Gardasil

(30)

Data of a New Medicine Application

Evaluator: [redacted] s9(2)(a)
Date: 19.3.06
TT50-7571

Product Details

Active Substance: HPV 6 L1 protein
HPV 11 L1 protein
HPV 16 L1 protein
HPV 18 L1 protein

Proprietary Name: Gardasil

Dose Form: Solution for injection

Potency: HPV 6 L1 protein, 20µg
HPV 11 L1 protein, 40µg
HPV 16 L1 protein, 40µg
HPV 18 L1 protein, 20µg

Therapeutic use: Vaccine

Administration: Intramuscular injection

Dosage: Gardasil is recommended to be administered as 3 separate 0.5mL doses.
The dose regime has been described in the datasheet and will be assessed by clinical evaluators.

Packaging: A glass vial or syringe

Pack size: 1 x vial
10 x vials
1 x syringe
10 x syringes

Proposed Shelf-Life: Unopened: 3 years stored at 2-8°C (refrigerate, do not freeze). Protect from light.

Opened: not applicable, single use only.

Active Substance Manufacturer
Merck & Company Inc.
770 Sumneytown Pike
West Point
Pennsylvania 19486
USA

GMP certification: A TGA GMP Clearance letter has been provided for this site. The TGA GMP clearance expires 21/4/2007.

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Finished Product Manufacturer:

Merck & Company Inc.
770 Sumneytown Pike
West Point
Pennsylvania 19486
USA

GMP certification: A TGA GMP Clearance letter has been provided for this site. The TGA GMP clearance expires 21/4/2007.

Packers:

Primary packaging
Merck & Company Inc.
770 Sumneytown Pike
West Point
Pennsylvania 19486
USA

GMP certification: A TGA GMP Clearance letter has been provided for this site. The TGA GMP clearance expires 21/4/2007.

Secondary Packaging for vials
Merck Sharp & Dohme (Australia) Pty Limited
54-68 Ferndell Street
South Granville
NSW 2142

GMP certification : Current TGA GMP certification has been provided for this site. The GMP certification expires 25/6/2006.

Secondary packaging for syringes
Merck Sharp & Dohme BV
Waarderweg 39
Haarlem 2931 BN
Netherlands

GMP certification : A TGA GMP clearance certificate has been provided for this site. The TGA GMP clearance expires 24/9/2006.

Batch Release

Merck & Company Inc.
770 Sumneytown Pike
West Point
Pennsylvania 19486
USA

GMP certification: A TGA GMP Clearance letter has been provided for this site. The TGA GMP clearance expires 21/4/2007.

	Satisfactory evidence of GMP has been provided for the active ingredient manufacturer, finished product manufacturer and packer, secondary packing sites, and the batch release site.
Overseas approvals	At the time of submission of the dossier, the product was also under review by the EMEA, TGA, and FDA.

Evaluation

Note: No overseas reports were available for this application

Composition

Gardasil consists of highly purified virus-like particles (VLPs) of the recombinant major capsid (L1) protein of HPV types 6, 11, 16, and 18.
Gardasil is not a live virus vaccine and contains no viral DNA.

Table 1: Composition of Gardasil

Ingredient	Quantity per 0.5mL dose	Function	Reference Standard
Actives			
HPV 6 L1 Protein	20µg	Active	In House
HPV 11 L1 Protein	40µg	Active	In House
HPV 16 L1 Protein	40µg	Active	In House
HPV 18 L1 Protein	20µg	Active	In House
Excipients			
Aluminium (as amorphous aluminium hydroxyphosphate sulphate adjuvant	225µg	Adjuvant	In House
Sodium chloride	9.56mg	Stabiliser	Ph Eur, USP
L-Histidine	0.78mg	Buffer	Ph Eur
Polysorbate 80	50µg	Stabiliser	Ph Eur, NF
Sodium Borate	30µg	Buffer for adj.	Ph Eu, NF
Water for Injection	q.s	solvent	Ph Eur, USP

Information is also in datasheet

The vaccine contains no preservatives or antibiotics.
The vaccine is filled into single-dose vials or syringes to ensure a minimum recoverable volume of 0.5mL for intramuscular injection.

Clinical trial formulations
Three different yeast host strains were used to prepare the clinical trial lots, including the strain proposed for commercial manufacture:

- Clinical lots for protocols 001 and 002 used [redacted] for manufacture of Type 11 and [redacted] for manufacture of Type 16. Clinical lots manufactured using these strains used developmental manufacturing processes that were at [redacted] fermentation scale and [redacted] purification scale.
- Clinical lots for protocols 004, 005, 012, 007, and 006 all used the proposed commercial yeast strain CANADE 3C-5. Developmental manufacturing processes were used for the fermentation and purification procedures. The fermentation scale was [redacted], except for lot 006 which was [redacted]. The purification batch size was [redacted] for al lots.
- Clinical lots for protocols 011, 012, 015, 016, and 018 all used the commercial yeast strain CANADE 3C-5 and the proposed commercial fermentation and purification

processes. All HPV types were manufactured at [redacted] for fermentation and [redacted] for purification.

The development strains [redacted] have been adequately described in the dossier. The proposed commercial strain, CANADE 3C-5, was developed from strain [redacted].

Development pharmaceutics

Early clinical studies used [redacted] Some antigencity loss was observed during storage in this formulation and additional excipient matrixes were screened to investigate a more stable formulation.

[redacted]

The adjuvant concentration was selected based on the currently licensed adjuvant adsorbed vaccines manufactured by Merck & Co.

[redacted]

Active ingredient manufacturing process

The drug substance consists of four Monovalent Bulk Adsorbed Products (MBAPs), one for each HPV type L1 protein.

The process for the manufacture of MBAPs consists of two main steps:

i) fermentation and harvest of the recombinant yeast cells.

ii) purification of the VLPs and adsorption of the purified VLPs onto the aluminium adjuvant

A flow diagram providing an overview of the MBAP manufacturing process is attached at the end of this report.

Fermentation

The VLPs are generated by the fermentation process, [redacted]

[redacted]

Individual flow diagrams for the fermentation and harvest of all four HPV types are attached at the end of this report. Critical in-process controls are highlighted on the flow diagrams and tables in bold face font. Approximate values have been given for the non-critical in-process controls.
Tables describing the composition of the [redacted] Medium and the [redacted] Medium are also attached at the end of this report.

Harvest
The yeast cells, containing the VLPs, are harvested by a [redacted] process using [redacted]

Purification
The purification process consists of a number of process steps.
[redacted]

6

The purification process is initiated by [redacted]

7

[redacted]

[redacted] *Sterile Filtration (for all Types)*

[redacted] The following release tests are used for the FAP:

[redacted]

[redacted] *Adjuvant Adsorption (for all Types)*

[redacted] The MBAP is sampled for the following release tests: [redacted]

[redacted] *Filling and Storage*

The MBAP for each HPV type is dispensed into bulk storage containers, and stored at [redacted] until required to be transferred to the formulation/filing area. [redacted]

Satisfactory information has been provided in the dossier regarding [redacted]

The 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.***

The manufacturing process does not describe a 'mixing time' as in-process control to ensure maximum adsorption. The applicant needs to 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.

Definition of a production batch

[redacted]

Process validation for the active ingredient

A matrix approach was used to validate both the fermentation and purification processes. Prior to process validation, critical process parameters (CPP) and critical quality attributes (CQA) were established based on data from the laboratory, pilot scale and full scale manufacturing processes.

The following are definitions for CPPS and CQAs:

- A CPP is defined as a parameter for which a deviation from a predetermined range has significant potential to cause failure of a CQA.
- A CQA is defined as a measurable property of an intermediate or final product such that meeting the prescribed acceptance criteria ensures final product quality.

After process validation some of the CPPs were reviewed and in some instances revised to better reflect additional full scale manufacturing experience. All changes to the CPPs have been adequately documented and justified in the dossier and the proposed in-process controls attached at the end of this report included the revised CPPs.

Fermentation

The fermentation process [redacted] Therefore, the company considered that production of 2 lots each of [redacted] would provide sufficient data to validate the process for [redacted] For [redacted] therefore, 3 consecutive were manufactured each for [redacted]

Due to equipment failures or failure of the fermentation batches to meet acceptance criteria a number of fermentation runs were initiated but not completed:

- Type 6 – Two validation lots were initiated and completed. Both lots meet the fermentation process validation acceptance criteria.
- Type 11 – Three validation lots were initiated. The first fermentation lot failed the release test for purity, and as a result two further consecutive validation batches were completed that met validation acceptance criteria. The likely source of the contamination for the first fermentation lot was identified and the problem adequately addressed.
- Type 16 – Nine validation lots were initiated to obtain three consecutive lots that met validation acceptance criteria. For the remaining six lots, fermentation was either not completed due to equipment failure or batches failed the validation acceptance criteria. Appropriate investigations were undertaken where equipment or acceptance criteria failures occurred, and appropriate actions were taken to rectify the problems.
- Type 18 – Four validation lots were initiated. The first lot was stopped at the seed fermentation stage due to equipment failure. Three consecutive validation lots were then completed that met the fermentation validation acceptance criteria.

Of the 18 batches initiated for fermentation process validation, 17 of the batches meet the CPP acceptance criteria at the seed fermentation stage. The exception was one batch for Type 18, which had equipment failure at the seed fermentation stage. The fermentation validation results demonstrated that consecutive production batches for each HPV Type can be produced with very consistent results for CPP and CQA. Although a number of validation batches were initiated and either not completed or failed

validation acceptance criteria, the issues that caused these failures were adequately identified and addressed.
All validation lots that meet validation acceptance criteria were subsequently used for purification process validation.

Purification
For purification, two lots each of Types 6, 11 and 16 were produced as [redacted] For Type 18 [redacted] 3 lots of Type 18 were produced for process validation. A total of nine purification lots were produced to validate the purification processes.
All purification lots met the validation acceptance criteria, CPPs and CQAs, which were pre-determined prior to validating the purification process. Although the validation studies demonstrated a consistent manufacturing process, the studies have not demonstrated that the manufacturing process is robust. The CPPs are parameters that have pre-determined ranges, from which a deviation may have significant potential to cause failure of a CQA. ***Throughout the 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 following describes the various steps of the purification process that have not adequately validated the range of the CPPs in the full scale validation studies.***
Purification process steps for Types 6, 11, and 16;

- [redacted]
- [redacted]
- [redacted]

[redacted]

11

[redacted]

[redacted]

As the full ranges of CPPs were not adequately tested, it can not be concluded that the manufacturing process, and consequently quality of the drug substance, is robust to the upper and lower limits proposed as the CPPs. ***Either the CPPs need to be tightened to reflect those actual tested in the process validation, or additional process validation data is required to demonstrate that the proposed ranges of the CPPs are acceptable.***

All validation lots met the active ingredient release criteria that were in place at the time of the process validation study. Since the process validation study some of the active ingredient release limits have been changed; however, all process validation lots also comply with the revised active ingredient release criteria.

Impurity Clearance

The manufacturing process for each validation lot was assessed for impurity clearance. Clearance targets were set for [redacted]

For all of the above mentioned impurities, target clearance levels were consistently met for all process validation batches. The proposed drug substance release specifications do not include any specifications for above mentioned impurities. As the process validation data demonstrates consistent clearance of the impurities for all HPV Types, the absence for tests for product and process related impurities could be considered acceptable. ***However, as the CPPs for the manufacturing process have not been adequately validated over the proposed CPP ranges, the absence of tests for impurities in the drug substance can only be considered acceptable if the CPPs are tightened to the values tested in the actual process validation data. Some of the proposed CPPs that can affect purity clearance include [redacted] For each HPV type the [redacted] were not tested. If the CPP ranges are not tightened then impurities, e.g. [redacted], need to be tested in the release specifications for the drug substance.***

FAP Hold Time

For one lot of each HPV Type, a proportion of the dilute final aqueous product (DFAP) was held in a [redacted] and then adsorbed onto the adjuvant. ***The applicant needs to describe the proportion of full scale manufacture the DFAP sample was that was assessed for stability.***

All HPV lots met the acceptance criteria [redacted], demonstrating that the proposed storage time for the DFAP is acceptable.

Filter Validation – Sanitisation, Regeneration and Reuse
All filters used in the manufacturing process have all been tested for extractables. Analytical methods used to asses filter extractables included: [redacted]. The dossier states that all results of the extractable testing for each filter met the acceptance criteria (section 3.2.S.25.4, p3). ***The study, or a tabulated summary of the study data and study acceptance criteria have not been provided and is required***
The dossier states that the sterilising filter has been satisfactorily validated for microbial retention. ***The applicant needs to submit the study to support this claim***
The sterilising filters are integrity tested to determine the bubble point prior to use. All filters that are supplied in a storage solution or preservative are required to be flushed. Validation studies have been completed that adequately demonstrate the flush procedures used for the filters remove storage solutions or preservatives.
Validation studies have also been completed to demonstrate the efficacy of the sanitisation procedures for new filters. ***However these studies or a tabulated summary of study data have not been submitted in the dossier and are required.***
Reuse studies have been completed for the [redacted] filters that are intended for multiple uses. [redacted] is performed using [redacted] Filter suitability for the next [redacted] is determined by [redacted]. Only one HPV type is used per filter and the [redacted] filter has been satisfactorily validated for [redacted]. The filter reuse validation is dependant on the fact that new filters have been satisfactorily validated for a minimum [redacted]. This is the minimum contact time for new filters which are stated to be more difficult to sanitise than reused filters. The tabulated data for the reused columns showed that the lowest [redacted]
The information in the dossier regarding sanitisation of the new filters only states that the minimum [redacted], no actual study or tabulated summary of study data has been provided, and is required.

Column Reuse validation
The [redacted] and the [redacted] have both been validated for reuse. [redacted]
Each column was reused only for the same HPV type. The validation studies included the regeneration and sanitisation of the used columns as well as the sanitisation of a newly packed column. One of the CPPs for sanitisation of a new column required a [redacted] All new column material was satisfactorily validated for this maximum time, but no minimum contact time appears to have been set, which should also be a critical process parameter. ***The applicant needs to explain why a minimum contact time with [redacted] has not been set for the sanitisation of new columns.***
The [redacted] has been successfully validated for up to [redacted] for Types 11, 16, and 18 and up to [redacted] for Type 6. The CPPs for the sanitisation of used and stored columns is [redacted] and the [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] ***The applicant needs to explain why the CPP, [redacted], was not tested, and confirm that the CPP limit for***

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[redacted] ***will be amended to*** [redacted] ***for all future sanitisation procedures for the*** [redacted]

The [redacted] uses two methods for column regeneration. The first method, Method 1, was used prior to July 2003, and the second method, Method 2, was used after July 2003. Both regeneration methods have been successfully validated:

- Using Method 1, the [redacted] has been validated [redacted]
- Using Method 2, the [redacted] has been validated for up to [redacted]

For both methods the lower limits of the CPPs set for [redacted] were not tested. These limits were set prior to sanistisation/regeneration validation. However the validation summary acknowledges that [redacted] have been validated.

Sterility of the MBAP adsorption process

Three bulk media challenges were performed in December 2000 to validate the aseptic procedure. Routine annual media challenges are performed to re-qualify the aseptic process. Since the initial qualification, three bulk media challenges have been completed, and all results submitted in the dossier demonstrate an aseptic process.

Finished product manufacturing process

The final vaccine may be produced in approximately [redacted] batches. The batch formula for each batch size has been adequately described in the dossier (Section 3.2.P.3.2).

The manufacturing process for the final vaccine in vials or syringes consists of two main steps: formulation and filling.

The formulated Quadrivalent Bulk Adsorbed Product (QBAP) is prepared by adding [redacted] for formulation. The Type 6, 11, 16 and 18 MBAPs are then added [redacted] All formulation processes are [redacted]

The QBAP is mixed to ensure homogeneity, aseptically sampled to test [redacted], before it is transferred to a filling line. The QBAP is agitated to ensure homogeneity and aseptically filled into vials or syringes.

Vials are washed and depyrogenated [redacted], and stoppers are washed, siliconised, and sterilised [redacted] in preparation for filling. The glass syringe barrels and tip cap are received assembled, clean, sterilised ([redacted]), and ready to fill. The plunger stoppers are received in bulk, and are clean, siliconised, sterilised ([redacted]) and ready for insertion.

Flow diagrams and tables summarising the manufacturing process and in-process controls respectively are attached at the end of this report.

The manufacturing process includes several mixing/agitation steps [redacted] However, the manufacturing process does not describe any time limits or mixing speeds as in-process controls for these mixing steps. The validation section of the dossier 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.

Process validation for the finished product

Six formulation lots were manufactured to prepare three batches of vials and three batches of syringes. All process validation results met the process validation acceptance criteria, and all QBAPs meet the release criteria. The process validation results demonstrated a robust and consistent process.

The equipment sterilisation procedures used for the finished product manufacturing suite, including [redacted] has been adequately described in the dossier. The sterilisation processes are routinely validated.

Successful media challenges have also been performed to validate the following aseptic processes:

- formulation and holding of the final bulk product in the formulation tanks
- vial filling
- syringe filling.

Media challenges are performed routinely on an annual basis to validate the aseptic finished product processes.

Need to see more !!

Cell Bank System

Extensive information has been provided in the dossier regarding construction of the yeast expression vectors, construction of the parental yeast host strain, and transformation of the parental yeast host strain with the HPVL1 vectors. The following is only a very brief summary of some of the information provided in the dossier regarding construction of the cell bank system.

Expression vector

[redacted]

[redacted]

Parental Yeast Host Strain

The *Sacchromyces cerevisiae* host strain, CANADE 3C-5, was used for the Quadivalent HPV VLP vaccine. The host strain was specifically developed to contain the following:

- [redacted]

Transformation of the CANADE 3C-5 host strain

[redacted]

Establishment of the Master Seeds

[redacted]

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[redacted]

A flow diagram summarising the steps used for manufacture of the master seeds is attached at the end of this report.
The master seeds were tested for the following parameters: [redacted] A copy of the tabulated specifications used to test the master seeds is attached at the end of this report. In addition to these tabulated specifications, the dossier also states that the master seeds and working seeds were also tested for Viable Count. However, this specification has not been included on the table listing the specification used to test the master and working seeds. ***The applicant needs to 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.***
All master seeds met specification requirements.

Establishment of the working seeds

[redacted] A flow diagram summarising the manufacturing process for the working seeds is attached at the end of this report.
The working seeds were tested for the same specifications as those used for the master seeds and all test results met specification requirements.
As of August 2004 the following quantities of working seed were available: [redacted] The estimated use of working seed is expected to be [redacted] Based on the proposed usage, working seeds for Types 11 and 16 were expected to be exhausted by [redacted], and for Types 6 and 18, by [redacted].
It has been estimated that working seeds would need to be generated [redacted] Future working seeds would be manufactured in the same way as the existing working seeds have been manufactured. The new working seeds would be tested for the following parameters: [redacted] The specifications proposed to test new working seeds are attached at the end of this report. Based on the testing that has already been completed for the master seeds and existing working seeds, the proposed specifications for control of new working seeds are acceptable.

End of Production (EOP) Cells and Genetic Stability
For each working seed HPV type, one large scale fermentation ([redacted]) was completed and tested to [redacted]

[redacted]

To analyse genetic stability, [redacted] This analysis was performed on a one-time only basis for the master seeds, working seeds, and EOP cells. The results confirmed the retention of the plasmid from the master seed through to the EOP cells, indicating genetic stability of the cell line during seed expansion and fermentation.

Characterisation of the drug substance

Extensive characterisation tests were performed to confirm the primary structure of the HPV VLP proteins, and characterise the secondary, tertiary, and higher order structures. The characterisation tests were performed on a minimum of 3 full scale manufacturing lots per HPV type for each assay. The following characterisation tests were performed:

- [redacted]

Results for [redacted] showed that the majority of the [redacted] For types 6, 11, and 16, all lots analysed had [redacted]. Type 18 had approximately [redacted]

The characterisation studies concluded that [redacted] supporting the conclusion that the HPV VLPs are homogenous with respect to size.

The [redacted] results confirmed that for types 6, 11 and 16, the [redacted] of the manufacturing process enhances the [redacted] of the VLPs.

A number of studies were completed to support the correlation between [redacted] The study results supported the use of the [redacted] as a replacement for the [redacted] and that the correlation is robust to different sample types:

- samples from different manufacturing processes,
- different types of physical stress,
- different aging mechanisms.

The correlation study results also indicated that [redacted] is more sensitive to detecting VLP damage compared to the [redacted]
Results for the [redacted] tested on both the MBAP and the FAP showed that formulation with the aluminium based adjuvant had no impact on the sample [redacted]
Also the presence of the aluminium based adjuvant in the sample matrix had not impact on the [redacted]

Drug substance specifications

The proposed drug substance specifications are attached at the end of this report. The specifications include release tests on the [redacted], which is a process intermediate, and the Monovalent Bulk Adsorbed Product (MBAP), which is the drug substance.
Tests performed [redacted]

A detailed description of all the test methods has been provided in the dossier. In summary:

- [redacted]

All test methods have been satisfactorily validated according to ICH guidelines where appropriate. In some instances the assays were only validated for one or two of the four

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HPV types. The justification for this was that the samples matrixes, and/or manufacturing processes were sufficiently similar to conclude that validation for one HPV type would be applicable to another HPV type. In all instances where only one or two HPV types were used for validation, the justification was acceptable.

[redacted]

Justification for specifications:

Nearly all proposed specifications have been satisfactorily justified.

The submitted batch data show that some release specifications have been discontinued or replaced with updated test methods, as manufacturing experience and test methods were developed.

The release specifications for the drug substance initially included specifications for [redacted]

The test method was discontinued as:

[redacted]

2

[redacted]

The applicant's justification for removal of the release specifications for [redacted] is acceptable based on the batch data and the proposed process controls.

[redacted]

Drug Substance reference material

[redacted]

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The selection, storage, and the process of monitoring stability of the current working standard is acceptable. Batch release data for the current working standard have been submitted in the dossier. All future working standards will be obtained from full-scale manufacturing lots, must meet all release specifications, and will be calibrated against the primary standards. The process for selection of future working standards is acceptable

[redacted]

Drug Substance batch data

Extensive batch analysis data have been provided for all drug substance batches used for non-clinical studies, pivotal clinical studies, primary stability studies, process validation, and characterisation. Not all batches have been manufactured using the proposed commercial process, but the dossier adequately documents what batches have been manufactured using various processes. All batches were manufactured at the proposed finished product manufacturing site.

The tests and acceptance criteria for the batch data reflect the criteria at the time the lots were tested and released. The following summarises the batch data submitted per HPV type:

- Type 6 : Complete batch data have been submitted for 6 lots, and 5 of these lots were manufactured using the proposed commercial process. In addition to these 6 lots, [redacted] data have been provided for 13 routine manufactured batches.
- Type 11: Complete batch data have been provided for 9 lots, and 8 of these have been manufactured using the proposed commercial process. In addition to these 9 lots, [redacted] data have been provided for 16 routine manufactured batches.
- Type 16: Complete batch data have been submitted for 14 lots, and 7 of these have been manufactured using the proposed commercial process. In addition to these 14 lots, [redacted] data have been provided for 18 routine manufactured batches.
- Type 18: Complete batch data have been submitted for 5 lots, and 4 of these lots have been manufactured using the proposed commercial process. In addition to these 5 lots, [redacted] data have been provided for 11 routine manufactured batches.

All batch data demonstrate that the manufacturing processes for each HPV type VLP produces a consistent quality product, and that in most instances the proposed specification limits are appropriate for the batch data obtained. Where specifications are recommended to be tightened, this has been discussed above under the section titled 'Drug substance specifications'.

Process Excipients

No animal derived, TSE-risk materials are used in the manufacturing process. [redacted] is used in the culture medium and is obtained from bovine milk that is sourced from healthy animals in the same way that milk is for human consumption. Milk is considered compliant with regard to the EMEA Note for Guidance on "Minimising the Risk of Transmitting TSE Agents via Human and Veterinary Medicinal Products'.

All tests and specifications used for the manufacturing process raw materials have been tabulated in the dossier (Section 3.2.S.2.3.1, pp 4-8). Nearly all raw materials are tested appropriately for their intended use. The purification process buffers and solutions are

formulated with Water for Injection. The excipients that are formulated for the aluminium adjuvant are all controlled according to USP/NF, and BP/Ph Eur specifications. [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.***
Tables listing the excipients that are used in the culture mediums, buffers, and solutions used in the fermentation and purification process are attached at the end of this report.

Finished Product Excipient specifications
All excipients are controlled according to compendial specifications, except for the aluminium adjuvant. There is no monograph available for aluminium hydroxyphosphate sulphate adjuvant; however the raw materials used in its manufacture meet compendial specifications, except for [redacted]. A [redacted] is used in preparation of the adjuvant and there is no pharmacopoeial monograph available for this solution. The in-house specifications have been provided for the [redacted]. The specifications use a reduced testing regime, where the excipient is accepted based on the suppliers Certificate of Analysis, and is tested by the finished product manufacturer for the following criteria: [redacted]
Quality control of the finished product excipients is acceptable.

Container/closure specifications
Drug Substance
The sterile HPV process intermediate (Dilute Final Aqueous Product) and sterile MBAP may be stored in [redacted]. Alternatively the Dilute Final Aqueous Product may also be stored in [redacted]. Schematic diagrams have been submitted for both types of container/closure vessels. Both storage containers have successfully completed container/closure integrity studies and demonstrated that they prevent the intrusion of contaminants under normal processing conditions.

Finished product
There are two finished product presentations: a vial, and a syringe.
The Type 1 glass vials are stated to be compliant with the Ph Eur and USP. Two types of stoppers are proposed for use with the vials: a 13mm fluoropolymer-coated stopper (referred to as stopper A) and Teflon-coated ([redacted]) stoppers (referred to as stopper B). Both types of stoppers have been found to provide equivalent and satisfactory stability in stability studies.
The dossier states that the all stoppers are compliant with chemical test requirements for Type 1 closures as described in the Ph Eur, and with physiochemical test requirements as listed in the USP.

The 1.5mL Type 1 (Ph Eur and USP) glass syringe is lubricated with [redacted]. Two types of plunger stoppers can be used for the syringes: 1-3mL fluoroploymer-coated and uncoated stoppers. Both types of stoppers have been found to provide equivalent and satisfactory stability in stability studies.
The dossier states that both types of plunger stoppers are compliant with chemical test requirements for Type 1 closures as described in the Ph Eur, and with physiochemical test requirements as listed in the USP.

The syringe barrels can be equipped with a passive safety device, but this device does not come into contact with the product.

Container/closure integrity has been successfully demonstrated for both the vial and the syringe presentation.

Finished product specifications

The proposed finished product specifications are attached at the end of this report. The specifications control for: [redacted] s18(c)(i)

There are no specifications to test for [redacted], but [redacted] is adequately tested in the drug substance at release, and drug substance stability data submitted to date show no apparent trends in [redacted] with time. Therefore, absence of a [redacted] specification in the finished product is acceptable.

The test methods used for [redacted] are the same as those used for release testing of the drug substance.

Satisfactory descriptions of all test methods used for the finished product specifications are provided in the dossier. The same test method validation studies completed for the drug substance are applicable to the finished product. [redacted]. The results from this study showed that there was no matrix interference from the QBAP samples with the [redacted] obtained for each HPV type.

The validation summary for the [redacted] states that the [redacted] However, no actual summary of the validation results has been submitted. ***The applicant needs to provide the results for the*** [redacted]

Justification for specifications

The initial finished product specifications contained additional release criteria compared to those currently proposed, and these were: [redacted]

The applicant has proposed the removal of the tests for [redacted] as results from 30 batches manufactured at the time of submission of the dossier, demonstrated very consistent results, i.e. all batches had [redacted] and all batches met [redacted] criteria.

The specification for [redacted] is now included in [redacted]

The specification for [redacted] was based on a calculation from the [redacted] As no [redacted] was actually performed on the finished product, and in-process controls adequately ensure the correct [redacted] in the finished product, the specification for [redacted] has been removed. This is acceptable.

The proposed [redacted] take into account the variability of the manufacturing process, variability of the analytical method, the stability of the MBAPs, and the minimum

expected [redacted] at release. A mathematical model and statistical analysis (which has been extensively described in the dossier) have been used to determine the lower limits. The applicant has indicated that these limits are considered interim, and these limits will be revised in April 2006 based on statistical analysis of additional batch data. Based on the batch data observed to date, it could be anticipated that [redacted] was selected to ensure that the total dose is below that which has been demonstrated to be safe in the clinical setting. A total dose of [redacted] has been tested in the clinical setting and the upper limit was based on this dose and three sigma to take into account assay variability. The upper limit far exceeds that observed for any of the batches manufactured according to this 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 [redacted] batch results. ***The lower interim limits are acceptable, but the upper limit should be revised to reflect actual data from the manufacturing process obtained to date.***

Finished product batch data

Batch analysis data have been submitted for lots used in: non-clinical safety studies, pivotal clinical studies, stability studies, and process validation studies. Data have been provided for a total of 42 batches, but only 6 of these have been manufactured at full scale and these are the process validation batches. The remainder of the batches have been manufactured at pilot scale with batch sizes ranging from [redacted]. Not all batches have been manufactured using the proposed finished product formulation, i.e. some batches have different excipient and drug substance concentrations compared to the proposed vaccine. However, all data showed that batches met release criteria that were in place at the time the batches were tested and released. All batches were filled at the proposed finished product manufacturing site.

The data demonstrate that the quality of the product is consistent and able to meet the proposed release specifications.

Finished product reference material

The finished product reference material is the same as that described for the drug substance.

Drug Substance

At the time of submission of the dossier stability studies were being performed on the [redacted] and the MBAP under long term storage conditions, and on the MBAP under accelerated storage conditions, [redacted].

The proposed hold times for the [redacted] and the MBAP are [redacted] respectively.

The stability specifications used for the stability studies are attached at the end of this report. All stability test methods have been successfully validated. The stability specifications used for the MBAPs are wider than those proposed for release of the MBAP. ***Based on the 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. The applicant needs to 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***

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batches will readily detected, so that it is apparent if batches have different stability characteristics to those observed in this dossier.

[redacted] is being stored at [redacted]. The stability protocol requires that [redacted] Type 11 is not being tested at the intermediate time points as it is structurally homologous to Type 6 and is expected to perform equivalently. One lot of each type has been placed on the stability studies and all lots are stored in the same type of [redacted] as those proposed for use in production. Stability results have been submitted up to the [redacted] point. Data supplied to date do not show any significant trends, and all results meet specification acceptance criteria.

The applicant anticipated [redacted] data for all lots would be available in 2005, and this data should now be available and submitted to Medsafe. This data will need to be reviewed before a [redacted] shelf life for the [redacted] can be approved.

MBAP

Three full scale lots of MBAP per type have been placed on stability at [redacted] i.e not the closure proposed for commercial production. Each stability bottle was filled to [redacted] to mimic an [redacted] fill in the production bottles.

Stability data that has been provided to date for these batches include:

- Type 6: [redacted] for two batches, [redacted] for one batch
- Type 11: [redacted] for two batches [redacted] for one batch
- Type 16: [redacted] for two batches [redacted] for one batch
- Type 18: [redacted] for two batches [redacted] for one batch.

In addition to the above, another stability study was initiated using one lot of MBAP per type, manufactured at full scale, and stored in [redacted] i.e. the same fittings as those proposed for commercial production. Each bottle has been filled to [redacted] to mimic the [redacted] fill volume in the production bottles. Batches are being stored under long term ([redacted]) and accelerated conditions ([redacted]).Stability data that has been submitted includes:

- Type 6: 1 batch, [redacted]
- Type 11: 1 batch, [redacted]
- Type 16: 1 batch, [redacted]
- Type 18: 3 batches, [redacted]

Long term stability studies are ongoing up to [redacted].

All stability results provided to date, including the accelerated storage conditions, demonstrate no significant trends throughout the storage period. Using statistical analysis a slight decrease in [redacted] was detected for some types, but the decrease was very small and results still met release specification requirements at the [redacted] time point.

Based on the stability data submitted, the proposed shelf life of [redacted] for the MBAPs is acceptable. ***However, updated stability data for the MABP stability batches should now be available and submitted to Medsafe to confirm that the proposed shelf life is appropriate. If the stability data is not available, the applicant needs to indicate when the stability studies will be completed and submitted to Medsafe.***

Drug Substance Post-Approval Stability Protocol

A cumulative stability study will be completed to evaluate the impact of the hold time for the MBAPs on the stability of the finished product. The protocol requires that MBAPs manufactured at full scale will be stored for [redacted], and then formulated at laboratory scale into final bulk product. The final bulk product will be stored [redacted] and then filled into glass vials (finished product) and stability monitored at 2-8°C. ***The applicant needs to indicate when these stability studies are likely to be completed and submitted to Medsafe.***

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

Finished product

The proposed finished product shelf life for both the vial and syringe presentations is 36 months at 2-8°C. The stability specifications used for the stability studies are attached at the end of this report. Updated stability specifications have been proposed for post-approval stability batches, and these are also attached at the end of this report (refer to below under the heading 'Post-approval stability studies' for a discussion on the proposed specifications). The stability results submitted in the dossier indicate that some limits could be significantly tightened for future stability studies

Stability data submitted for the vials

Two different vial presentations are being monitored for the vials: glass vials with Teflon coated stoppers, and glass vials with Flurotec stoppers. The Teflon coated stoppers are either coated with [redacted] or [redacted] ([redacted] is a form of [redacted] that is manufactured by a modified process, and both [redacted] are considered equivalent).

The stability batches have been stored under long term (2-8°C) and accelerated storage conditions (23-27°C). The batch data submitted for the vial presentation includes:

- Three [redacted], pilot scale batches manufactured with Teflon coated stoppers. All batches (V501 VAI 020 I001, V501 VAI 020 I002, V501 VAI 025 T003) have been stored at 2-8°C (data provided to 24 months), and one of these batches has also been stored under accelerated conditions (data provided to 6 months)
- Two [redacted] pilot scale batches manufactured with Teflon coated stoppers. One of these batches (V501 VAI 025 T005) has been stored under accelerated conditions only (data provided to 6 months), and the other batch (V501 VAI 043 T001) has been stored under long term (data provided to 3 months) and accelerated conditions (data provided to 3 months).
- Two [redacted] pilot scale batches manufactured with Flurotec stoppers. Both batches (V501 VAI 037 T001, and V501 VAI 037 T002) have been stored under long term (data provided to 9 months) and accelerated storage conditions (data provided to 6 months).
- One [redacted] pilot scale batch manufactured with Fluortec stoppers. This batch (V501 VAI 037 T003) has been stored under both long term (data provided to 9 months) and accelerated conditions (data provided to 6 months).
- One [redacted] full scale batch manufactured with Flurotec stoppers. This batch (0650435) has been stored under both long term (data provided to 3 months) and accelerated conditions (data provided to 3 months)

Long term stability studies are ongoing up to 36 months with some parameters also being monitored at 42 months. Accelerated stability studies are ongoing up to 12 months.
Different batches of MBAP have been used to formulate the vial stability batches.

Stability data submitted for syringes
Two different syringe presentations are being assessed for stability: Luer-Lok syringes with uncoated stoppers, Luer-Lok syringes with Flurotec stoppers. Stability batch data submitted includes:

- Three [redacted] pilot scale batches (V501 VAS 032 T001, V501 VAS 032 T002, V501 VAS 032 T003) manufactured with uncoated stoppers and stored under long term conditions. Data has been provided for 12 months, but [redacted] have been provided at the 12 month time point as these parameters are not required to be measured at this time point according to the stability protocol.
- Two [redacted] pilot scale batches (V501 VAS 032 T004, and V501 VAS 032 T005) manufactured with uncoated stoppers and stored under accelerated conditions. Data has been provided for 3 months.
- One [redacted] pilot scale batch (V501 VAS 032 T006) manufactured with uncoated stoppers and stored under accelerated conditions. Data has been provided for three months.
- Three [redacted] pilot scale batches (V501 VAS 033 T001, V501 VAS 033 T002, and V501 VAS 033 T003) manufactured with Flurotec stoppers and stored under long term conditions. Data has been provided for 12 months, but no [redacted] have been provided at the 12 month time point as these parameters are not required to be measured at this time point according to the stability protocol.
- One full scale ([redacted]) batch (0650543) manufactured with Flurotec stoppers and stored under long term and accelerated storage conditions. Data have been provided up to three months for long term conditions, and only for the initial time point for accelerated conditions. The full scale batch stability study was initiated in 2004.
- One [redacted] pilot scale batch (V501 VAS 033 T007) manufactured with Flurotect stoppers and stored under accelerated conditions. The initial time point stability results have been provided only.

Different batches of MBAP have been used to formulate the syringe stability batches.

Summary of stability data for both vials and syringes
All finished product batches have been formulated with full scale MBAPs manufactured according to the proposed drug substance manufacturing process.
Predominantly pilot scale batch data has been submitted to support the finished product shelf life. The finished product formulation process is a relatively simple procedure, and formulation of the finished product at pilot scale or full scale is unlikely to affect the stability of the drug product. However only very limited full scale batch data have been provided; one stability batch only for each full scale vial and syringe presentation, and data have only been submitted up to the 3 month time point. As the stability studies for the full scale batches were initiated in 2004, updated stability data for the full scale batches, as well as the pilot scale batches, should now be available. The updated stability data should now include 36 month stability data for some of the pilot scale vial batches. ***The applicant needs to submit:***

- ***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, then the applicant needs to confirm the dates the studies will be completed and submitted to Medsafe.

The stability data submitted in the initial dossier demonstrated no apparent differences in stability trends between the vial or syringe presentations, or between the different stoppers proposed for used with the vials or syringes. No significant trends were observed for the following physiochemical parameters: [redacted] A small decrease in [redacted] was observed for some lots when stored under long term conditions. A statistical analysis to determine the loss rate of [redacted] was completed. As the statistical analysis only used data from batches stored up to nine months or more for both vials and syringes, i.e. a very limited data set, the data pool was widened to include MBAP lots. The statistical analysis estimated the following [redacted] loss rates for each HPV type:

- Type 6: 0.79% per year, or 2.3% over the proposed 36 month shelf life
- Type 11: 0% over the proposed 36 month shelf life
- Type 16: 1.2% per year, or 3.5% over the proposed 36 month shelf life
- Type 18: 2.3% per year, or 6.6% over the proposed shelf life.

Although these loss rates have been estimated statistically, the stability data submitted to date demonstrate no consistent loss between batches, i.e. only some batches showed a slight decrease in [redacted]. Also, all batches were released with [redacted] well above the proposed release limits, and throughout storage [redacted] values were still well above the proposed release limits even if a slight decrease was observed.

No statistical analysis has yet been completed for the accelerated studies. ***Some of these studies should now be completed, and the updated accelerated stability data and statistical analysis submitted to Medsafe.***

Based on the stability data submitted in the dossier, a 24 month shelf life stored at 2-8°C could be recommended. Although the product appears to be very stable and a 36 month shelf life could be considered, this is only supported by the pilot scale batches. Only 3 months of stability data have been submitted for two full scale batches, representing one full scale batch of vials and one full scale batch of syringes. Updated stability data should now be available and submitted to Medsafe. ***A final decision on a product shelf life of 36 months stored at 2-8°C cannot be made until this updated data is reviewed.***

Photostability

Photostability studies have been completed according to ICH guidelines and demonstrate that one of the drug substance components, Type 18 L1 protein, is sensitive to UV light. Therefore the final container is packaged in an opaque secondary container, and the labelling includes the storage description 'Protect from light'.

Finished product post-approval stability protocol

All long term stability studies described in the previous section of this report will be ongoing up to 36 months. The applicant has also confirmed that the stability of the next two full scale vial and syringe lots manufactured will also be monitored to create a total of three full scale lots per presentation.

An annual stability program will be maintained in which one lot of syringes and one lot of vials will be placed on stability studies each year and will be monitored up to 36 months stored at 2-8°C.
The proposed stability specifications that will be used to test future stability batches are attached at the end of this report. The specifications that will be tested include: [redacted] s18(2)(i)
[redacted]
The tabulated specifications do not include a specification for [redacted] yet the dossier states (Sec 3.2.P.8.2.1 pp4, and Sec 3.2.P.8.2.2pp4) that this parameter is monitored throughout shelf life with a limit of [redacted] ***The applicant needs to 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]

The proposed stability limits for [redacted] are too low when compared to the actual batch data obtained. All stability lots have been released with [redacted] values well above the proposed release limits, and even with a slight decrease in [redacted] observed for some batches, no [redacted] results fell below or were even close to the proposed release limits. The applicant has based the proposed stability limits on the current release limits, the stability loss rate, and two standard deviations for the stability loss rate. The applicant has indicated that the [redacted] stability limits are interim only, until approximately 40-50 final container lots are obtained. The dossier comments that stability acceptance criteria are well above the [redacted] values for the lowest clinical dose tested that resulted in acceptable levels of antibodies.
Although the applicants rationale behind the proposed [redacted] stability limits is understandable, the limits do not take into appear to take into account that batches manufactured with this vaccines target protein concentration are consistently released with [redacted] values well above the release [redacted] limits. The applicant has also indicated in the dossier that the interim release limits submitted in the dossier will be revised in April 2006. It is likely, based on the data observed to date, that [redacted]. 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.

Stability in use
N/A – finished product presentations are for single use only.

Virological and TSE assessment
There are no live viruses and no cell lines of human or animal origin used in the manufacture of this vaccine.

[redacted], which is used in the fermentation culture medium, is the only raw material from animal origin used in the manufacturing process. [redacted] is obtained from bovine milk, and is sourced in the same manner as milk used for human consumption. It is therefore compliant with the EMEA Note for Guidance regarding TSE.

Coloured copies of the proposed labels for the vial, syringe, and single pack and 10 pack cartons have been submitted.

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The proposed labelling complies with the New Zealand Medicine Regulations with the following exceptions:

- The 10 pack syringe carton and single pack syringe carton do not indicate where the batch number and expiry date are to be placed.
- The height of the letters on the small labels for the syringe and the vial do not meet the regulatory requirement of 0.75mm. The text size of the small writing is only approximately 0.5mm, and the information written at this size is unreadable.

The applicant needs to:

- ***indicate where the batch number and expiry date will be placed on the 10 syringe pack and the single syringe pack***
- ***submit syringe and vial labels that have lettering height that meet 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 number of items have been highlighted in the evaluation report that the applicant needs to satisfactorily address before consent can be considered.

Attachments:

1. Overview of MBAP manufacturing process.

2. Flow diagrams for the fermentation and harvest of all four HPV types

3. Fermentation mediums for the [redacted] fermenters

4. Tabulated in-process controls for the [redacted] fermentor.

5. Purification process flow diagrams

6. Buffers solutions and raw materials used in the Purification and Adsorption process.

7. Fermentation and purification process culture medium, buffers and solutions, and their excipients.

8. Plasmid maps of the yeast expression vector, [redacted], and the individual HPV type expression vectors.

9. Flow diagram summarising the key steps used to construct the expression vector [redacted]

10. Flow diagrams for the manufacturing processes used to establish the master seeds and working seeds.

11. Master seeds, working seeds and EOP cell specifications, TT50#1, Section

12. Specifications proposed for testing new working seeds

13 Active ingredient specifications

14 Finished product manufacturing process flow diagrams

15 Finished product in-process controls

16 Finished product release specifications

17 Stability specifications used for the vial and syringe stability studies

18 Stability specifications proposed for future stability batches.

Gardasil

Gardasil

File number: TT50-7571

Evaluation of additional information dated 24 May 2006

The company have responded to the questions raised from the initial assessment of the dossier.

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.

The applicant has explained that all filters used in the manufacturing process are tested for filter integrity.

The filters that are used upstream, i.e. the non-sterilising filters, are filter integrity tested using a pressure hold test.

The product sterilising filters are integrity tested by the vendor prior to shipment to Merck. Sterile filtration of the product is completed by two 0.22µm filters connected in series. The applicant has confirmed that:

- the first filter of the series is integrity tested prior to use by Merck
- filter two is post use integrity tested
- upon recommendation by the TGA, the first filter will also be post use integrity tested.

The proposed filter integrity testing is acceptable.

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.

Adsorption of the Dilute Final Aqueous Product (DFAP) to the adjuvant is achieved using [redacted]. The applicant has explained that the adsorption process is instantaneous upon mixing. The [redacted] has a [redacted] to ensure a consistent and robust adsorption process. All validation lots had >99% completeness of adsorption, demonstrating the adsorption/mixing process is robust, with consistent adsorption observed.

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.

The applicant has explained that the proposed CPP ranges have been based on accumulated experience in the pre-validation and engineering studies.

A discussion has been provided for each step of the manufacturing process, describing how the CPP's have been selected based on development studies and/or factorial

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designs, and in some instances based on statistical analysis. Overall it appears that the proposed CPP ranges have been adequately tested during manufacturing development. The [redacted] process had a proposed [redacted]. The applicant's response states that this limit was based on the maximum measured capability of the [redacted]. The applicant response indicates that this limit has since been changed, and is now based on the results for the initial full scale process lots. However, the revised [redacted] have not been provided to Medsafe. ***The applicant needs to describe the proposed in-process limits for [redacted] for the [redacted] process.***

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.
The sample used to assess hold time stability of the DFAP was [redacted]. Full scale batch size at this manufacturing step ranged from [redacted]. The DFAP sample was stored in the same container type ([redacted]) as that used for the full scale manufacturing process. The sample size and storage container for the DFAP stability is adequately representative of the commercial manufacturing process.

5. Please provide the drug substance filter(s) extractable study that was completed, or a summary of the study data and the acceptance criteria.
A summary of the filter extractable tests performed by the company has been provided. All filters used in the manufacturing process have been adequately tested for extractables, and the results for [redacted] have been provided for each filter.
In addition to the extractable testing the applicant has stated that each filter supplier has tested the filters according to USP<88> Biological Reactivity Tests, In Vivo. The applicant states that the reports provided by the filter suppliers showed no adverse in vivo reactions.
Adequate studies have been completed by the company to analyse filter extractables.

6. Please provide the study that demonstrates the sterilising filter used in the drug substance manufacturing process has been satisfactorily validated for microbial retention.
The applicant has described laboratory scale studies that were completed to validate microbial retention of the sterilising membrane. The studies demonstrated successful retention of the challenge organism *Brevundimonas diminuta* of at least 1.0×10^7 cfu/cm^2.

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.
A summary has been provided of the studies completed to validate the sanitisation procedures for the [redacted]. All validation results demonstrate that the [redacted] procedures provide adequate control of the bioburden and endotoxin levels.

8. Please explain why a minimum contact time with [redacted] has not been set for santisation of the new [redacted].
A minimum contact time, [redacted] has been set at [redacted] for a new [redacted]. The minimum contact time is validated by ensuring that the Critical Quality

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Attrtibutes (CQA) for [redacted] are met for rinse samples taken immediately prior to loading the column.

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].
The applicant has confirmed that after validation was completed the CPPs were amended to correspond to the amounts actually used during the validation studies. The CPP has been amended to [redacted] and the sanitisation procedures for the [redacted] columns for all types are verified to be [redacted]
The [redacted] used for sanitisation and reuse now adequately reflects the amount used in the validation studies.

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.
The applicant has submitted finished product manufacturing flow diagrams that include the mixing times, mixing speeds, agitator speeds and recirculation rates.

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.
The applicant has submitted the viable count results for the Master Seed and Working Seed. Results ranged from [redacted] and results from these studies were used to establish the acceptance criteria for future working seeds. The proposed viable count acceptance criteria for release of new Working Seeds is [redacted] ***The applicant needs to explain how the acceptance limit has been established.***

Drug Substance specifications
12. Please describe the [redacted] that has been calculated in the validation of the [redacted] method used for the drug substance.
The [redacted] has been calculated for the MBAP to be [redacted] for each HPV type. [redacted] validation has been completed and the applicant has submitted results for the three most recent lots of each MBAP HPV type used for qualification testing. Based on the results a routine test [redacted] has been selected.

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.

The applicant has explained that the proposed limits have not been based on process capability, but instead have been established based on a qualitative evaluation of data from lots manufactured at full scale and lots used in clinical studies. The applicant has explained that the [redacted] are due to [redacted] The proposed limits, although not based on statistical analysis of the batch data, will ensure sufficient quality of the vaccine with respect to [redacted]

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.

The applicant has submitted a table that lists the [redacted] excipients and the specifications used to control the excipients. The table shows that the components of the [redacted] are controlled according to pharmacopoeial specifications (USP and/or Ph Eur). Quality control of the excipients for the [redacted] is now satisfactory.

Finished product specifications

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

Two methods are used for [redacted] A summary of the validation completed for both methods has been provided.

For the [redacted] method the [redacted] has been calculated to be [redacted] Qualification of the sample matrix for [redacted] has also been performed, and the applicant has submitted qualification results for three final container lots, and no [redacted] was observed across the [redacted] The [redacted] method has also been adequately validated. The [redacted] was calculated to be [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.

of what.

The applicants response indicates that they have no intention of changing the proposed upper limit, and have justified the proposed limit based on:

- clinical studies showing that higher doses have no safety or immunogenicity concern. The applicant states that based on this, setting upper specification limits is not warranted.
- The manufacturing process has been validated and demonstrated to be robust and consistent.
- For each lot, [redacted] data for each HPV type are reviewed internally and compared to alert limits based on process capability. Results outside these limits are investigated, and the impact on product quality is assessed before determining whether the lot is acceptable for release.

?antigen?

It is not uncommon for vaccines to have no upper limit for [redacted], where safety and immunogenicity of higher doses is of no concern. In this instance the proposed upper limit for [redacted] has been established based on the maximum dose clinically tested that was shown to be safe and efficacious. The upper limit therefore has no relevance to the batch results obtained from the validated process, and is therefore unlikely to provide any quality control as the proposed upper limits far exceeds any [redacted] results observed for the validation batches.

The applicant has explained that alert limits based on process capability are in place for [redacted] to assess product quality prior to release. However, no alert limits have been provided in the dossier, or in this additional information. ***The applicant should provide the alert limits that are used to assess*** [redacted].

If the alert limits for [redacted] are in place and adequately monitor batch to batch consistency, then the proposed 'batch release' upper limit for [redacted] is acceptable as a safety limit, ensuring that no batches are released that exceed the [redacted] tested and found safe in clinical trials.

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.

The applicant has explained that since the time of preparation of the original dossier, additional release and stability data have been obtained and the expiry specifications for MBAP [redacted] have been revised to:

Type 6 [redacted]
Type 11
Type 16
Type 18

Updated sections of the dossier relating to stability of the drug substance have been submitted, and these sections show that a small decrease in [redacted] was observed. Statistical analysis of pooled lots was used to calculate the estimated annual loss:

Type 6	0.32%
Type 11	0.73%
Type 16	0%
Type 18	1.45%

The [redacted] stability limits have been calculated based on the release specifications, the estimated annual loss rate, and also taking into account [redacted] loss rate variability and assay variability. The proposed stability limits for MBAP [redacted] are very conservative when compared to the actual stability data obtained, but have been adequately justified.

The proposed release specifications for [redacted] described in the original dossier are:
Type 6
Type 11
Type 16
Type 18 [redacted]

In the updated sections of the dossier submitted with the additional information dated 24 May 2006, the proposed drug substance release specifications for [redacted] have been revised based on additional batch data:
Type 6
Type 11
Type 16
Type 18 [redacted]
The updated release specifications are acceptable.

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.
Updated [redacted] stability data have been submitted for the [redacted] lots and all data support the proposed [redacted] expiry period.

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.
Updated sections of the dossier relating to drug substance stability data have been provided. Updated drug substance stability data continue to support the proposed [redacted] expiry date.

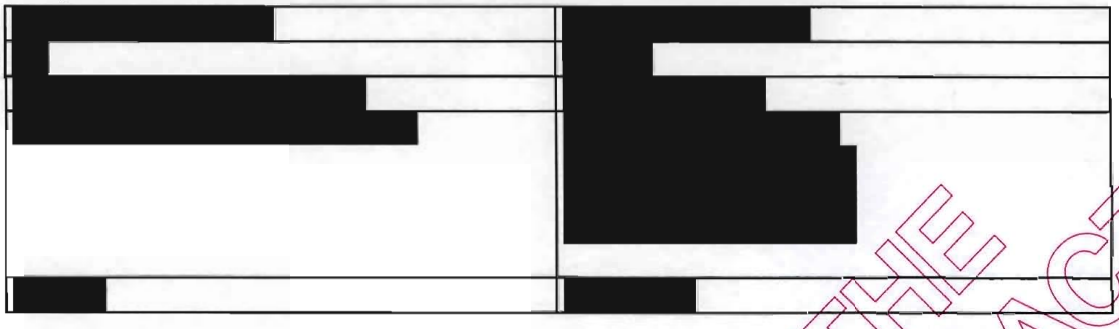
Drug Substance post-approval stability protocol
20. Please indicate when the cumulative stability studies for the MBAP and finished product will be completed and submitted to Medsafe.
The cumulative stability study will be completed by March 2009. The applicant has confirmed that the cumulative stability data will be 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.
The applicant has confirmed that one batch of MBAP for each HPV type will be placed on stability every year that the MBAP for that HPV type is manufactured.

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.
Updated drug product stability sections of the dossier have been provided. These sections of the dossier include updated statistical analysis of both the long term and accelerated stability data. No significant trends are observed. A slight decrease in [redacted] was observed for some lots, but all results were still well within release limits. The updated statistical analysis has calculated [redacted] loss rates for each HPV type based on pooling the MBAP and finished product vial and syringe stability lots. These are the same loss rates calculated for the MBAP.
Revised stability specifications have been proposed:

40



The [redacted] limits have been slightly tightened for Types 11, 16, and 18, but are still much lower than the lowest stability results observed. The revised stability limits have been justified using the following rationale:

- The expiry specification has been calculated from the lower limit release specification, taking into account the stability loss rate, and factors influencing the variability of results (variability in loss rates, and assay variability)

The calculated stability limits are very conservative, i.e. anticipating the worst case scenario. However, as highlighted by the applicant, the proposed [redacted] limits are supported by clinical studies which have shown this low dose level to be efficacious. Based on the fact that the proposed [redacted] stability limits are supported by clinical data the proposed stability specifications are acceptable.

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]

The applicant has confirmed that the [redacted] test will be performed on an annual basis for future stability batches. The limit for this test has been tightened from [redacted] to [redacted]. The tightened specification limit is acceptable.

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.

See response assessment for question 22.

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. !! Yet again !!.

Response to questions 25 and 26.

Updated coloured labelling has been provided for all containers and cartons. The proposed labelling now includes the proposed location for the batch number and expiry date on the single and 10x syringe pack. The text size on the syringe and vial labels has also been increased.

The proposed labels now comply with the New Zealand Medicine Regulations requirements.

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The additional information submitted by the applicant, dated 24 May 2006, has been reviewed and the following items require further information.

1. The additional information provided in response to question 3 (Medsafe Request for Information letter dated 20 March 2006) indicates that the limit for [redacted] of the drug substance has been changed based on the results for the initial full scale process lots. Please describe the proposed [redacted] as the only limit Medsafe currently has is that proposed in the original dossier, [redacted] which is too high and does not accurately monitor [redacted] for the manufacturing process.

2. The proposed viable count acceptance criteria for release of the new Working Seed is [redacted]. Please explain how this limit has been established, as viable count results submitted for the Master Seed and Working Seed ranged from [redacted].

3. The additional information provided in response to question 16 (Medsafe Request for Information letter dated 20 March 2006), states that alert limits are in place for [redacted] for each HPV type. Please provide these alert limits.

EAI 2 4 July 2006

Additional information received 4.7.06 reviewed by Rob Allman with comment as follows:
I have reviewed the 3 responses provided by the company and consider tham acceptable to resolving the questions raised during the review process.
Rob Allman,
Team Leader Evaluation Team,
4.7.2006.

5.7.06, database details amended as per information and data received with email 27.6.2006.

Extract from minutes of MAAC meeting relevant to Gardasil

20 June 2006

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 (VaIN) 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]

s 18(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 Papillomavirus (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 Papillomavirus (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.**