injection site rash	63	(9.9)	62	(9.8)	0.1 (-3.2, 3.4)
wheezing	19	(3.0)	18	(2.8)	0.1 (-1.8, 2.1)
collapse or shock-like state (onset within 48 hours of vaccination)	0	(0.0)	0	(0.0)	0.0 (-0.6, 0.6)
unexpected serious adverse experience that was potentially an allergic reaction	0	(0.0)	0	(0.0)	0.0 (-0.6, 0.6)

[†] Risk differences and confidence intervals are based on the pooled incidence rates across study centers.
[‡] Determined by the investigator to be possibly, probably, or definitely related to the study vaccine.
[§] Adverse experiences of special interest included urticaria, angioedema, non-injection site rash (this included maculopapular and generalized erythematous rashes but excluded eczematous and other simple, localized rashes), wheezing, collapse or shock-like state (onset within 48 hours of vaccination), and any unexpected serious adverse experiences that were potentially allergic reactions.
Percentages were calculated based on the number of subjects with follow-up.
N=Number of subjects vaccinated in each treatment group.
rHA=Recombinant human albumin.
HSA=Human serum albumin.

There was no statistically significant difference between the 2 treatment groups with respect to the proportion of subjects who experienced elevated temperatures (≥102°F [38.9°C], oral equivalent) during the 42 days postvaccination (17.6% of the recipients of M-M-R™$_{II}$ with rHA and 14.6% of the recipients of M-M-R™$_{II}$ with HSA [risk difference=3.0 percentage points, p-value=0.159]). No subjects in either treatment group developed antibodies to albumin. Similar proportions of subjects in both treatment groups (13.7% of the recipients of M-M-R™$_{II}$ with rHA and 13.8% of the recipients of M-M-R™$_{II}$ with HSA) reported 1 or more adverse experiences of special interest, with the most commonly reported adverse experience of special interest being non-injection-site rash. The number and proportion of adverse experiences of special interest considered to be vaccine-related appeared comparable between the 2 treatment groups.

Conclusion: This safety and immunogenicity study was conducted in healthy, 12- to 18-month-old children who were vaccinated with a single dose of either an investigational formulation of M-M-R™$_{II}$ with rHA or M-M-R™$_{II}$ with HSA, which is the currently licensed product. In conclusion, this clinical trial supports the replacement of HSA with rHA in the manufacturing of

the viral bulks for M-M-R™$_{II}$ based on the following study results: (1) M-M-R™$_{II}$ with rHA induced acceptable antibody response rates for measles, mumps, and rubella that are similar to those induced by M-M-R™$_{II}$ with HSA. (2) M-M-R™$_{II}$ with rHA was generally well tolerated and had safety and tolerability profiles comparable with those of M-M-R™$_{II}$ with HSA, the currently licensed vaccine. (3) No subjects had detectable anti-albumin antibodies in their serum at baseline or 42 days postvaccination.

7.1.4 Protocol 009 Extension 10

Title: A Comparison of the Safety and Tolerability of a Second Dose of M-M-R™II Manufactured With Recombinant Human Albumin (rHA) Versus M-M-R™II Manufactured With Pooled-Donor Human Serum Albumin (HSA) in Healthy Children

Objective: Primary: to demonstrate that a second dose of M-M-R™II manufactured with rHA is generally well tolerated. Secondary: (1) to summarize the incidence of antibodies to albumin in children who receive a second dose of either M-M-R™II manufactured with rHA or M-M-R™II manufactured with HSA and (2) to summarize the incidence of potentially allergic adverse experiences of special interest in children who receive a second dose of either M-M-R™II manufactured with rHA or M-M-R™II manufactured with HSA.

Results: Clinical adverse experienced reported during the 42 days postvaccination are summarized in the following table. Overall, the proportion of subjects with injection-site adverse experiences, systemic adverse experiences, and elevated temperatures (oral temperature ≥102°F [38.9°C] or equivalent) were comparable between both treatment groups. Although the number of subjects reporting vaccine-related injection site and systemic adverse experiences was numerically higher among recipients of a second dose of M-M-R™II with rHA than among those vaccinated with a second dose of M-M-R™II with HSA, no statistically significant difference was observed when comparing the two treatment groups. Only 10 out of 373 (2.7%) subjects (7 among recipients of M-M-R™II with rHA and 3 among recipients of M-M-R™II with HSA) reported an adverse experience of special interest; the difference in the incidence rates of these adverse experiences of special interest between the two treatment groups was not statistically significant. No subjects had detectable antibodies to albumin immediately before or 6 weeks postvaccination.

Summary of Overall Clinical Adverse Experiences and Adverse Experiences of Special Interest
(Days 1 to 42 Following Vaccination in the Extension Study)

	M-M-R™ II With rHA (N=194) n (%)		M-M-R™ II With HSA (N=179) n (%)		Risk Difference ([M-M-R™ II with rHA]-[M-M-R™ II with HSA]) Percentage Points (95% Confidence Interval)†
Subjects in analysis population	194		179		
Subjects without follow-up	4		5		
Subjects with follow-up	190		174		
Number (%) of subjects:					
with no adverse experience	44	(23.2)	42	(24.1)	-1.0 (-9.8, 7.8)
with one or more adverse experiences	146	(76.8)	132	(75.9)	1.0 (-7.8, 9.8)
injection-site adverse experiences	99	(52.1)	82	(47.1)	5.0 (-5.3, 15.2)
systemic adverse experiences	111	(58.4)	110	(63.2)	-4.8 (-14.7, 5.3)
with vaccine-related‡ adverse experiences	111	(58.4)	92	(52.9)	5.5 (-4.7, 15.7)
injection-site adverse experiences	99	(52.1)	82	(47.1)	5.0 (-5.3, 15.2)
systemic adverse experiences	27	(14.2)	20	(11.5)	2.7 (-4.3, 9.7)
with serious adverse experiences	0	(0.0)	0	(0.0)	0.0 (-2.2, 2.0)
with serious vaccine-related‡ adverse experiences	0	(0.0)	0	(0.0)	0.0 (-2.2, 2.0)
who died	0	(0.0)	0	(0.0)	N/A
discontinued due to an adverse experience	0	(0.0)	0	(0.0)	N/A
discontinued due to a vaccine-related‡ adverse experience	0	(0.0)	0	(0.0)	N/A
discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)	N/A
discontinued due to a serious vaccine-related‡ adverse experience	0	(0.0)	0	(0.0)	N/A
with no adverse experiences of special interest§	183	(96.3)	171	(98.3)	
with one or more adverse experiences of special interest§	7	(3.7)	3	(1.7)	2.0 (-1.7, 5.9)
urticaria	1	(0.5)	0	(0.0)	0.5 (-1.6, 2.9)
angioedema	0	(0.0)	0	(0.0)	0.0 (-2.2, 2.0)
non-injection site rash	3	(1.6)	1	(0.6)	1.0 (-1.7, 4.0)
wheezing	4	(2.1)	2	(1.1)	1.0 (-2.2, 4.3)
collapse or shock-like state (onset within 48 hours of vaccination)	0	(0.0)	0	(0.0)	0.0 (-2.2, 2.0)
any unexpected SAE that is a potential allergic reaction	0	(0.0)	0	(0.0)	0.0 (-2.2, 2.0)

† Risk differences and confidence intervals are based on the pooled incidence rates across all study centers.
‡ Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
§ Adverse experiences of special interest include urticaria, angioedema, non-injection site rash (this includes maculopapular and generalized erythematous rashes but excludes eczematous and other simple, localized rashes), wheezing, collapse or shock-like state (onset within 48 hours of vaccination), and any unexpected serious adverse experiences that are potentially allergic reactions.
Percentages are calculated based on the number of subjects with follow-up.
N = Number of subjects vaccinated in each treatment group in the extension study.
rHA = Recombinant Human Albumin.
HSA = Human Serum Albumin.

Conclusion: This clinical trial supports results from the base study and demonstrates that the safety profile of a first dose and second dose of M-M-R™II with rHA is not different from that of the currently licensed vaccine (M-M-R™II with HSA), lending support for the replacement of HSA with rHA in the manufacturing of the viral bulks for M-M-R™II based on the following study results: (1) a second dose of M-M-R™II with rHA is well tolerated among subjects previously immunized with a first dose of the same vaccine and the vaccine has safety and tolerability profiles comparable with those of M-M-R™II with HSA, the currently licensed vaccine; (2) in comparison to the first dose given at 12 to 18 months of age, a second dose of M-M-R™II with rHA given at 3 to 5 years of age is not associated with an increase in the

incidence and severity of clinical symptoms, including those suggestive of hypersensitivity reaction; and (3) no subjects had detectable anti-albumin antibodies in their serum approximately 2 years after their first dose, prior to receipt of their second dose and 42 days postvaccination.

7.1.5 Protocol 010

Title: A Comparison of the Safety, Tolerability, and Immunogenicity of M-M-R™II Manufactured From the 2003 Measles Stock Seed Versus Currently Licensed M-M-R™II Manufactured From the 1967 Measles Stock Seed in Healthy Children 12 to 18 Months of Age

Primary Objectives:

1. To demonstrate that the antibody response rate to measles among children who receive M-M-R™II† (measles, mumps, and rubella virus vaccine live) manufactured from the 2003 Measles Stock Seed will be similar (noninferior) to the antibody response rate among children who receive M-M-R™II manufactured from the 1967 Measles Stock Seed (control group).
2. To demonstrate that M-M-R™II manufactured from the 2003 Measles Stock Seed will induce an acceptable antibody response rate to measles.
3. To demonstrate that M-M-R™II manufactured from the 2003 Measles Stock Seed will be generally well tolerated.

Safety Findings: Clinical adverse experiences reported during the 42 days postvaccination are summarized in the following table. A lesser percentage of the subjects who received M-M-R™II manufactured from the 2003 Measles Stock Seed than of the subjects who received M-M-R™II manufactured from the 1967 Measles Stock Seed reported 1 or more adverse experiences (80.6% and 85.1%, respectively), and the risk difference was nominally significant . More subjects who received M-M-R™II manufactured from the 2003 Measles Stock Seed than subjects who received M-M-R™II manufactured from the 1967 Measles Stock Seed reported 1 or more serious adverse experiences (10 and 2, respectively), and the risk difference (1.4%) was nominally significant. None of the reported serious adverse experiences, however, was assessed by the investigator to have been causally related to the study vaccine. This lack of causal relationship to the study vaccine and their rare occurrence seem to reflect a random distribution among subjects rather than a true difference in incidence rates between the 2 vaccines. Fewer recipients of M-M-R™II manufactured from the 2003 Measles Stock Seed than recipients of M-M-R™II manufactured from the 1967 Measles Stock Seed reported 1 or more injection-site adverse experiences (180 and 199, respectively), but the risk difference (-3.7%) was not significant. No subjects were discontinued from the study because of an adverse experience. There was no significant difference between the 2 treatment groups with respect to the proportion of subjects who experienced elevated temperatures (102°F [38.9°C], oral equivalent) during the 42 days postvaccination (17.6% of the recipients of M-M-R™II manufactured from the 2003 Measles Stock Seed and 15.4% of the recipients of M-M-R™II manufactured from the 1967 Measles Stock Seed [risk difference=2.2 %, p-value=0.343]).

Comparison of Treatment Groups with Respect to Clinical Adverse Experiences
(Days 1 to 42 Following Vaccination)

	M-M-R™II (2003 Measles Stock Seed) (N=572) n	(%)	M-M-R™II (1967 Measles Stock Seed) (N=567) n	(%)	Risk Difference ([M-M-R™II (2003 Measles Stock Seed)] – [M-M-R™II (1967 Measles Stock Seed)]) Percentage Points (95% Confidence Interval)
Number of subjects:	572		567		
Subjects without follow-up	16		15		
Subjects with follow-up	556		552		
Number (%) of subjects:					
with no adverse experience	108	(19.4)	82	(14.9)	
with one or more adverse experiences	448	(80.6)	470	(85.1)	-4.6 (-9.0, -0.1)
injection-site adverse experiences	180	(32.4)	199	(36.1)	-3.7 (-9.3, 1.9)
systemic adverse experiences	409	(73.6)	425	(77.0)	-3.4 (-8.5, 1.7)
with vaccine-related† adverse experiences	233	(41.9)	254	(46.0)	-4.1 (-9.9, 1.7)
injection-site adverse experiences	179	(32.2)	198	(35.9)	-3.7 (-9.2, 1.9)
systemic adverse experiences	101	(18.2)	108	(19.6)	-1.4 (-6.0, 3.2)
with serious adverse experiences	10	(1.8)	2	(0.4)	1.4 (0.3, 3.0)
with serious vaccine-related† adverse experiences	0	(0.0)	0	(0.0)	0.0 (-0.7, 0.7)
who died	0	(0.0)	0	(0.0)	N/A
discontinued due to an adverse experience	0	(0.0)	0	(0.0)	N/A
discontinued due to a vaccine-related† adverse experience	0	(0.0)	0	(0.0)	N/A
discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)	N/A
discontinued due to a serious vaccine-related† adverse experience	0	(0.0)	0	(0.0)	N/A

† Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
Percentages were calculated based on the number of subjects with follow-up.
N=Number of subjects vaccinated in each treatment group.
N/A=Not applicable.

Conclusion: In 12- to 18-month-old, healthy children who were vaccinated with a single dose either of an investigational M-M-R™II manufactured from the 2003 Measles Stock Seed or of the currently licensed M-M-R™II manufactured from the 1967 Measles Stock Seed:
(1) M-M-R™II manufactured from the 2003 Measles Stock Seed induced an acceptable antibody response rate to measles that was similar to that induced by M-M-R™II manufactured from the 1967 Measles Stock Seed and (2) M-M-R™II manufactured from the 2003 Measles Stock Seed was generally well tolerated and had safety and tolerability profiles comparable to those of M-M-R™II manufactured from the 1967 Measles Stock Seed. These results support using the 2003 Measles Stock Seed to manufacture measles viral bulks for M-M-R™II.

7.1.6 Protocol A3R21

Title: Safety and Immunogenicity of the Simultaneous Administration of a Liquid Hexavalent Combined Vaccine (Hexavac®) and a Trivalent Measles-Mumps-Rubella Combined Vaccine (M-M-R®II) in Healthy 12 Month Old Children

Objectives: Primary—To determine whether the simultaneous administration of Hexavac® and M-M-R®II to 12-month-old children interferes on the primary evaluation criteria, as compared with the measures obtained with the separate administration of each vaccine at the same age. Secondary—To describe at 13 months of age, the other immunogenicity parameters after the

simultaneous administration of Hexavac® and M-M-R®II or after the separate administration of each vaccine at 12 months of age; To describe the 6-month immune response to Hexavac® antigens in children who received two doses of Hexavac® at 3 and 5 months of age; To describe the reactogenicity after simultaneous administration of Hexavac® and M-M-R®II to 12 month-old children or after the sequential administration of Hexavac® followed one month later by M-M-R®II or after the sequential administration of M-M-R®II followed one month later by Hexavac®; To describe the reactogenicity after the primary series of Hexavac® given at 3 and 5 months of age.

Safety Findings:

Primary Series
During the primary series, 319 subjects (46.6%) did not experience any AE and 366 (54.4%) reported at least one AE (a total of 802 AEs were experienced). Two (2) subjects experienced an immediate reaction, 215 a local reaction, and 234 a systemic event (considered to be related to the vaccination for 146 of them).

There were two immediate reactions, one after the first dose of Hexavac® (fever) and one after the second (induration). The 215 subjects who experienced at least one local reaction within 30 days (31.4% of assessable subjects) reported 465 local reactions. These reactions were mild for most of the subjects (28.0%), moderate for 6.4% of the subjects, and severe for 2.8% of the subjects. One hundred and five (105) subjects reported 158 reactions after the first dose of Hexavac® and 161 subjects reported 307 local reactions after the second dose.

Two hundred and thirty-four (234) subjects (34.2%) experienced at least one systemic event within 30 days after administration of Hexavac®. A total of 146 systemic AEs related to vaccination were recorded during the primary series; they were moderate in intensity for most of the subjects (11.5%), mild for 9.9% of the subjects, and severe for 1.9% of the subjects. Altogether, 75 subjects experienced 93 AEs after the first dose, versus 78 subjects who reported 112 AEs after the second dose.

A total of 38 subjects presented with fever within three days after the first dose of Hexavac®. One of them had fever ≥40°C (rectal temperature). After the second dose of Hexavac®, 94 subjects had fever, the majority of cases (81) being mild. There were 11 moderate episodes and one episode ≥40°C.

Booster
During the booster phase, 212 subjects (35.0%) did not experience any AE, and 394 reported at least one AE. A total of 505 AEs were experienced: four subjects experienced an immediate reaction, 188 had a local reaction, and 313 had a systemic event (considered as related to vaccination for 245 of them).

A total of 66 subjects in Group 1 (32.8%), 68 in Group 2 (33.3%), and 60 in Group 3 (29.9%) experienced at least one local reaction within 30 days. A total of 134, 147, and 141 local reactions were recorded in Groups 1, 2 and 3, respectively. Local reactions were mild in 59 subjects (29.4%), 57 subjects (27.9%), and 44 subjects (21.9%) in Groups 1, 2, and 3 respectively. They were moderate in 12 subjects (6.0%), 15 subjects (7.4%), and 26 subjects (12.9%) in the same groups respectively. Local reactions were severe in 3 subjects (1.5%), 8 (3.9%), and 6 subjects (3.0%) in the same groups respectively. Local reactions were more

frequently observed after the administration of Hexavac® than M-M-R®II, since 186 subjects experienced at least one local reaction with Hexavac®, compared to 19 subjects with M-M-R®II. As expected, the most frequent local reactions were redness, swelling, and induration.

A total of 33 subjects in Group 1 (16.4%), 66 in Group 2 (32.4%), and 57 in Group 3 (28.4%) experienced at least one systemic event leading to a visit to a physician.

Within seven days after the first dose of the booster phase (12 months of age), 69 (34.3%), 66 (32.4%), and 44 (21.9%) subjects experienced fever in Groups 1, 2 and 3 respectively. Fever episodes were mostly mild: 50 (24.9%), 55 (27.0%), and 31 (15.4%) subjects in Groups 1, 2, and 3 respectively. Some were moderate: 19 (9.5%), 12 (5.9%), and 14 (7.0%) of subjects in the same groups respectively. Only two subjects (one in Group 1, the other in Group 3) had fever ≥40°C (rectal temperature). Within seven days after the second dose of the booster phase (13 months of age), 34 (16.9%) and 50 (25.1%) subjects experienced fever in Groups 2 and 3 respectively. Most episodes were mild: in 21 (10.4%) and 39 (19.6%) subjects in Groups 2 and 3 respectively. Two subjects in Group 2 and three in Group 3 had fever ≥40°C (rectal temperature).

The number of subjects who reported fever within seven days was similar in all groups. The concomitant administration of both vaccines (at different sites) did not increase the total number of episodes of fever during the first seven days. In Group 1 indeed, a first peak of incidence was measured within the first three days, then a secondary increase at Days 6 and 7. In Groups 2 and 3, the same trend was observed.

Cases of fever occurred mainly with two peaks, one within three days after the administration of Hexavac®, and the other starting 6 days after M-M-R®II. The concomitant administration of both vaccines (at different sites) did not increase the total number of fever episodes for the first seven days. The incidence peaks of fever were observed: in Group 1, a first peak of incidence was measured within the first three days, then a secondary increase at Days 6 and 7.

A total of 45, 120, and 103 systemic AEs were recorded in Groups 1, 2 and 3 respectively. In Groups 1, 2, and 3 respectively, these events were moderate in 15 (7.5%), 40 (19.6%), and 46 (22.9%) subjects, mild in 15 (7.5%), 31 (15.2%), and 21 (10.4%) subjects, and severe in 5 (2.5%), 10 (4.9%), and 8 (4.0%) subjects.

More systemic AEs were observed after the first booster injection (either with Hexavac® or M-M-R®II) than after the second booster injection in Groups 2 and 3, since 43 to 44 subjects experienced a systemic AE after the first booster dose compared to 27 to 36 subjects after the second.

Serious Adverse Events
Thirty-five (35) subjects experienced 36 serious adverse events (SAEs). Three were considered as "possibly or probably related" to Hexavac® and reported to the Health Authorities: one episode of torticollis, 26 days after the first dose of Hexavac® in Group 3, one episode of fever one day after the third dose of Hexavac® in Group 2, and fever and convulsions during flu syndrome two days after the third dose of Hexavac® in Group 3.

Conclusion: Given that the concomitant administration of Hexavac® and M-M-R®II result in similar (i.e. non-inferior) immunogenicity and is generally safe and well tolerated, the study supports the concomitant administration of both vaccines at separate injection sites.

7.2 Targeted New Safety Studies

During the reporting period of this PSUR, there was 1 targeted safety study for measles, mumps, and rubella virus vaccine live that had completed enrollment but had not been summarized.

Protocol 011, entitled "A Open, Randomised, Comparative, Multicentre Study of the Immunogenicity and Safety of M-M-R™II Manufactured with Recombinant Human Albumin (rHA) and VARIVAX® When Administered Concomitantly by Intramuscular (IM) Route or Subcutaneous (SC) Route at Two Separate Injection Sites in Healthy Subjects 12 to 18 Months of Age," performed the last subject visit on 05-Sep-2005. During the reporting period of this PSUR, 752 subjects received measles, mumps, and rubella virus vaccine live manufactured with rHA. This study is now complete and safety analysis will be provided in an upcoming PSUR.

7.3 Published Safety Studies

During the reporting period of this PSUR, there were 8 published safety studies that described new and potentially important safety information. These 8 published safety studies identified involved the following: type 1 diabetes, febrile seizures, vaccination in early infancy, developmental disorders, gait disturbance, hearing loss, vaccination safety and adverse events for recombinant human albumin, and vaccination in bone marrow transplant recipients.

1. Hviid A, Stellfeld M, Wohlfahrt J and Melbye M
Childhood vaccination and type 1 diabetes
N Engl J Med 350(14): 1398-1404, Apr. 1, 2004

A longitudinal cohort study was conducted using data on all children born in Denmark from 1990 through 2000 to evaluate the relationship between type 1 diabetes and routine childhood vaccinations. Data from the Danish Civil Registration System were linked with data from the National Board of Health Register and the Danish National Hospital Register. The cohort consisted of 739,694 children. During 4,720,517 person-years of follow-up, 681 children were diagnosed with diabetes at a mean age of 5.2 yr. The rate ratio for type 1 diabetes was 40.05 (95% confidence interval [CI], 26.90-59.63) for children who had at least 1 sibling with diabetes, compared with children who had no diabetic siblings. The rate ratio for diabetes in children who received at least 1 dose of vaccine compared with unvaccinated children was 0.91 (95% CI, 0.74-1.12) for Hib vaccine, 1.14 (0.90-1.45) for measles-mumps-rubella vaccine, and similar values for other childhood vaccines. Adjusted rate ratios did not differ significantly after multiple doses of a vaccine, and there was no evidence of clustering of diabetes cases 2-4 yr after administration of any vaccine. Within the subset of children with diabetic siblings, there was also no significant association with vaccination. Results did not support a significant association of type 1 diabetes with vaccination against childhood diseases during up to 4 yr after receipt of any vaccine.

2. Vestergaard M, Hviid A, Madsen K M, Wohlfahrt J, Thorsen P, Schendel D, Melbye M and Olsen J
MMR vaccination and febrile seizures: evaluation of susceptible subgroups and long-term prognosis
JAMA 292(3): 351-357, July 21, 2004

A population-based cohort study was performed to examine the relationship between MMR vaccination and the occurrence of febrile seizures in 537,171 children born in Denmark between January 1, 1991 and December 31, 1998; these children were followed up until December 31, 1999. The rate of febrile seizures was 10% higher among vaccinated children than among unvaccinated children (relative risk (RR) 1.10, 95% confidence interval (CI) 1.05-1.15); however, the rate of febrile seizures was only higher among vaccinated children during the first and second weeks after vaccination (RR 2.46 and 3.17, respectively). Although the rate of febrile seizures was higher in vaccinated children than in unvaccinated children during the first 2 wk after vaccination, there were no statistically significant differences in the risk of febrile seizures among subgroups based on a family history of seizures, sex, birth order, gestational age at birth, birth weight, or socioeconomic factors. Siblings of children with a history of epilepsy had a 4-fold higher rate of febrile seizures in the first 2 wk after vaccination than did unvaccinated children; siblings of children with no history of epilepsy had a 2.7-fold higher rate of febrile seizures in the first 2 wk after vaccination than did unvaccinated children. A total of 10,541 children had a personal history of febrile seizures; 175 of these children experienced a febrile seizure within 2 wk of receiving MMR vaccine (RR 2.75, 95% CI 2.32-3.26). The risk difference of febrile seizures during the first 2 wk after MMR vaccination compared with children who were not vaccinated was 1.56 per 1000 for children vaccinated between the ages of 15 and 17 mo (95% CI 1.44-1.68), was 1.46 per 1000 for children vaccinated between the ages of 18 and 20 mo (95% CI 1.10-1.91), and was 0.64 per 1000 for children vaccinated between the ages of 21 and 23 mo (95% CI 0.22-1.40). The highest risk difference occurred in children with a personal history of febrile seizures and in children with a family history of febrile seizures. Children who experienced a febrile seizure during the first 2 wk after MMR vaccination had a 19% increased risk of experiencing a recurrent febrile seizure (RR 1.19, 95% CI 1.01-1.41); however, during the 105-mo follow-up period, these children did not have a greater risk of epilepsy than did unvaccinated children who experienced a febrile seizure. The authors conclude that MMR vaccination is associated with a transient increase in the rate of febrile seizures among infants; however, the increased risk is small and does not lead to an increased rate of epilepsy.

3. Pool V and Russell M
Inadvertent administration of measles vaccine in early infancy: a review of safety data in the U.S.
Pharmacoepidemiol Drug Safety 13(Suppl. 1): S280-S280 (#556), July 2004 (in Soc. Proc.)

Data from the Vaccine Adverse Event Reporting System (VAERS) were examined to determine adverse events reported after inadvertent use of live measles virus-containing vaccines in infants aged 0-8 mo. Among more than 158,000 reports received by VAERS between Jan. 1991 and Mar. 2003, there were 36 reports of inadvertent administration of measles vaccine alone or in combination in infants younger than 9 mo. There were no adverse events in seven cases. Injection-site or systemic reactions occurring within 3 days of vaccination were reported in 14 infants who received measles vaccine with other vaccines. These were considered not to be associated with measles vaccine. Fifteen reports included adverse events that were more likely to be associated with measles vaccine. These included nine cases with seizures and high fever that lasted for up to 10 days. There were no deaths or disabling conditions. The authors note that this analysis revealed only a small number of young children who had adverse events that might have been related to measles vaccine. They conclude that, because inadvertent vaccination seems to be rare, these reports suggest that measles vaccine might have increased reactogenicity in susceptible young infants.

4. Smeeth L, Cook C, Fombonne E, Heavey L, Rodrigues L C, Smith P G and Hall A J
MMR vaccination and pervasive developmental disorders: a case-control study
Lancet 364(9438): 963-969, Sept. 11-17, 2004

This case-control study was conducted in the UK to investigate whether measles-mumps-rubella vaccination is associated with an increased risk of pervasive developmental disorders, such as autism. The UK General Practice Research Database was searched for patients who were born in or after 1973 and who were diagnosed with a pervasive developmental disorder between 1987 and 2001. The analysis included 1294 (222 F, age 3.6-9.7 yr, median age 5.4 yr) cases and 4469 (768 F, age 3.5-8.8 yr, median age 4.9 yr) controls. The analysis revealed that 1010 (78.1%) patients and 3671 (82.1%) controls underwent measles-mumps-rubella vaccination before the diagnosis of pervasive developmental disorder was made. Among the 1010 patients, 991 were diagnosed with autism and 303 with other pervasive developmental disorders. After adjusting for age, the odds ratio for the existence of an association between measles-mumps-rubella vaccination and a pervasive developmental disorder was 0.86. The authors conclude that measles-mumps-rubella vaccination does not increase a child's risk of developing a pervasive developmental disorder.

5. Reisinger K, Wiedmann R, Sheaffer C, Malacaman E, Senders S, Marchant C, Giacoletti K, Shaw E, Schodel F and Musey L K
Safety and immunogenicity of M-M-R II with recombinant human albumin (rHA) in children
Paper presented at the 42nd Annual Meeting of IDSA, September 30-October 3, 2004, Boston, Massachusetts, USA, Abstract 1024

A randomized double-blind study was conducted in 1279 children aged 12-18 mo to compare M-M-R II manufactured with recombinant human albumin (rHA) vs standard M-M-R II (manufactured with regular human albumin) with regard to immunogenicity and safety. A single dose of vaccine was administered. Antibodies to measles, mumps, rubella, and albumin were measured by enzyme-linked immunosorbent assay before and 6 wk after vaccination. Seroconversion to measles, mumps, and rubella occurred in 98.3%, 99.5%, and 99.7%, respectively, of children vaccinated with the rHA vaccine and 98.8%, 97.9%, and 99.6% of children vaccinated with the standard vaccine. The rHA vaccine produced numerically higher geometric mean titers for each viral antigen. There were no detectable antibodies to albumin before or after vaccination. The overall incidence rate for adverse experiences was not significantly different between the groups. Injection-site reactions were significantly more frequent with the rHA formulation (35.8%) compared with the standard formulation (29.7%). These were usually mild and lasted about 48 hr. The rate of possible allergic reactions to the rHA vaccine (13.7%) was similar to that with the standard vaccine (13.8%). The authors conclude that the immunogenicity and safety profiles of the rHA formulation are similar to those of the licensed formulation of M-M-R II in this study.

6. Miller E, Andrews N, Grant A, Stowe J and Taylor B
No evidence of an association between MMR vaccine and gait disturbance
Arch Dis Child 90(3): 292-296, Mar. 2005

This study used data from computerized immunization and hospital admission records for children aged 12-24 mo living in the former South and North Thames region of England to determine whether any association between measles-mumps-rubella vaccination and gait

disturbance exceeded the age-related background rate for gait disturbance. This analysis, which covered the time period from April 1995 to June 2001, included data from self-control case series and record linkage. It focused on new-onset gait disturbances that occurred in patients within 60 days of measles-mumps-rubella vaccination. A total of 127 patients were admitted for a possible gait disturbance; 114 (90%) had received a measles-mumps-rubella vaccine. Sixty-five of the 127 patients were diagnosed with non-ataxic, non-viral gait disturbances (category 4). The remaining 62 patients were included in this analysis: 19 with probable post-viral ataxias (category 2); 19 with probably not post-viral ataxias (category 3); and 24 with gait disturbances considered to be probable "post-viral" transient synovitis (category 5). There was no evidence of an increased rate of either general practice consultations or hospital admissions for gait disturbances during the observed 60-day postvaccination period.

7. Machado CM, de Souza V A U F, Sumita LM, da Rocha IF, Dulley FL and Pannuti CS
Early measles vaccination in bone marrow transplant recipients
Bone Marrow Transplant 35(8): 787-791, Apr. 2005

This prospective study was conducted to evaluate the effects of early measles vaccination using MMR-II in 64 patients who were alive on day +365 post-BMT. Sixty-one (age 6-55 yr, median age 25 yr) of the 64 patients were vaccinated with 1 dose of MMR-II between 9 and 18 mo after BMT. The remaining 3 patients were not vaccinated due to severe complications and hospitalization that occurred close to day +365. Fifty-one patients fulfilled the inclusion criteria. Twenty-seven of the 51 patients were treated with immunosuppressive drugs: cyclosporine A, prednisolone, prednisone, and/or mycophenolate mofetil. Five patients had localized chronic graft-vs-host disease and 22 had extensive chronic graft-vs-host disease. Nine patients were susceptible (IgG <=100 mIU/ml) to measles prior to vaccination; all seroconverted after vaccination. Following vaccination, 5 patients reported myalgia and 1 reported low-grade fever. During follow-up, sustained immunity 24 mo after early measles vaccination was significantly lower in patients with specific IgG levels between 200 and 499 mIU/ml at vaccination than it was in those with specific IgG levels either <200 mIU/ml or >=500 mIU/ml at vaccination. The overall probabilities of sustained immunity at 12, 18, and 24 after early measles vaccination were 94.5%, 89.8%, and 78.6%, respectively. The authors conclude that early measles vaccination is safe for patients who have undergone BMT. However, since few patients are susceptible on day +365, vaccination should be reserved for epidemic situations that place the patients at significant risk of infection.

8. Asatryan A, Pool V and Chen R T
Sensorineural hearing loss following measles-mumps-rubella vaccination: Vaccine Adverse Event Reporting System, United States, 1991-2004
Pharmacoepidemiol Drug Safety 14(Suppl. 2): S200-S200 (#401), Aug. 2005 (Paper presented at the 21st International Conference on Pharmacoepidemiology and Therapeutic Risk Management, August 21-24, 2005, Nashville, Tennessee, USA)

The authors identified and reviewed reports of sensorineural hearing loss (SHL) in VAERS to see if any of the reports were compatible with MMR vaccine causation. There were 663 reports of SHL: 213 following MMR and 450 after other vaccines. Of the 663 reports, 475 met the exclusion criteria of other known etiologies. Of the remaining 187 reports describing apparent idiopathic SHL after vaccination, 59 occurred after MMR. Of these 59 reports, 12 had transient SHL with onset on the day of vaccination suggesting a possible allergic mechanism. Of the other 47 reports (age 1-52 yr), 33 had dose information provided: 20 occurred after dose 1, 13 occurred

following dose 2. SHL was bilateral in 23 cases, unilateral in 17 cases, and unspecified in 7. The onset of hearing loss ranged from 2-89 days after vaccination, with 2 small peaks on days 10 and 14, consistent with the incubation period for MMR vaccine viruses. The authors conclude that there might be a very rare link between MMR and SHL.

8. Other Information

8.1 Late-Breaking Information

There was no important or new late-breaking information that would alter the currently known safety profile as described in the current CCDS of measles, mumps, and rubella virus vaccine live, MSD.

9. Overall Safety Evaluation

The data presented in this PSUR represent the marketed and clinical study experience with measles, mumps, and rubella virus vaccine live for reports that meet the criteria described in Section 6, Presentation of Individual Case Histories, that were received by Merck & Co., Inc., from worldwide sources, between 01-Jan-2001 to 31-Dec-2005.

Most of the ADRs reported during the period of this PSUR are either already listed or represent situations for which conclusions cannot be drawn. Those events, which are unlisted, have been reviewed against cumulative data and relevant safety-related issues are summarized in this section.

9.1 Summary Tabulation of Reports

During the reporting period of this PSUR, there were a total of 5,149 reports with ADRs spontaneously received from healthcare providers for measles, mumps, and rubella virus vaccine live. A total of 23 serious, vaccine-related study reports were received during the reporting period and 7 study reports were serious and unlisted.

Table 9.1.1 is a summary tabulation of the number of spontaneous reports of ADRs for measles, mumps, and rubella virus vaccine live (presented by System Organ Class [SOC]), which were received during the reporting period of this PSUR. Table 9.1.2 is a summary tabulation of the number of spontaneous reports of ADRs for measles, mumps, and rubella virus vaccine live (presented by SOC), which were received from Market Introduction (International Birthdate for measles, mumps, and rubella virus vaccine live is 01-Apr-1978, in Ireland) to 31-Dec-2005. A summary tabulation of the number and percent of spontaneous reports of unlisted serious and nonserious ADRs and spontaneous reports of listed serious and non-serious ADRs are presented in both Table 9.1.1 and 9.1.2.

Table 9.1.1
Measles, Mumps, and Rubella Virus Vaccine Live
Summary Tabulation of Reports From Healthcare Providers by System Organ Class
01-Jan-2001 to 31-Dec-2005

System Organ Class	Total Reports N (%)	Reports with Serious ADRs			Reports with Non-serious ADRs		
		Total N (%)	Listed N (%)	Unlisted N (%)	Total N (%)	Listed N (%)	Unlisted N (%)
Blood and lymphatic system disorders	308 (6)	150 (10)	106 (11)	50 (5)	160 (4)	149 (8)	15 (1)
Cardiac disorders	44 (1)	28 (2)	0 (0)	28 (3)	16 (<1)	0 (0)	16 (1)
Congenital, familial and genetic disorders	11 (<1)	10 (1)	0 (0)	10 (1)	1 (<1)	0 (0)	1 (<1)
Ear and labyrinth disorders	55 (1)	26 (2)	10 (1)	16 (2)	30 (1)	0 (0)	30 (1)
Endocrine disorders	6 (<1)	1 (<1)	0 (0)	1 (<1)	5 (<1)	0 (0)	5 (<1)
Eye disorders	159 (3)	69 (5)	17 (2)	53 (5)	90 (2)	34 (2)	58 (2)
Gastrointestinal disorders	352 (7)	130 (9)	83 (9)	63 (6)	229 (6)	156 (8)	90 (3)
General disorders and administration site conditions	2625 (51)	418 (29)	302 (32)	181 (18)	2233 (55)	1148 (58)	1278 (43)
Hepatobiliary disorders	13 (<1)	9 (1)	0 (0)	9 (1)	4 (<1)	0 (0)	4 (<1)
Immune system disorders	125 (2)	98 (7)	82 (9)	16 (2)	27 (1)	20 (1)	7 (<1)
Infections and infestations	713 (14)	250 (17)	84 (9)	192 (19)	477 (12)	284 (14)	227 (8)
Injury, poisoning and procedural complications	1706 (33)	30 (2)	6 (1)	24 (2)	1681 (42)	0 (0)	1681 (56)
Investigations	133 (3)	26 (2)	4 (<1)	23 (2)	108 (3)	10 (1)	98 (3)
Metabolism and nutrition disorders	101 (2)	49 (3)	0 (0)	49 (5)	52 (1)	0 (0)	52 (2)
Musculoskeletal and connective tissue disorders	206 (4)	69 (5)	24 (3)	53 (5)	140 (3)	85 (4)	70 (2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	10 (<1)	7 (<1)	0 (0)	7 (1)	3 (<1)	0 (0)	3 (<1)
Nervous system disorders	949 (18)	741 (51)	435 (46)	383 (38)	238 (6)	116 (6)	140 (5)
Pregnancy, puerperium and perinatal conditions	27 (1)	25 (2)	0 (0)	25 (3)	4 (<1)	0 (0)	4 (<1)
Psychiatric disorders	217 (4)	100 (7)	0 (0)	100 (10)	123 (3)	0 (0)	123 (4)
Renal and urinary disorders	15 (<1)	8 (1)	0 (0)	8 (1)	7 (<1)	0 (0)	7 (<1)
Reproductive system and breast disorders	22 (<1)	8 (1)	1 (<1)	7 (1)	14 (<1)	3 (<1)	11 (<1)
Respiratory, thoracic and mediastinal disorders	314 (6)	150 (10)	38 (4)	124 (12)	172 (4)	75 (4)	122 (4)
Skin and subcutaneous tissue disorders	1361 (26)	265 (18)	180 (19)	111 (11)	1102 (27)	762 (38)	441 (15)
Social circumstances	7 (<1)	6 (<1)	0 (0)	6 (1)	1 (<1)	0 (0)	1 (<1)
Surgical and medical procedures	7 (<1)	5 (<1)	0 (0)	5 (1)	2 (<1)	1 (<1)	1 (<1)
Vascular disorders	85 (2)	42 (3)	0 (0)	42 (4)	44 (1)	0 (0)	44 (1)
DISTINCT NUMBER OF REPORTS	**5,149**	**1,466**	**938**	**1,000**	**4,048**	**1,983**	**2,978**

Table 9.1.2
Measles, Mumps, and Rubella Virus Vaccine Live
Summary Tabulation of Reports of From Healthcare Providers by System Organ Class
Market Introduction to 31-Dec-2005

System Organ Class	Total Reports N (%)	Reports with Serious ADRs			Reports with Non-serious ADRs		
		Total N (%)	Listed N (%)	Unlisted N (%)	Total N (%)	Listed N (%)	Unlisted N (%)
Blood and lymphatic system disorders	1009 (8)	356 (12)	224 (11)	153 (8)	671 (6)	610 (9)	89 (1)
Cardiac disorders	128 (1)	74 (2)	0 (0)	74 (4)	54 (<1)	0 (0)	54 (1)
Congenital, familial and genetic disorders	36 (<1)	27 (1)	0 (0)	27 (1)	9 (<1)	0 (0)	9 (<1)
Ear and labyrinth disorders	159 (1)	68 (2)	38 (2)	31 (2)	92 (1)	16 (<1)	76 (1)
Endocrine disorders	9 (<1)	2 (<1)	0 (0)	2 (<1)	7 (<1)	0 (0)	7 (<1)
Eye disorders	399 (3)	114 (4)	24 (1)	91 (5)	290 (3)	100 (1)	209 (3)
Gastrointestinal disorders	949 (7)	251 (8)	161 (8)	112 (6)	713 (6)	498 (7)	261 (4)
General disorders and administration site conditions	6909 (52)	878 (29)	647 (32)	346 (18)	6107 (55)	3504 (51)	3234 (45)
Hepatobiliary disorders	54 (<1)	34 (1)	0 (0)	34 (2)	20 (<1)	0 (0)	20 (<1)
Immune system disorders	287 (2)	162 (5)	132 (7)	30 (2)	128 (1)	110 (2)	35 (<1)
Infections and infestations	2225 (17)	481 (16)	152 (8)	375 (20)	1797 (16)	1235 (18)	677 (9)
Injury, poisoning and procedural complications	3210 (24)	56 (2)	13 (1)	43 (2)	3161 (28)	0 (0)	3161 (44)
Investigations	312 (2)	71 (2)	7 (<1)	65 (3)	244 (2)	16 (<1)	228 (3)
Metabolism and nutrition disorders	264 (2)	113 (4)	0 (0)	113 (6)	156 (1)	0 (0)	156 (2)
Musculoskeletal and connective tissue disorders	731 (6)	171 (6)	90 (5)	98 (5)	576 (5)	400 (6)	234 (3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	24 (<1)	15 (<1)	0 (0)	15 (1)	10 (<1)	0 (0)	10 (<1)
Nervous system disorders	2495 (19)	1449 (48)	956 (48)	628 (33)	1144 (10)	759 (11)	460 (6)
Pregnancy, puerperium and perinatal conditions	127 (1)	50 (2)	4 (<1)	46 (2)	84 (1)	51 (1)	49 (1)
Psychiatric disorders	443 (3)	145 (5)	0 (0)	145 (8)	308 (3)	0 (0)	308 (4)
Renal and urinary disorders	52 (<1)	24 (1)	0 (0)	24 (1)	30 (<1)	0 (0)	30 (<1)
Reproductive system and breast disorders	61 (<1)	13 (<1)	3 (<1)	11 (1)	48 (<1)	18 (<1)	30 (<1)
Respiratory, thoracic and mediastinal disorders	692 (5)	243 (8)	53 (3)	207 (11)	466 (4)	182 (3)	342 (5)
Skin and subcutaneous tissue disorders	3871 (29)	522 (17)	379 (19)	183 (10)	3366 (30)	2658 (39)	992 (14)
Social circumstances	15 (<1)	10 (<1)	0 (0)	10 (1)	5 (<1)	0 (0)	5 (<1)
Surgical and medical procedures	39 (<1)	23 (1)	0 (0)	23 (1)	16 (<1)	1 (<1)	15 (<1)
Vascular disorders	233 (2)	75 (2)	0 (0)	75 (4)	159 (1)	0 (0)	159 (2)
DISTINCT NUMBER OF REPORTS	**13,258**	**3,029**	**1,997**	**1,921**	**11,142**	**6,877**	**7,259**

Comment

Review of Table 9.1.1 and Table 9.1.2 reveals that the percentages of ADR reports by System Organ Class for the reporting period of this PSUR are generally consistent with those percentages from Market Introduction. The majority of reports with unlisted ADRs were nonserious. The distribution of unlisted reports received during the period of this PSUR remained reasonably consistent with the percentages of total reports received since Market Introduction. Similarly, the majority of reported listed ADRs were nonserious. There were no substantial increases in percentages of reports with listed ADRs by System Organ Class in the time frame of this PSUR, as compared to the overall percentages of reports with listed ADRs since Market Introduction.

C

9.2 Reports with Fatal Outcomes

During the reporting period for this PSUR, 60 spontaneous reports involving fatal outcomes in patients treated with measles, mumps, and rubella virus vaccine live were received from health care professionals, regulatory agencies, or published literature articles. Of these 60 reports, the Company received 27 use-during-pregnancy reports in which the pregnancy resulted in an elective abortion (6), spontaneous abortion (19), intra-uterine death (1), and twin pregnancy with fetal loss and retention of one foetus (1). Per Company policy, these reports are recorded as adverse events with a fatal outcome. These 27 reports are discussed in Section 9.6 Use During Pregnancy. The remaining 33 reports are summarized in the Table 9.2.1 below.

The remaining 33 reports involved 19 males, 14 females, and ranged in age from 12-months to 25-years with an average age of 5-years. Three of these 33 reports were identified from published literature articles. The remaining 30 reports were received from the following countries: United States (10), Sweden (6), United Kingdom (3), Norway, (2), France (2), China (2), Denmark (1), and Malta (1).

Table 9.2.1
Measles, Mumps, and Rubella Virus Vaccine Live
Reports of Fatal Outcomes
01-Jan-2001 to 31-Dec-2005

WAES	Age/ Gender	Reported Cause of Death	Comment
[redacted]	13 m / M	Aspiration; gastritis	Information received from a published literature article. The patient died [redacted] 8 days after vaccination with measles, mumps, and rubella virus vaccine live. Forensic autopsy disclosed the cause of death as aspiration of vomit caused by acute gastritis.
[redacted]	14 m / F	Multi-organ failure	Information was received from a physician concerning a 14-month-old female with failure to thrive and possible immunodeficiency who was vaccinated with measles, mumps, and rubella virus vaccine live. Subsequently, the patient experienced encephalitis, seizures, and combined immune deficiency which required hospitalization. The patient continued to deteriorate and eventually developed pneumonitis, hepatitis, and multiple organ failure which prolonged hospitalization. The cause of death was multiple organ failure.
[redacted]	18 m / M	Bacterial sepsis	Information was received from a health professional concerning the patient who was vaccinated with measles, mumps, and rubella virus vaccine live. [redacted] He was ventilated and the next day, the ventilator was switched off and the patient died. The cause of death was sepsis.
[redacted]	15 m / F	Cardio-respiratory arrest	Information was received from a company representative concerning the patient with reactive airway disease who was vaccinated with measles, mumps, and rubella virus vaccine live. Concomitant therapy included varicella virus vaccine live and streptococcus pneumoniae vaccine. [redacted] the patient experienced an unexplained cardiorespiratory arrest and died. The cause of death was later reported as unknown.

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WAES	Age/ Gender	Reported Cause of Death	Comment
[redacted]	12 m / M	Cardio-respiratory arrest	Information was received from CBER concerning the patient with gastroenteritis and chronic obstructive airway disease and a history of prematurity who was vaccinated subcutaneously in the right leg with measles, mumps, and rubella virus vaccine live. Concomitant vaccine therapy included varicella virus vaccine live, streptococcus pneumoniae vaccine, and haemophilus b conjugate vaccine. Other concomitant medication included albuterol and fluticasone propionate. Subsequently, the patient died of cardiopulmonary arrest of unknown etiology.
[redacted]	12 m / F	Bacterial sepsis; cardio-respiratory arrest; dehydration; erythema multiforme; fever; lethargy; measles; meningitis meningococcal; shock; vomiting	Information was received from a physician concerning the Asian patient with a past history of allergies, eczema, and a hematoma on the forehead, who received measles, mumps, and rubella virus vaccine live, varicella virus vaccine live, and streptococcus pneumoniae vaccine. [redacted] The cause of death on the death certificate was meningococcal meningitis. The pediatrician reported that the cause of death could not possibly be meningococcal meningitis because the blood cultures done on the patient at the height of the rash were negative, and the fever and rash had gone away without any prophylaxis treatment. The physician confirmed that the child did eat a different type of fish and wondered if the child may have contracted a Vibrio infection from ingesting infected raw fish.
[redacted]	5 y / F	Yellow fever	Information was received from the physician of a published literature article concerning the patient with a history of low birth weight, diarrhea, bronchitis during childhood and aseptic meningitis 3 months before the current illness, who was vaccinated with measles, mumps, and rubella virus vaccine live and a separate vaccine of yellow fever virus vaccine live. [redacted] The cause of death was yellow fever. It was concluded that the vaccine virus was the probable cause of fatal infections, which closely resembled wild-type yellow fever.
[redacted]	11 y / F	Death	Information was received from a newspaper reporter concerning the patient who was vaccinated with a first dose of measles, mumps, and rubella virus vaccine live at age 1 and at age 5 was vaccinated with a second dose of measles, mumps, and rubella virus vaccine live. [redacted] The brain biopsy tissue confirmed that the child was infected with wild type measles virus. Subsequently, the patient died.

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WAES	Age/ Gender	Reported Cause of Death	Comment
[redacted]	25 y / M	Death	Information was received from a physician concerning the patient with no known allergies or psychiatric history and a history of varicella, who was vaccinated with measles, mumps, and rubella virus vaccine live. Concomitant therapy included hepatitis B vaccine recombinant (yeast). There was no other concomitant medication and no known illness at the time of vaccination. No adverse reactions were reported or observed and the student left the health center without incident. [redacted] Follow-up information indicated that there is no connection between the vaccinations and the death.
[redacted]	14 m / M	Acute respiratory distress syndrome; cyanosis; encephalopathy; fever; neurological examination abnormality; viral infection; lower respiratory tract infection	Information was received from a health professional concerning the patient with a history of varicella, who was vaccinated with measles, mumps, and rubella virus vaccine live. The infant did not present with any pathology and had an excellent psychomotor development. [redacted] He died a few days later. The diagnosis was acute respiratory distress syndrome, probably secondary to an infectious pulmonary pathology, from probable viral origin. The exact cause of death was not specified. No autopsy was performed.
[redacted]	7 y / M	Subacute sclerosing panencephalitis	Information was received from a physician concerning the patient who was vaccinated with measles, mumps, and rubella virus vaccine live. The patient presented with a history of recent psychomotor retardation without any associated history or signs of an infectious or neoplastic process. Investigations concluded that the etiology lay in a subacute sclerosing panencephalitic process attributable to measles, mumps, and rubella virus vaccine live. [redacted] the patient died. The reporter felt that subacute sclerosing panencephalitic process was related to therapy with measles, mumps, and rubella virus vaccine live.
[redacted]	18 m / F	Sudden infant death syndrome	Information was received from a health authority concerning the patient who was vaccinated with the first dose of measles, mumps, and rubella virus vaccine live. After vaccination, the patient developed a common cold with fever. [redacted]

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WAES	Age/ Gender	Reported Cause of Death	Comment
			[redacted] Follow-up information indicated that an autopsy had been done and the result showed no abnormalities.
[redacted]	2 y / M	Wolf-Hirschhorn syndrome	Information was received from a health authority concerning the patient with Wolf-Hirschhorn syndrome, a disease with a defection in chromosome No. 4 and epilepsy, who was vaccinated with measles, mumps, and rubella virus vaccine live. Concomitant therapy included oral sulfamethoxazole/ trimethoprim, valproate sodium 4 ml/d, and valproic acid. Two days later, the boy was found dead [redacted] It was reported that 35% of children with Wolf-Hirschhorn syndrome will die before the age of 2 years. An autopsy was performed and there was no indication for any other explanation for his death than the Wolf-Hirschhorn syndrome.
[redacted]	18 m / F	Sepsis	Information was received from a journalist concerning the patient (also reported as male) with a history of coli infection of urinary tract at 2 months of age and frequent outpatient visits and hospitalizations due to various infections especially upper respiratory and otitis media, who was vaccinated with a 0.5 ml dose of measles, mumps, and rubella virus vaccine live. The patient was previously vaccinated against BCG, diphtheria, tetanus x3, and polio 1 and 2 without reactions. [redacted] The patient received intensive treatment with hydrocortisone sodium succinate and cefuroxime sodium, but the patient subsequently died.
[redacted]	18 m / M	Pneumonia	Information was received from a journalist concerning the previously healthy male who was vaccinated with a 0.5 ml dose of measles, mumps, and rubella virus vaccine live. [redacted] the patient was found dead [redacted] The autopsy showed inflammation of the lungs and respiratory system. The reporter felt that pneumonia was not related to therapy with measles, mumps, and rubella virus vaccine live.
[redacted]	18 m / M	Sepsis	Information was received from a journalist concerning the healthy patient who was vaccinated with measles, mumps, and rubella virus vaccine live. [redacted] The cause of death was unclear. The physicians assessed that it is possible that the child has some kind of sepsis that has lead to severe edema of the brain. No results were reported from the autopsy. Further information received reported that the investigations pointed at sepsis and that there is not causal relationship to the vaccine.
[redacted]	1 y / F	Sepsis	Information was received from a journalist concerning the patient who was vaccinated with measles, mumps, and rubella virus vaccine live. Subsequently, the patient died. The diagnosis was reported as sepsis. The patient's death was assessed as not related to the vaccination with measles, mumps, and rubella virus vaccine live.

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WAES	Age/ Gender	Reported Cause of Death	Comment
[redacted]	18 m / F	Cerebral hemorrhage; thrombocytopenia	Information was received from a journalist the patient who was vaccinated with a 0.5 ml dose of measles, mumps, and rubella virus vaccine live. Low platelet counts were measured. Her condition deteriorated and she was referred to the hospital for further investigation. [redacted] The girl died shortly thereafter due to the large intracerebral hemorrhage. The report was assessed as possibly related to vaccination with measles, mumps, and rubella virus vaccine live.
[redacted]	25 m / M	Sudden infant death syndrome	Information was received from a health authority concerning the patient with a history of 2 episodes of uncomplicated fever convulsions who was vaccinated with measles, mumps, and rubella virus vaccine live. There was no concomitant medication. [redacted] The autopsy showed no certain cause of death and the cause of death was classified as borderline SIDS.
[redacted]	Unk / F	Death	Information was received from a physician concerning the adult patient who was vaccinated with a dose of measles, mumps, and rubella virus vaccine live, while in the hospital. Concomitant therapy included a dose of tetanus toxoid. The physician "heard" that the patient "may have had a serious adverse event" and requested information regarding measles, mumps, and rubella virus vaccine live, encephalitis, and coma. He reported that she went on to develop encephalitis and later died.
[redacted]	Unk / M	Death	Information was received from a physician concerning the patient who was vaccinated with a dose of measles, mumps, and rubella virus vaccine live. At the time of vaccination, the "patient had an unknown immune deficiency." Following vaccination, the patient developed a "morbilliform rash and fever," got better, then developed "another morbilliform rash and fever for 3-4 days, then a serious illness." The patient had been diagnosed with "hematophagocytic syndrome" and Epstein-Barr virus was found. The patient was hospitalized and subsequently died (cause unknown).
[redacted]	12 y / F	Brain compression	Information was received from a health authority concerning the patient who was vaccinated with a dose of measles, mumps, and rubella virus vaccine live. It was noted that the patient had a history of "intern hydrocephalus and signs of meningoencephalitis," but the onset of these is unclear. There was no concomitant medication. [redacted] The results of autopsy showed, "big, swollen, fluid-filled and slightly asymmetric brain with thick membrane and compressed under side. The content of the stomach has been found in the airpathways.
[redacted]	18 y / M	Meningitis bacterial	Information was received from a health professional concerning the patient who was vaccinated with a dose of measles, mumps, and rubella virus vaccine live. Concomitant therapy included hepatitis A vaccine (inactive), hepatitis B virus vaccine rHBsAg (yeast), pneumococcal vaccine 23 polyvalent (MSD), tuberculin purified protein derivative, influenza virus vaccine, and meningococcal polysaccharide vaccine. The patient presented

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WAES	Age/ Gender	Reported Cause of Death	Comment
			with an acute onset of a rash on his feet that spread to his face over a few hours, a 3-day history of a cough, and sore throat. [redacted] autopsy showed that the cause of death was Neisseria Meningitidis Septicemia (Meningococcemia). It was confirmed that the patient was positive for serogroup C Meningococcal infection.
[redacted]	Unk / M	Airways obstruction	Information was received from an internet news site concerning the infant, born prematurely at 28 weeks and suffers from a rare stomach disorder, who was vaccinated with a dose of measles, mumps, and rubella virus vaccine live. Secondary suspect therapy included poliovirus vaccine inactivated (unspecified). [redacted] The coroner recorded a verdict of accidental death after the patient "inhaled some gastric contents." No further information was obtained in follow-up.
[redacted]	Unk / M	Subacute sclerosing panencephalitis	Information was received from a newspaper article concerning the patient, who was vaccinated with a dose of measles, mumps, and rubella virus vaccine live. It was reported that over the eighteen months following vaccination, the patient developed subacute sclerosing panencephalitis and lost the ability to do everything. It was reported that the patient died at 18 years of age from subacute sclerosing panencephalitis.
[redacted]	22 y / F	Lupus-like syndrome; pulmonary haemorrhage	Information was received from a newspaper article concerning a the Army reservist, with no history of skin problems or immune system problems, who was vaccinated with a dose of measles, mumps, and rubella virus vaccine live. Additional suspect therapies included vaccination on the same day with hepatitis B vaccine, smallpox vaccine, anthrax vaccine and typhoid vaccine (unspecified). Subsequently, she became ill with aches and fever resembling the cold that other members of her unit had. When the symptoms worsened, they resembled lupus. The patient died of a complicated illness, diagnosed as 'like lupus'". It was noted that she eventually died from bleeding in her lungs. The Army said two civilian medical panels looked into the case and agreed that the death was "probably" or "possibly" an adverse reaction to vaccines, though they did not single out one.
[redacted]	34 m / F	Salivary gland cancer	Information was received from a physician concerning the Asian patient who was vaccinated with measles, mumps, and rubella virus vaccine live. [redacted] the girl died due to parvicellular malignant tumour in right parotid gland. The reporting physician felt the girl's parvicellular malignant tumour in right gland region was definitely not related to the vaccination with measles, mumps, and rubella virus vaccine live.
[redacted]	8 y / M	Measles; pneumonia	Information was received from a published literature article. A patient with acute lymphoblastic leukemia, T-cell count decreased and chemotherapy was vaccinated in approximately 1988 with one dose of measles, mumps, rubella virus vaccine live. [redacted]

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WAES	Age/ Gender	Reported Cause of Death	Comment
			[redacted] The patient died 18 days after hospitalization. An autopsy was performed: "The cause of death was clearly the recent measles infection causing the giant cell pneumonia with diffuse damage to the lining epithelium of the respiratory tract from tracheal to alveolar levels." The authors also stated that they "believed that the single dose of vaccine failed to protect our patient. We believed that the child with leukemia likely had depression of T-cell function as a result of chemotherapy" "and further believe that he developed measles in part because he received only a single dose of vaccine, but that the infection proved fatal because of immunosuppression."
[redacted]	12 m / M	Brain death; complex partial seizures; brain edema; hypertension	Information has been received regarding a case in litigation. The patient with multiple food allergies, a skin reactions, and medical history of fevers, vomiting, seizure, nasal symptoms, sore throat, urinary discomfort, low thyroxine(T4) value, and an ear infection. [redacted]

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WAES	Age/ Gender	Reported Cause of Death	Comment
			[redacted] the patient died. Discharge/death diagnoses included hypertension and seizures. An autopsy was not performed. The reported cause of death was cerebral edema, seizures and hypertension. Fever was noted to be a condition contributing to the patient's death but not resulting in the underlying cause. It was reported that the encephalitis may be temporally related to the measles, mumps, rubella virus vaccine live but there is no direct evidence that it was the cause of the event.
[redacted]	13 y / M	Acute lymphocytic leukemia	Information was received from an agency official concerning the Asian patient who on 21-APR-2004 was vaccinated with measles, mumps, rubella virus vaccine live. [redacted] the patient died of acute lymphocytic leukemia and respiratory failure. The physician considered respiratory failure was caused by acute lymphocytic leukemia and acute lymphocytic leukemia was definitely not related to the vaccination.
[redacted]	Appr. 13 m / M	Encephalitis post measles	Information was received from a physician concerning the patient with no allergies who in [redacted] was vaccinated with a first dose of varicella virus vaccine live and a dose of measles, mumps, rubella virus vaccine live. It was reported that the patient had a primary immune deficiency and an antiviral T-cell function that was defective clinically. [redacted] The cause of death was measles inclusion body encephalitis (MIBE). A brain biopsy was "positive for measles" and "CLAD A" type, which was consistent with the vaccine strain measles virus. The patient's immunodeficiency was not confirmed but thought to be a "non-killer T-cell problem."
[redacted]	20 m / M	Cardiac arrest; sepsis; respiratory distress	Information has been received from a physician concerning a Caucasian male with a chronic lung condition (bronchopulmonary dysplasia, immunocompromised, severe respiratory distress syndrome, "trach in

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WAES	Age/ Gender	Reported Cause of Death	Comment
			place"(due to bronchopulmonary abnormalities), who on [redacted] was vaccinated with first dose of measles, mumps, rubella virus vaccine live. Concomitant therapy included a first dose of varicella virus vaccine live (MSD). [redacted] The patient failed to respond, remained asystolic and was pronounced dead. The reporting physician did not feel his illness was due to the vaccine. An autopsy report was pending. Another physician reported that primary cause of patient's cardiac arrest may be related to overwhelming sepsis or related to congestive heart failure.
[redacted]	6 y / F	Myocarditis; pyrexia; vomiting; abdominal pain	Information has been received from a health professional and health authority. The patient had no relevant medical history and no safety problems following previous vaccinations. On [redacted]5, she was vaccinated with a second dose of measles, mumps, rubella virus vaccine live. [redacted] She died on [redacted] 15-days after vaccination. A diagnosis of myocardial infarction likely related to viral myocarditis was made. The echocardiography revealed no abnormality in coronary arteries. No autopsy was done. Viral serologies performed were negatives or corresponded to previous immunity. The health authority considered acute myocarditis, fever, abdominal pain, and vomiting to be disabling.

Comment

Of the 33 reports of fatal outcome, 23 reports indicate that the patients died of their underlying disease(s) or other concurrent illnesses. Two reports of fatal outcome were due to sudden infant death syndrome (SIDS). In the 8 remaining reports, a relationship between measles, mumps, and rubella virus vaccine live and these deaths could not be established. No new safety issues with fatal outcomes were identified during the ongoing monitoring of the safety of measles, mumps, and rubella virus vaccine live. The Company will continue to monitor all adverse experiences as part of its ongoing evaluation of the safety of this product.

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9.3 Drug Interactions

During the reporting period for this PSUR, no reports of drug interaction with measles, mumps, and rubella virus vaccine live were identified.

9.4 Overdose

During the reporting period for this PSUR, 60 reports were identified as reports of overdose with measles, mumps, and rubella virus vaccine live out of approximately [redacted] doses distributed. None of these reports involved fatal outcomes. Two of the 60 reports involved patients who were reported to have experienced metal poisoning and neurotoxicity (WAES [redacted]. An overdose involving measles, mumps, rubella virus vaccine live was not reported in either patient and these reports are not considered further. For the purposes of this analysis, accidental exposures to measles, mumps, and rubella virus vaccine live are evaluated as 'overdoses'.

Of the 58 reports of overdose, 38 reports did not involve any adverse experiences (AEs) other then the overdose itself. Thirty-one of the 38 reports involved accidental exposures either due to an inadvertent splash into the eye during the administration of the vaccine (27), swallowing of the vaccine (1), vaccination in an HIV infected patient (1), vaccination in a bone marrow transplant patient (1), or exposure due to the shattering of a vial (1). Four of these 31 reports involved pregnant patients ([redacted] are also included in Section 9.6 Use During Pregnancy). Of the remaining 7 reports, 4 reports involved overdoses in patients who were inadvertently vaccinated with 2 doses of measles, mumps, rubella virus vaccine live (WAES [redacted]. Two reports (WAES [redacted], involved patients who experienced an overdose due to the administration of a third dose of the vaccine, and 1 report (WAES [redacted] involved a prescribed overdose in a 5-month-old patient who was intentionally vaccinated with measles, mumps, rubella virus vaccine live.

Twenty of the 58 reports involved an accidental exposure or overdose where the patient experienced adverse events. Nineteen reports (18 accidental exposure reports and 1 overdose report) involved adverse events that were considered to be nonserious and included the following: eye irritation, eye pruritus, dry eye, superficial injury of the eye, eye pain, eye redness, eye numbness, blepharitis, eye discomfort, abnormal feeling in the eye, contact dermatitis, joint swelling, injection site pain, pain, gastrointestinal disorder, and fever. The remaining 1 report involved adverse events that were considered to be serious. WAES [redacted] concerned a 24-year-old female healthcare worker who was inadvertently splashed in the eye while administering measles, mumps, rubella virus vaccine live. The patient developed pain, burning, and decreased visual acuity and was treated for cycloplegia and corneal keratitis. The patient subsequently recovered.

Comment

The majority of the 58 reports of overdose (38 reports) did not involve adverse events. The majority of the remaining 20 reports involved events that were considered to be nonserious. The Company will continue to monitor all reports of overdose with measles, mumps, and rubella virus vaccine live.

9.5 Drug Abuse and Misuse

The term 'Drug Abuse' is herein interpreted in the context of *use that is illegal or addictive*, though it is acknowledged that this has limited utility when applied to vaccines, as contrasted with pharmaceuticals.

The term 'Misuse' is herein interpreted in the context of *use that deviates from what is recommended*, i.e., what is described in the CCDS or the package circular (Prescribing Information). Misuse is applied broadly to conditions of shipping, storage and administration, including doses given when contraindicated, at an inappropriate age, too soon or too late, by an incorrect route, etc. In MedDRA, 'Misuse' maps to the preferred terms of 'Medication Error', which includes such lower level terms as *expired drug, wrong drug administered, wrong patient, inappropriate schedule, expired drug, vaccine not stored properly,* etc.

During the reporting period for this PSUR, there were no reports of drug abuse and 1,359 spontaneous reports of product misuse (medication error) with measles, mumps, and rubella virus vaccine live were identified from health care providers. These reports consisted of the following: drug maladministration (409*); inappropriate schedule of drug administration (210*); medication error (no other term specified) (182*); incorrect dose administered (15*); incorrect drug dosage form administered (2); incorrect route of drug administration (265*); poor quality drug administered (254*); wrong drug administered (14*); wrong technique in drug usage process (23*). One-hundred-seventy-two reports (approximately 13%) of the 1,359 reports described adverse events, the majority of which are known side effects of measles, mumps, rubella virus vaccine live, MSD as described in the CCDS or complications of known side effects.

Conclusion

The Company will continue to monitor reports of product misuse as part of the ongoing safety evaluation of measles, mumps, and rubella virus vaccine live.

9.6 Use During Pregnancy

9.6.1 New Reports of Pregnancy Exposures Between 01-Jan-2001 and 31-Dec-2005

During the reporting period of this PSUR, the Company received a total of 281 spontaneous reports of maternal exposure to measles, mumps, and rubella virus vaccine live during pregnancy identified from health care providers and consumers.

A prospective report of exposure during pregnancy is defined as a report for which the Company first learned of the exposure during the pregnancy and the outcome of the pregnancy may be subsequently reported. A retrospective report of exposure during pregnancy is defined as a report for which the Company first learned of the exposure after the outcome of the pregnancy was known.

Two-hundred forty-seven of the reports were prospective and the remaining 34 were retrospective reports. The pregnancy outcomes of these 281 reports are presented in Table 9.6.1.

* Thirteen patients were identified where 2 medication errors were reported for each. One patient had 3 medication errors reported.

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Table 9.6.1
New Reports Received
Summary of Pregnancy Exposures
01-Jan-2001 to 31-Dec-2005

	Total Reports of Pregnancy Exposure	Live Births	Elective Abortions	Spontaneous Abortions	Fetal Death	Outcome Unknown
Prospective Reports	247	34	4	11		198
Retrospective Reports	34	21[a]	3	8	2[b]	

[a] One report of limb hypoplasia congenital
[b] One report of a twin pregnancy w/ fetal loss and retention of one fetus.

9.6.1.1 Prospective Reports

The pregnancy outcomes of the 247 prospective reports of exposure to measles, mumps, and rubella virus vaccine live during pregnancy were: 34 live births, 4 elective abortions and 11 spontaneous abortions. The pregnancy outcomes of the remaining 198 reports are unknown.

9.6.1.2 Retrospective Reports

The pregnancy outcomes of the 34 retrospective reports of exposure to measles, mumps, and rubella virus vaccine live during pregnancy were: 21 live births, 3 elective abortions, 8 spontaneous abortions, and 2 fetal (intra-uterine) death.

9.6.2 Congenital Anomalies

During the reporting period of the PSUR, in all of the new reports of exposure to measles, mumps, and rubella virus vaccine live during pregnancy, there were no prospective reports of congenital anomalies and 1 retrospective report of congenital anomalies. In WAES [redacted], information was received concerning a 22-year-old female who was vaccinated with the first dose of dose of measles virus vaccine live (+) mumps virus vaccine live (+) rubella virus vaccine live (second generation) one month before the beginning of her pregnancy. At 29 weeks gestation, an echography was performed and a congenital anomaly (i.e., a pathology of the fetus' lower limbs) was observed. At 40 weeks gestation, the patient gave birth by Cesarean to a male with an "ectromelia consisting of hypoplasia of the fibula." The male infant was evaluated: Apgar score test = 9/10, weight = 4,270 g, height = 50 cm, and cranial perimeter = 37 cm.

Comment
Among the pregnancy reports with known outcomes, 1 retrospective report of congenital anomalies has been received during the reporting period. It is not known whether measles, mumps, and rubella virus vaccine live can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Therefore, the vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for three months following vaccination. The CCDS includes text stating that exposure to

mumps infection during the first trimester of pregnancy may increase the rate of spontaneous abortion.

9.6.3 Previously Identified Reports

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During the reporting period of this PSUR, follow-up information was received concerning the outcomes of 8 previously identified reports in which women were exposed to measles, mumps, and rubella virus vaccine live during pregnancy and in which the pregnancy outcomes were unknown at the time of previous PSURs (prospective reports). In the 8 reports with follow-up information, 4 pregnancies resulted in normal healthy newborns, 3 reports involved patients who were lost to follow-up and 1 report involved a patient who underwent an elective abortion.

Table 9.6.3
Summary of Pregnancy Exposures from Previously Identified Reports
(Follow-up Information Received)
01-Jan-1999 to 31-Dec-2003

	Total Reports of Pregnancy Exposure	Live Births	Elective Abortions	Lost to Follow-Up
Prospective Reports	8	4	1	3

Comment

Merck & Co., Inc. will continue efforts to obtain outcome information for all reports of exposure to measles, mumps, and rubella virus vaccine live during pregnancy.

9.6.4 Use During Lactation

During the reporting period of this PSUR, 7 reports of exposure during lactation involving measles, mumps, and rubella virus vaccine were identified. In 3 of the 7 reports, there were no adverse effects reported. One report (WAES [redacted] concerned a male infant who was breast fed by his mother, who had been vaccinated with a dose of measles, mumps , rubella virus vaccine live on 25-Oct-2002. Subsequently, after breast feeding, the infant "broke out with measles like rash" for 2 days.

The remaining 3 reports were obtained from a published literature article entitled, "Adverse Outcomes Associated with Postpartum Rubella or MMR Vaccine". In 2 of the 3 reports (WAES [redacted]), 15-month-old males were breast fed by their mothers who were vaccinated post-partum with a dose of measles, mumps, rubella virus vaccine live. The infants did not experience any adverse events due to possible vaccine exposure from breast milk. Both infants were reported to have developed normally during the first year of life. At 15-months of age, both infants were vaccinated with a dose of measles, mumps, rubella virus vaccine live and were diagnosed with autism. The third report (WAES [redacted]) involved a 4-day-old male patient whose mother was vaccinated with a dose of measles, mumps, rubella virus vaccine live in the postpartum period after his birth in May 1993, on his fourth day

of life. Subsequently, the infant curled up in a ball and cried for 24 hours. He suffered from severe constipation during his first year of life, and has had persistent diarrhea ever since. He was also diagnosed with autism. It was reported that the patient was breast-fed.

Comment

Although the specific cause of autism is not fully understood, it is clearly a biologically determined disorder and is not caused by poor parenting, adverse childhood conditions, or vaccination. Autism occurs in 5 out of every 10,000 children and is 2 to 4 times more common in boys than girls.[1] The Company will continue to monitor all reports of exposure during pregnancy and lactation as part of its ongoing evaluation of the safety of measles, mumps, and rubella virus vaccine live.

9.7 Consumer Reports

Line listings, period summary tabulations and cumulative summary tabulations of consumer reports for measles, mumps, and rubella virus vaccine live, for which no information has been received from a health care professional, are listed in Addendum 1. In all cases, attempts have been made to obtain medical follow-up. Review of these reports raises no additional safety concerns.

[1] The Merck Manual of Medical Information: Second Home Edition, Autism in Ch. 286, Mental Health Disorders

10. Overall Conclusion

Examination of the data contained within this PSUR supports the conclusion that measles, mumps, and rubella virus vaccine live is generally well tolerated. Analysis of these data is consistent with the current CCDS in terms of product safety.

As with all Merck & Co., Inc. products, the safety profile of measles, mumps, and rubella virus vaccine live is closely monitored on a continuing basis.