Product Approval Information - Licensing Action

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

June 8, 2006

Our STN: BL 125126/0

Merck & Co., Inc.
Attn: Dr. Patrick Brill-Edwards
Director
Worldwide Regulatory Affairs
Vaccines/Biologics
P.O. Box 4 , BLB-22
West Point , PA 19486-0004

Dear Dr. Brill-Edwards:

We have approved your biologics license application (BLA) for Quadrivalent Human Papillomavirus (Types 6, 11, 1 6, 18) Recombinant Vaccine effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine under your existing Department of Health and Human Services U.S. License No. 0002. Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine is indicated for vaccination in females 9 to 26 years of age for prevention of the following diseases caused by Human Papillomavirus (HPV) Types 6, 11, 16, and 18:

- Cervical cancer
- Genital warts (condyloma acuminata)
  and the following precancerous or dysplastic lesions:
- Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Cervical intraepithelial neoplasia (CIN) grade 1.

Under this authorization, you are approved to manufacture Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine at Merck & Co., Inc., West Point, PA. The final formulation and filling is performed by Merck & Co., Inc., West Point, PA. Labeling and packaging will be performed by Merck & Co., Inc., West Point, PA. You may label your product with the proprietary name GARDASIL®. The vaccine will be supplied as a 0.5 mL single-dose vial, a carton of ten 0.5 mL single dose vials, a 0.5 mL single-dose prefilled syringe and a carton of six 0.5 mL single-dose prefilled syringes. The prefilled

syringes will be preassembled with Ultra Safe® Passive™ Needle Guard devices.

The dating period for GARDASIL® vaccine shall be 36 months from the date of manufacture of the final filled container when stored at 2 to 8 °C. The 36 month shelf life includes all of the time that the final filled container is held at 2 to 8 °C prior to packaging. The date of manufacture shall be defined as the start date of filling into final containers. ---------- ---------- ---------- ---------- ---------- --------- ---------- ---------- ---------- ---------- ----------

Please submit final bulk samples and final container samples of the product together with lot release protocols in electronic format showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of GARDASIL® vaccine, or in the manufacturing facilities.

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring pediatric studies for GARDASIL® in girls less than 9 years of age and in boys and adolescent males less than 18 years of age.

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

We acknowledge the postmarketing clinical commitments outlined in your submission of June 6, 2006, as follows:

1. You have committed to conduct a short-term safety surveillance study in a U.S. Managed Care Organization (MCO). The study will include approximately 44,000 vaccinated subjects who will be followed for 60 days for assessment of general short-term safety (i.e., emergency room visits, hospitalizations, and deaths). The subjects will also be followed for 6 months subsequent to vaccination for new autoimmune disorders, rheumatologic conditions, or thyroiditis. Also, a sufficient number of children 11-12 years of age will be studied to permit an analysis of safety outcomes. The final study protocol will be submitted by December 31, 2006. Patient accrual will be completed by December 31, 2008. The study will be completed by June 30, 2009. The final study report will be submitted by September 30, 2009.

2. You have committed to collaborate with the cancer registries in four countries in the Nordic Region (Sweden, Norway, Iceland, and Denmark) to assess long-term outcomes following administration of GARDASI®. In this study, approximately 5,500 subjects enrolled in Protocol 015 (one half from the placebo group that will have been vaccinated shortly after approval) will be followed for a total of 14 years. Two major goals of this study are: 1) to assess the long-term effectiveness of GARDASIL® by evaluating biopsy specimens for presence of HPV 6/11/16/18-related incident breakthrough cases of CIN 2/3, AIS and cervical cancer, VIN 2/3 and vulvar cancer, and VaIN 2/3 and vaginal cancer; and 2) to assess whether administration of GARDASIL® will result in replacement of these diseases due to vaccine HPV types with diseases due to non-vaccine HPV types. This study is designed to accomplish these goals as discussed in the June 6, 2006, submission to your BLA. The final protocol

for this study will be submitted by December 8, 2006. Patient accrual for this study was previously completed in the context of Protocol 015. This study will be completed by December 31, 2017, (14 years from initiation of the last patient enrolled in Protocol 015 in the four Nordic countries). The final study report will be submitted by December 31, 2018.

3. You have committed to conduct a study in collaboration with the Norwegian Government, if GARDASIL ® is approved in the European Union and the Government of Norway incorporates HPV vaccination into its national guidelines, to assess the impact of HPV vaccination on the following in Norway:

    a. The long-term burden of HPV disease including the incidence of HPV 6/11/16/18-related cervical disease;
    b. The long-term burden of HPV disease caused by types other than HPV 6/11/16/18;
    c. The overall incidence of cervical HPV disease;
    d. The incidence of HPV-related cancers and pre-cancers (CIN 2/3, AIS and cervical cancer; VIN 2/3 and vulvar cancer; and VaIN 2/3 and vaginal cancer);
    e. The interaction between administration of GARDASIL ® and pregnancy outcomes, especially congenital anomalies, by linking the vaccination registry with the Medical Birth Registry.

    The size and age range of the population studied will depend on the final vaccination guidelines implemented by the Norwegian Government. Although at this time no other governments in the Nordic region have committed to similar population studies, you will notify CBER of any other collaborations if they occur. The projected date of submission of the final study protocol is pending collaboration with the Norwegian Government as noted above. Patient accrual will be completed 6 years after study initiation. The study will be completed 7 years after study initiation. The final study report will be submitted 8 years after study initiation. In the event that approval of GARDASIL® does not occur in Norway, you will notify CBER and propose alternative approaches to obtain this information in a timely manner.

4. You have committed to submit final Clinical Study Reports (CSRs) for Protocols 013 and 015 when completed. As discussed, for these studies, an "all CIN 2/3, AIS or cervical cancer" analysis will evaluate the evidence for replacement of disease due to HPV types 16 and 18 with non-vaccine HPV types. Similar analyses will be done for VIN 2/3, VaIN 2/3, vulvar cancer and vaginal cancer. Protocol 013 was submitted in December 2001, and Protocol 015 was submitted in May 2002. Protocol 013 accrual was completed in March 2003, and Protocol 015 accrual was completed in May 2003. These analyses will be completed by April 30, 2007. The final reports for these studies (i.e., CSRs) to include the results of these analyses will be submitted by June 30, 2007.

5. You have committed to provide data concerning duration of immunity following administration of GARDASIL® as follows from the studies noted:

    a. The Nordic Long-Term Follow-up Study:
    Interim reports of effectiveness (i.e., incident breakthrough cases of CIN 2/3, AIS and cervical cancer; VIN 2/3 and vulvar cancer; and VaIN 2/3 and vaginal cancer) and immunogenicity results will be submitted in 2009, 2011, 2013, and 2015. The final study report will be submitted by December 31, 2018.

    b. Protocol 018 (Adolescent Sentinel Cohort):

- Periodic reports beginning with Month 24 immunogenicity and long-term safety data will be submitted starting no later than March 30, 2007.
- Publication of one year Post-dose 3 data will be submitted by January 30, 2007.
- A Biologics License Supplement (BLS) for 1.5 year Post-dose 3 data will be submitted by June 30, 2007.
- A Biologics License Supplement (BLS) for 2.5 year Post-dose 3 data will be submitted by December 31, 2007.
- A Biologics License Supplement (BLS) for 5.5 year Post-dose 3 data will be submitted by December 31, 2010.

c. Protocol 007:
Publication of five-year immunogenicity data will be submitted by December 31, 2006.

d. Protocol 005:
Publication of seven and one half year immunogenicity data will be submitted by December 31, 2007.

6. You have agreed to establish a pregnancy registry in the U.S. to prospectively collect data on spontaneously-reported exposures to GARDASIL® during pregnancy. You have committed to submit a protocol for the U.S. pregnancy registry by July 20, 2006. You have agreed to address elements found in FDA's Guidance for Industry on Establishing Pregnancy Exposure Registries (9/2/2002) (http://www.fda.gov/cber/gdlns/pregexp.htm), as well as relevant Company Standard Operating Procedures. Furthermore, you have stated that you will notify CBER of significant deviations from this guidance and/or specify the deviations in the protocol. Patient accrual/data collection will begin at time of CBER's approval of the protocol and end five years later. You will submit annual reports and a final summary report of the U.S. pregnancy registry's findings five years after initiation of patient accrual/data collection. The U.S. pregnancy database will be considered completed one month after discontinuation of patient accrual for the purpose of preparing a five-year final summary report. The five-year final summary report will be submitted to CBER five years and six months after initiation of patient accrual/data collection. After reviewing the five-year data, Merck and CBER will meet to discuss the need to continue further data collection in the U.S. pregnancy registry. CBER will have final approval regarding any decision to discontinue the U.S. pregnancy registry.

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

We acknowledge the postmarketing clinical commitment outlined in your submission of June 6, 2006, as follows:

7. You have committed to provide CBER and simultaneously the FDA contractor for the Vaccine Adverse Events Reporting System (VAERS) all initial postmarketing "periodic" adverse experience reports received that are subject to periodic reporting (i.e., not covered under the "15-day Alert report" requirement under 21 CFR 600.80) on a monthly basis. Initial reports received by Merck in a given month will be submitted on VAERS forms to CBER and to the VAERS contractor by Working Day 10 of the following month. You have also agreed to provide, in accordance with 21 CFR 600.80, the Quarterly Periodic Adverse Experience Report to the VAERS contractor. The Quarterly Adverse Experience Report will contain a recapitulation of all initial reports submitted for the current reporting period and will include all follow up information on VAERS forms collected during that three-month period. You have committed to providing CBER this information using the aforementioned process,

for the first three years after the date of licensure.

We acknowledge the postmarketing quality commitments outlined in your submission of June 2, 2006, as follows:

You have committed to providing all available stability data on all final container lots (both vials and syringes) currently on stability study to support the requested product shelf-life of 36 months at 2 to 8 °C by July 31, 2006. Additional updates to the stability data for these lots will be submitted as they become available, through the study endpoint (-- months storage at 2 to 8 ° C).

We request that you submit clinical protocols to your IND ----, with a cross-reference letter to this biologics license application (BLA), STN BL 125126. We request that you submit n onclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA, STN BL 125126. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments, as appropriate:

- **Postmarketing Study Protocol**
- **Postmarketing Study Final Report**
- **Postmarketing Study Correspondence**
- **Annual Report on Postmarketing Studies**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted), and
- an explanation of the status including, for clinical studies, the subject accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to FDA's Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (February 2006) (see http://www.fda.gov/cber/gdlns/post130.htm) for further information.

Please submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80), and distribution reports as described in (21 CFR 600.81). Under 21 CFR 600.80(c) (2) [Periodic Adverse Experience Reports], you must report each adverse experience not reported under paragraph (c) (1) (i) of this section at quarterly intervals for the first 3 years following approval, and then at annual intervals. We note your clinical commitment in item 7 above to submit certain reports on a monthly basis for the first three years following approval. Since your product is characterized as a vaccine, submit these reports to the Vaccine Adverse Event Reporting System (VAERS) using the pre-addressed form VAERS-1.

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, Center for

Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit all final printed labeling and implementation information on FDA Form 356h. Please provide a PDF-format electronic version of the label.

In addition, you may wish to submit two draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Two copies of final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253. All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have submitted data to support such claims to us and received CBER approval for such claims.

If you have any questions, please contact Dr. Gopa Raychaudhuri at 301-827-3070.

Sincerely yours,

Norman W. Baylor, Ph.D.
Director
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research

Updated: June 8, 2006