Extract from minutes of MAAC meeting relevant to Gardasil

(33)

20 June 2006

5.1.6. Gardasil (quadrivalent Human Papillomavirus [Types 6, 11, 16, 18]) recombinant vaccine.

The Committee considered an application submitted by Merck Sharp & Dohme (NZ) Ltd for Gardasil (quadrivalent Human Papillomavirus [Types 6, 11, 16, 18]) recombinant vaccine. The proposed indication is Gardasil is indicated for the prevention of

- Cervical cancer, cervical intraepithelial neoplasia (CIN) grade 2 and 3, vaginal cancer, and vulvar cancer caused by Human Papillomavirus (HPV) types 16 and 18
- HPV infection, CIN grade 1, external genital warts, perianal warts, vulvar intraepithelial neoplasia (VIN) grade 1, 2 and 3 and vaginal intraepithelial neoplasia (ValN) grade 1, 2 and 3 caused by HPV types 6, 11, 16, or 18

The Committee noted that the data relating to the composition, manufacture, quality control, stability and bioavailability of this product are adequate and acceptable except for the following outstanding issues.

Drug substance manufacture

1. The drug substance manufacturing process uses a number of filtration steps, yet the manufacturing process does not include any 'filter integrity tests' as in-process controls. The manufacturing process needs to include 'filter integrity' testing as in-process controls for all the filtration steps.

2. The drug substance manufacturing process does not describe a 'mixing time' as in-process control to ensure maximum adsorption. Please describe if there is a minimum mixing time required to ensure maximum adsorption, and if so, demonstrate that the mixing time has been adequately validated.

3. Throughout the drug substance purification validation studies, the upper and lower limits of the CPPs were not adequately tested to demonstrate the process was robust to variations in the CPPs and still able to meet the established CQA criteria. The individual CPPs that were not adequately tested have been described in the Medsafe Evaluation Report. Either the CPPs need to be tightened to reflect those actually tested in the process validation, or additional process validation data is required to demonstrate that the proposed ranges of the CPPs are acceptable.
The absence of impurity testing [redacted] in the drug substance specifications can only be considered acceptable if the CPPs are tightened to those tested, or additional process validation data is completed that demonstrates impurity clearance is consistent for the proposed CPP ranges.

4. Please describe the size of the DFAP sample that was used to assess stability and what proportion it was compared to full scale manufacture.

5. Please provide the drug substance filter(s) extractable study that was completed, or a summary of the study data and the acceptance criteria

6. Please provide the study that demonstrates the sterilising filter used in the drug substance manufacturing process has been satisfactorily validated for microbial retention.

7. Please provide the validation study, or a tabulated summary of the study data, that demonstrates the efficacy of the sanitisation procedures used for new filters in the drug substance manufacturing process.

8. Please explain why a minimum contact time with [redacted] has not been set for sanitisation of the new [redacted].

9 The reuse validation studies for the [redacted] had CPPs for [redacted] and [redacted] The minimum contact time [redacted] was successfully validated, but the CPP for the [redacted] was not tested. All reuse validation studies used approximately [redacted] Please explain why the CPP, [redacted] was not tested, and confirm that the CPP limit for [redacted] will be amended to [redacted] for all future sanitisation procedures for the [redacted]

Finished product manufacturing process

10. Finished product manufacturing validation states that the mixing times and mixing speeds were identified as 'critical process parameters (CPPs)' prior to process validation, but after process validation it was determined that these process parameters were well controlled and robust and did not impact upon final product quality. Mixing times, mixing speeds, agitator speed and recirculation rate [redacted] were therefore no longer identified as 'critical process parameters'. Although mixing times, mixing speeds, agitation speeds and recirculation rates may no longer be identified as 'Critical Process Parameters' as they are well controlled, they should still be identified as 'in-process controls' for the manufacturing process. Please provide manufacturing flow diagrams that list these parameters as in-process controls, and the values associated with them.

Cell bank system

11. Please confirm if the master seeds and working seeds were tested for viable count and provide the specification limits that were applied for the test of viable count.

Drug Substance specifications

12. Please describe the [redacted] that has been calculated in the validation of the [redacted] method used for the drug substance.

13. No statistical analysis appears to have been used to determine the proposed drug substance release limits for [redacted] The proposed limits appear to be too conservative and based on the batch data the limits could be tightened to [redacted] Please explain how the limits have been selected and why they are appropriate considering batch data generated to date indicate the limits could be tightened.

Quality control of drug substance process excipients

14. [redacted] is used to create the FAP, and the FAP along with aluminium adjuvant is used to formulate the MBAP, i.e. the drug substance. The components of the [redacted] are not controlled according to pharmacopoeial specifications and need to be as excipients of the FAP become part of the finished product.

Finished product specifications

15. Please provide the results for the finished product [redacted] method validation study, [redacted]

16. The [redacted] limit far exceeds that observed for any of the batches manufactured according to the vaccine's target protein concentration. Although it is apparent that the upper limit has been introduced as a safety factor, the limit should be based on data from manufacturing experience as the very high upper limit can allow for a very wide variation in vaccine [redacted] batch results. The upper [redacted] limit should be revised to take into account the actual batch data obtained to date from the manufacturing process.

Drug Substance Stability

17. Based on the drug substance stability data, which show no significant trends, the stability specifications need to be tightened to those used for release of the MBAP, as all stability results were well within the release specifications. Please confirm that the stability specifications will be tightened to those used at release. The tightened stability specifications will ensure that any trends in future stability batches will readily detected, so that it is apparent if batches have different stability characteristics to those observed in this dossier.

18. In the dossier it was anticipated that [redacted] of data for all [redacted] lots would be available in 2005. This data should now be available and submitted to Medsafe.

19. Updated stability data for the MABP stability batches should now be available and submitted to Medsafe. If the stability data is not available, please indicate when the stability studies will be completed and submitted to Medsafe.

Drug Substance post-approval stability protocol

20. Please indicate when the cumulative stability studies for the MBAP and finished product will be completed and submitted to Medsafe.

21. No information has been provided in the dossier regarding the annual stability program for the drug substance. Please confirm that at least one batch of each HPV type MBAP will be placed on stability every year.

Finished product stability

22. Please submit for the finished product (for both the vial and syringe):
- updated stability data that is available to date,

- updated statistical analysis of the stability trends for both long term and accelerated storage,
- and proposed stability specifications (e.g. [redacted].
Where stability studies submitted in the initial dossier have not yet been completed, please confirm the dates the studies will be completed and submitted to Medsafe.

Finished product post-approval stability protocol
23. Please confirm whether or not the test for [redacted] will be included in the stability specifications for future stability batches. If so, the proposed limit needs to be tightened as all stability batch data to date demonstrate results [redacted]

24. The proposed stability limits for [redacted] are too low when compared to the actual stability batch data obtained to date. The justification for the limits has been reviewed, and the justification does not appear to take into consideration that:
i) all batches manufactured to date with the target protein concentration are consistently released with [redacted] values well above the [redacted] release limits,
ii) even with a slight decrease observed for some batches for the [redacted] stability results, no [redacted] values fell below or were even close to the release [redacted] limits.
Based on the release and stability data submitted to date, it is recommended that the stability limits for [redacted] be tightened to be the same as those proposed for release.

Labelling
25. Please indicate where the batch number and expiry date will be placed on the 10 syringe pack and the single syringe pack.

26. Syringe and vial labels must have lettering height that meets the NZ Medicine Regulations requirement of 0.75mm. The small text on the proposed vial and syringe labels is only 0.5mm and is unreadable.

A response to the Request for Information had been received and was currently being evaluated.

The Committee was shown the following SCRIP articles:
- *First vaccine against cervical cancer filed in the US.* No. 3114, December 9th 2005.
- *Gardasil cervical cancer vaccine gets US priority review status.* No. 3130, February 10th 2006.
- *US FDA panel to review Gardasil in May.* No. 3153/54, May 3rd/5th 2006.
- *Gardasil HPV vaccine gets strong endorsement from US FDA panel.* No. 3159, May 24th 2006.

Human Papillomavirus (HPV) has been associated with about 99.7% of cervical cancers, 64-100% of vulvar cancers and 33-73% of cervical abnormalities. Cervical screening has contributed to reducing the number of cervical cancer cases.

Most HPV infection is acquired in the first ten years after sexual debut, and takes up to five years to progress to CIN, and then up to 20 or more years to become invasive cancer. About half of all adults become infected with HPV in their lifetime. Vaccination needs to precede infection. Median age of sexual debut is 16 years in most countries.

Gardasil is a recombinant yeast expressed quadrivalent vaccine comprising the L1 proteins of HPV types 6, 11, 16, and 18, these proteins being assembled as virus-like particles. There is no viral DNA present, so that the vaccine is incapable of causing infection. The vaccine adjuvant is aluminium hydroxyphosphate sulphate.

s18(c)(i)

[redacted]

s18(c)(i)

[redacted]

The Committee recommended that the Australian approved indications be approved for use in New Zealand.

Committee recommendations:

That Gardasil (quadrivalent Human Papillomavirus [Types 6, 11, 16, 18]) be approved under Section 21 of the Medicines Act 1981 for following indications:

- Gardasil is indicated in females aged 9 to 26 years* for the prevention of cervical, vulvar and vaginal cancer, precancerous or dysplastic lesions, genital warts and infection caused by Human Papilliomavirus (HPV) types 6, 11, 16 and 18 (which are included in the vaccine)
- Gardasil is indicated in males aged 9 to 15 years for the prevention of infection caused by Human Papilliomavirus (HPV) types 6, 11, 16 and 18 (which are included in the vaccine).

* immunogenicity studies have been conducted to link efficacy in females aged 16 to 26 years to the younger populations.

This approval is subject to the following:

- The outstanding Part II issues are found to be satisfactory
- The company accepting the revised indications.

Format 10q HBsAg

Name of the company **Merck & Co., Inc.**	**Summary table referring to Part II.C of the dossier**	**(For National Authority use only)**
Name of finished medicinal product **Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine**		
Name of active ingredient **PRP-OMPC** **HBsAg**		

Part II.C:	**PRODUCTION AND CONTROL OF STARTING MATERIALS** **1 - ACTIVE INGREDIENTS - (VALIDATION OF THE PROCESS)** **HEPATITIS B SURFACE ANTIGEN**	
Characterization (cont.) **Volume 3/14, Part II.C.1.6.**	Page(s) 769 to 772	**COMMENTS (For National Authority use only)**

DNA Content
Method : hybridization

The final result was converted from picograms of ribosomal DNA/mL to picograms of genomic DNA per dose (Table 11-C). I

Format 10r HBsAg

Name of the company **Merck & Co., Inc.**	Summary table referring to Part II.C of the dossier	(For National Authority use only)
Name of finished medicinal product **Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine**		
Name of active ingredient PRP-OMPC HBsAg		
Part II.C: PRODUCTION AND CONTROL OF STARTING MATERIALS 1 - ACTIVE INGREDIENTS - (VALIDATION OF THE PROCESS) HEPATITIS B SURFACE ANTIGEN		
Characterization (cont.) Volume 3/14, Part II.C.1.6.	Page 773	COMMENTS (For National Authority use only)

Table 11-C. DNA Content in PFIII Product.

PFIII Product Lot	pg genomic DNA per 5µg dose

Biophysical Characterization	

Format 12i HBsAg

Name of the company **Merck & Co., Inc.**	**Summary table referring to Part II.C of the dossier**	**(For National Authority use only)**
Name of finished medicinal product **Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine**		
Name of active ingredient **PRP-OMPC** **HBsAg**		

Part II.C: PRODUCTION AND CONTROL OF STARTING MATERIALS
1 - ACTIVE INGREDIENTS - (ANALYTICAL DEVELOPMENT AND VALIDATION)
HEPATITIS B SURFACE ANTIGEN

Process Validation (cont.) **Volume 3/14, Part II.C.1.8.** Page (s) 926 to 928	**COMMENTS (For National Authority use only)**
Removal of Impurities For validation purposes, clearance of the following impurities during purification was measured: DNA, carbohydrates, lipids, and protein impurities. In addition, clearance of the processing chemicals Triton X-100, thiocyanate, and formalin are routinely monitored as part of release testing.	
Methods: *DNA :* · Molecular Devices Threshold™ Assay Kit for measuring picogram levels of total DNA · Levels in final purified bulks were measured using a hybridization method for yeast DNA.	

Table 21-C. Clearance of Impurities through the H-B-VAX™-II Purification Process

	RBP	ES	CLAP	DPAA	PFIII	SFP
EIA mcg/mL						
Lowry mcg/mL						
EIA/Protein Ratio (g/g)						
Lipid mcg/mL						
Lipid/Lowry Ratio (g/g)						
Carbohydrate mcg/mL						
CHO*/Lowry Ratio (g/g)						
DNA pcg/mL						
DNA.Lowry Ratio (pg/g)						

* CHO = Carbohydrate

Name of the company **Merck & Co., Inc.**	**Summary table referring to Part II.C of the dossier**	**Format 12l HBsAg (For National Authority use only)**
Name of finished medicinal product **Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine**		
Name of active ingredient **PRP-OMPC** **HBsAg**		

Part II.C: PRODUCTION AND CONTROL OF STARTING MATERIALS
1 - ACTIVE INGREDIENTS - (IMPURITIES)
HEPATITIS B SURFACE ANTIGEN

Impurities **Volume 3/14, Part II.C.1.9**	**Page(s) 937 to 938**	**COMMENTS (For National Authority use only)**
Potential impurities arising from the host system Each lot is tested for the presence of yeast proteins. The specification for yeast proteins is < 1.0 %. DNA clearance studies also demonstrated the removal of DNA in the process.		