MINISTERIO
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productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

CZV BOVINE TUBERCULIN PPD

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0180/001/MR
Name, strength and pharmaceutical form	CZV Bovine Tuberculin PPD 25,000 IU/ml, solution for injection
Applicant	CZ Veterinaria, S.A. La Relva s/n, 36400 Porriño (Pontevedra) SPAIN
Active substance(s)	Purified protein derivative from culture of *Mycobaterium bovis*, strain AN-5
ATC Vet code	QI02AR01
Target species	Cattle
Indication for use	*'In vivo* diagnosis of cattle from 6 weeks of age that have generated an immune response against *Mycobacterium bovis*, the causative agent of bovine tuberculosis (single intradermal tuberculin test). When used together with CZV Avian PPD Tuberculin, *in vivo* diagnosis of cattle from 6 weeks of age that have generated an immune response against *M. bovis*, differentiating animals reacting to *M. bovis* from those that have become sensitised to bovine tuberculin as a result of exposure to other mycobacteria or related genera (single intradermal comparative tuberculin test).

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	Day 90: 27/07/2011
Date product first authorised in the Reference Member State (MRP only)	25/10/1982
Concerned Member States for original procedure	BE, DE, EL, FR, HU, IE, PL, PT, UK.

I. SCIENTIFIC OVERVIEW

For public assessment reports for the first authorisation in a range*:*

CZV bovine Tuberculin PPD is a purified protein derivative (PPD) of *Mycobacterium bovis*, strain AN-5 to be administered to bovine. The product is used for "in vivo" diagnosis.

The product complies with the requirements indicated in the applicable legislation, as Commission Regulation (EC) 1226/2002 and European Pharmacopoeia monograph 01/2008: 0536.

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.

It has been shown that the product can be safely used in the target species. The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.

The efficacy of the product was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains: (per ml)

Active substances:

Purified protein derivative from culture of *Mycobacterium bovis*, strain AN-5 25,000 IU

Excipients

Phenol
Glycerol
Phosphate buffered saline (sodium chloride, disodium phosphate and potassium phosphate)
Water for injections

The containers are glass vials Type I, 6cc, containing 50 doses (5 mL), with butyl rubber stopper and aluminium seal. The particulars of the containers and controls performed are provided and conform to the regulation.

The production process and controls follows the specifications of European Pharmacopoeia and OIE Manual. The process has been properly validated. The inactivation process and the detection limit of the control of inactivation are correctly validated.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site, and in accordance with the European Pharmacopoeia and relevant European guidelines.

The bovine tuberculin purified protein derivative CZV Bovine Tuberculin PPD is a preparation obtained from products of culture and lyses of *Mycobacterium bovis* strain AN-5 that are heat-treated.

The bacterial strain of choice is the one recommended by European legislation and OIE Manual. The production process and controls follows the specifications of European Pharmacopoeia and OIE Manual. The process has been properly validated, including a study of inactivation kinetics.

As a summary, the tuberculin is obtained from water-soluble fractions prepared by inactivation under steam flow of *Mycobacterium bovis* cultures, and subsequent filtering. The active fraction of the filtrate (mainly proteins), is isolated by precipitation, washed and resuspended. The formulation of the final product is based on protein concentration and made by blending each of the components at an adequate rate. The stated potency for a dose of bovine tuberculin is 2.500 IU (0.1 mL). Phenol is added as an antimicrobial preservative and glycerol is added as stabiliser.

As indicated in Ph. Eur. monograph 01/2008:0536, an identification test is performed, in compliance with the requirements established.

Process validation data on the product have been presented, also in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance of the product is purified protein derivative from culture of *Mycobacterium bovis* strain AN-5. The active substance is established as described in the European legislation, and manufactured in accordance with the principles of good manufacturing practice. The master and working seeds have been produced according to the Seed Lot System as described in the relevant guidelines. The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification has been provided.
The biological starting materials used are in compliance with the relevant Ph. Eur. monographs and guidelines and are appropriately screened for the absence of extraneous agents according to the Ph. Eur Guidelines; any deviation was adequately justified.

Starting materials of non-biological origin used in production comply with the European Pharmacopoeia monographs where these exist. The applicant presents certificates of analyses of the starting materials showing that all the products are in compliance with the relevant Pharmacopoeia monographs in force.
For the substances where there is not such requirement, the company has identified the source of the substance, explained how its quality is controlled and has provided relevant certificates of analysis.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

The applicant presents a TSE risk assessment. The applicant has sent a TSE declaration of compliance together with format table.

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated. The Glycerol EDQM certificate has been included.

E. Control tests during production

The tests performed during production are described and the results of the tests applied during the production process for 34 batches of antigen are included in the dossier to show consistency between the batches. The company included the control test on batches at the extremes of protein content to support the consistency. All results obtained from the control tests are within the specified limits.

F. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. The tests include in particular:

Control tests on the bulk product: Appearance, pH, Sterility, Absence of acid-fast bacilli, Phenol content and Protein concentration.
Control test of finished product: Appearance, Sterility, Sensitising effect, Toxicity, Sterility, Potency, Presentation and Fill volume.

The controls applied are appropriate and follow the specifications of the Ph. Eur. for control tests of the finished product for bovine PPD tuberculin (monograph 536), as well as the specifications of the OIE for this product. They have been properly validated: sterility, phenol content, protein concentration and potency.
The results from the control tests carried out on 5 consecutive production batches are presented. All the controls performed comply with the acceptance criteria established, and the data demonstrate the consistence of the production process.

G. Stability

Antigen stability: Satisfactory data have been provided to justify a shelf life of 12 months at 2-8°C for the storage of the concentrate PPD bovine tuberculin until blending.

Finished product: Satisfactory results have been presented to justify a shelf life of 24 months at 2-8°C.

The product has been controlled for physical (appearance, pH), chemical (phenol concentration) and biological (sterility, toxicity and biological activity) characteristics, thereby ensuring that correct follow-up of the quality, safety and biological activity of the product has been carried out during the stability study. Antimicrobial preservative efficacy is demonstrated at the end of the stability study.

Stability data on the active substances and finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance and of the product throughout its shelf life when stored under the approved conditions.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life: 2 years
In-use shelf life: Use immediately once the vial is opened.

Storage conditions: Store and transport between +2 °C – +8 °C protected from light. Do not freeze

III. SAFETY ASSESSMENT

The applicant presents the following studies and bibliographical data to support the safety of the administration of the product and followed the Guideline on Data requirements for immunological veterinary medicinal products intended for minor use or minor species/limited markets “EMEA/CVMP/IWP/123243/2006-Rev-1”.

As presented in the SPC, the indication for use of the product is the diagnosis of bovine tuberculosis by means of the simple or the comparative intradermal tests. The comparative test implies one injection of avian PPD tuberculin and one injection of bovine PPD tuberculin, given simultaneously.

The laboratory and field studies have been conducted on the safety and efficacy of the product in bovine and details of batches used in these studies were provided.

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal is demonstrated in several studies. Some of the studies presented cover the combined administration of the bovine tuberculin with the avian tuberculin.

The dose used in the laboratory trials (0.1 ml) is the dose recommended by the OIE Manual, as well as by the European Union, as specified in Council Directive 64/432/EEC, and as last amended by Commission Regulation (EC) No. 1226/2002.

All safety tests were performed in cattle and in the most sensitive categories: animals experimentally infected/sensitised with *M. bovis, M. avium* subsp. *avium* or with *M. avium* subsp *paratuberculosis,in n*on-infected and non-sensitised animals and in pregnant cows.

The safety of the administration of a single dose for bovine PPD tuberculin was supported by the studies on the safety of the administration of an overdose, repeat dose and Pharmacovigilance data.

Safety of the administration of an overdose and repeated dose:
Three studies support the safety of an overdose and a repeated dose of the bovine tuberculin, alone or combined with the avian tuberculin.

In the first study a suitable number of calves, with a mean age of 3-4 months and found negative for tuberculosis and paratuberculosis, were selected. Each animal received a double dose of the product and a second dose 42 days after the first one. A slight increase in body temperature was noted in some animals at 4 hours post injection of an overdose. However, their body temperature gradually dropped and at all times remained within the acceptable physiological values for their species and age. The degree of local reaction at the injection sites was measured at different moments after injection. No systemic or local reactions were observed. No significant difference in skin thickness was present between the injections sites.

The second study assessed the safety and efficacy of an overdose administered concomitantly with avian tuberculin PPD to cattle experimentally infected with *M. bovis*. A suitable number of young calves found negative for bovine tuberculosis and paratuberculosis were assigned to infected group or to control group. After experimental infection with *M. bovis*, animals were inoculated with 8 injections of bovine tuberculin, corresponding to the International Standard for Bovine Tuberculin and to the trial batches. The degree of local reaction at the injection sites was measured at different moments after injection. No systemic or local reactions were observed. No significant difference in skin thickness was present between the injections sites. A transitory increase of the temperature was observed in animals infected and inoculated (8 doses) which disappeared between 24 to 48 hours after the inoculation.

The third study was intended to demonstrate the safety of administering an overdose of bovine tuberculin PPD and avian tuberculin PPD plus a second dose 42 days after the first dose to calves sensitised with M. *avium* subsp. *avium*. At 6 weeks of age, 30 days

post sensitisation with *M. avium* subsp *avium*, a comparative intradermal tuberculin test (CITT) was performed with an overdose of bovine tuberculin PPD and avian tuberculin PPD. A second comparative intradermal tuberculin test (CITT) was performed after 42 days with a regular dose.

The CITT was performed in accordance with the protocol described in the chapter 2.4.7 of the OIE Manual of Standards for Diagnostic Test and Vaccines, and with the provisions of ANNEX B of Council Directive 64/432/EEC, as last amended by Commission Regulation (EC) No. 1226/2002.

No adverse reaction of any kind was observed during the 2 hours post-inoculation of tuberculin, neither was any local or systemic reactions noted during the following 14 days after the first or second CITT 42 days later. A transitory increase of the temperature was observed in some animals of the sensitised and overdosed group. The temperature of these animals progressively dropped, returning to normal values at 48 hours post-inoculation. No temperature increases were noted in the non-sensitised control group. No statistically significant differences were detected between both groups throughout the test results. Neither was there significant differences noted between groups regarding mean temperatures recorded before and after administration of bovine tuberculin PPD and avian tuberculin PPD.

No statistically significant increases were observed in the control group after tuberculin inoculation as a response to any of the tuberculins and measurements were lower than 1.5 mm at 72 hours. However, the group sensitised with *M. avium* subsp. *avium* reported an increase to avian tuberculin greater than to bovine tuberculin.

From the results obtained, is concluded that the administration of an overdose was adequately demonstrated.

Safety of the repeated administration of one dose

The safety of the repeated administration of both tuberculins was also demonstrated in two-three months calves experimentally sensitised with *Mycobacterium avium* subsp *paratuberculosis.* They were subjected to comparative intradermal tuberculin test at intervals of 45, 105 and 180 days. No adverse reactions were observed. Delayed hypersensitivity responses shown, in all cases, to be more marked at CZV Avian Tuberculin PPD.

Examination of reproductive performance

A study was performed in order to demonstrate the safety of administering a single dose to pregnant cows at different stages of pregnancy and under field conditions. One hundred twenty-eight adult cows were obtained from three farms and all herds were accredited as officially tuberculosis free bovine at the time the study was performed. No statistically significant differences in skin fold thickness increase were observed between the different groups of pregnant cows (1st, 2nd and 3rd trimester of pregnancy), nor between pregnant and non-pregnant cows 72 hours after bovine tuberculin application.

No teratogenic effects, abortogenic capacity, stillbirths nor weak neonatal calves were associated with the administration of intradermal tuberculin test in any of the study herds. The survival rate at 15 days post-calving was 100 percent.

The applicant included pharmacovigilance data (1996-2009) for the bovine tuberculin PPD showing that no adverse effect on pregnancy has been reported after over 91 million administered doses.

The applicant also presented bibliographical studies to support this section. There is no information in literature that the preparation will have a negative effect on reproductive performance.

Examination of immunological functions
The tuberculin PPD is an allergen used in the intradermal tuberculin test to detect tuberculous animals. The intradermal administration of tuberculin induces a delayed hypersensitivity response in the infected animal that may be estimated 72 hours post-inoculation. The inoculated PPD is processed by antigen presenting cells and recognized by the sensitized T-cells in the infected animals, these cells release lymphokines that results in a delayed hypersensitivity response as skin thickening (swelling) at the injection site. Studies and bibliography were presented to support this section. The immunological response is described and the studies presented are adequate to demonstrate the immunological response induced by the product.

The allergen is inactivated and thus the specific tests to be performed for live vaccines are not applicable.

Interactions
In the Intradermal Comparative Test for tuberculosis the avian tuberculin is used simultaneously with bovine tuberculin. The two allergens are immunologically different and the difference between the skin swellings caused by both allergens is the criteria to determine whether or not the animal is infected with *M. tuberculosis*.

The studies of the combined administration of both tuberculins (overdose, repeat dose), detailed in the previous section, confirms the safety and the absence of any relevant interaction between both tuberculins. This is also supported by Pharmacovigilance data in animals subjected to the Intradermal Comparative Test. No adverse reactions were reported. This demonstrates again the absence of any relevant interaction between both tuberculins.

As an *in vivo* diagnostic reagent, the product should not be mixed or administered with any other veterinary product.

A lack of sensitivity to the test can occur in cattle that were recently or concurrently treated with immunosuppressive agents.

Field studies

The CITT results obtained within a field trial assessing the safety and efficacy of an inactivated vaccine against paratuberculosis, are provided as support to validate the safety of the bovine tuberculin PPD. Also the safety of the preparation under field conditions can be concluded from the Pharmacovigilance data and from the field use.

The applicant also presents bibliographical studies. Some of these studies were performed with the applicant's product and some others were not performed with it, but due to the standardization of tuberculins, all results have been considered as additional data to demonstrate the safety of the product.

The main objective of the field trial was to assess the safety and efficacy of the administration of an inactivated vaccine against bovine paratuberculosis in two dairy cattle herds (adult males, pregnant and non-pregnant females and replacement animals) with high prevalence of paratuberculosis. The comparative intradermal tuberculin test was performed before vaccination and at regular intervals after the procedure.

No adverse reaction of any kind was noted over the 14-day post-vaccination period or throughout the entire study. Neither was there any test-related adverse reactions reported by the study investigator nor by the official veterinary surgeons.

The CITTs results showed that the animals in the vaccinated groups from both farms had a positive response to avian tuberculin, whereas they all tested negative to bovine tuberculin.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the risk to the environment of the preparation is negligible. The dose of the preparation that is administered is extremely small and none of its components is excreted into the environment.
No warnings are therefore required.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed as well as for the user

Residues testing is not applicable, as the product contains no materials which require Maximum Residues Limit.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.B Clinical Studies

The efficacy of bovine tuberculin PPD has been assessed performing different types of controlled trials in cattle infected with M. *bovis,* M. *avium* subsp. *avium* or *M. avium* subsp. *paratuberculosis* and in catlle neither sensitised nor infected with *M. bovis* or *M. avium.*

Laboratory Trials

The efficacy of the product is supported by seven laboratory studies in accordance with the relevant requirements.

The first study is part of a safety and efficacy test that has been previously described in the “Safety” section. One of the objectives of this study was to confirm the activity (potency) established for CZV Bovine Tuberculin PPD in animals of the targets species infected experimentally with *M. bovis* AN5 aged 4 weeks and validate the batch potency test. Results showed the CZV Bovine Tuberculin test was able to identify the tuberculosis infection by producing a positive response for each of the three trials

batches and for the standards. No significant increase in skin fold thickness was recorded in the control group with any of the tuberculins employed. In all cases the estimated potency values obtained in calves, as well as in guinea pigs (batch potency test), felt within the acceptable range of the European Pharmacopoeia guidelines: no less than 66% and no more than 150% of the stated potency (25,000 IU/ml).The inoculation of CZV Avian Tuberculin PP and the avian international standard to cattle infected with *M. bovis* offered a negative response.
The results in skinfold thickness after CITT with both tuberculins indicated specific detection of animals experimentally infected with *M. bovis* and agreement with the specifications of Annex B of Council Directive 64/432/EEC (standard interpretation).

The cellular immune response to experimental infection was monitored using the interferon-gamma (IFN-□) assay before tuberculin inoculation to confirm infection by *M. bovis*. Non-infected control animals showed a negative response. However, experimentally infected animals developed strong cellular immunity to the bacteria, which was measured by *in vitro* stimulation with Bovine PPD. Immune response remained high up to the day of tuberculin inoculation and this confirmed that experimental infection had been successfully achieved in all animals from the treatment group. Experimental infection model was also confirmed by anatomopathological and culture results.

Additionally, two trials were presented to assess the potency of bovine tuberculin PPD in naturally infected cattle. In the first one, infected cattle that were positive to the routine CITT performed in the field (the bovine PPD response exceeding the avian PPD response by at least 12 mm) was selected. Bovine tuberculin was compared against the Irish Standard for bovine PPD (33,700 IU/ml, with a 0.93 and 1.00 relative potency). The potency of the CZV Bovine tuberculin was calculated as 31,434 IU/ml and 33,743 IU/ml in cattle. It was also shown that the potency value obtained in guinea pigs correlated with the product's response in the target species.

In the second study – included within the field trial carried out in Ireland using various combinations of tuberculins manufactured by different laboratories-, the potency of the tuberculins was assayed in sensitised guinea pigs (following the method described in Annex B of Council Directive 64/432/EEC and in its subsequent amendments) as well as in naturally infected tuberculous cattle. Results showed that potency value obtained in guinea pigs for CZV Bovine Tuberculin PPD correlated with the response in the target species.

In another study, 6 week old calves sensitised with *M. avium* subsp *avium* received 1 overdose of both tuberculins plus a second dose 42 days later. The increase in skinfold produced by the avian tuberculin was much greater than that produced by bovine tuberculin, indicating a positive identification due to *M. avium* subsp *avium*. The uninfected controls always yielded a negative response to both tuberculins. The results also demonstrated that the period of non-sensitisation (anergy) induced by an overdose of both tuberculins was less than 42 days, given that all animals showed reaction to the tuberculin test when the second dose was administered. Likewise, the results obtained in the non-sensitised control group show that an overdose of CZV Bovine and Avian Tuberculin PPD did not induce sensitisation, since the animals showed a negative response to the application of the second dose.

The efficacy of bovine tuberculin and the absence of sensitising effect 42 days after the administration of one overdose were also confirmed in non-infected cattle. A negative response after overdose inoculation of bovine tuberculin was observed, which

permitted to identify clearly non-tuberculous animals. In the same way, the administration of CZV Bovine Tuberculin PPD to non-infected cattle did not cause sensitisation as 42 days after the administration of an overdose, the inoculation of a second dose of the tuberculin continued to show a negative response.

In addition to this, the combined administration of CZV Bovine and Avian Tuberculin PPD to 2 month-old uninfected cattle at intervals of 0, 45, 105 and 180 days induced a negative response, showing again the absence of sensitisation to tuberculins.

The increase in skinfold thickness induced by avian tuberculin was much greater than the bovine tuberculin-induced increase, indicating positive identification of sensitisation by M. *avium*.

In the last trial, the combined administration of the both tuberculins (bovine and avian) shown to be able to diagnose animals of at least 2 months of age that were infected/vaccinated with *M. avium* subsp. *paratuberculosis.* The response to avian tuberculin was always stronger than that to bovine tuberculin, indicating that the results were negative for tuberculosis, according to the CITT interpretation criteria laid down in Annex B of Council Directive 64/432/EEC as amended.

Field Trials

The applicant has conducted several field studies:

A comparative Study of the Performance of Bovine and Avian Tuberculin from Different Manufacturers in the CITT was carried out by the Department of Agriculture, Fisheries and Food of Ireland in 2007 to compare the efficacy of the CITT on cattle naturally infected with *M. bovis*. CZV Bovine and Avian Tuberculin PPD, was one of the combinations included in the trial. The percentage of animals that showed the same infection status ranged between 90.2% and 94.9%. No significant differences were found between the infection statuses recorded with the CITTs using control tuberculins or trial tuberculins. Neither significant differences were found between the measures for avian and bovine tuberculin nor was the bovine-avian difference significant after the administration of control and trial tuberculins. Data demonstrated that both tuberculins (avian and bovine, manufactured by CZ Veterinaria) has an efficacy comparable to the standard combination of tuberculins used in Ireland, and the combinations produced by other laboratories.

The efficacy of the joint administration of both tuberculins was also assessed as part of a field trial conducted to evaluate the safety and efficacy of a vaccine against paratuberculosis in cattle. The specificity of a repeated dose of tuberculins administered under field conditions to herds with animals that have been infected and/or sensitised (vaccinated) with *M. avium* subsp. *paratuberculosis* was investigated, as well as the interference of vaccination with tuberculosis diagnostic test results. Data demonstrated that the combined administration of both tuberculins effectively permitted the discrimination due to vaccination and/or natural infection with *M. avium* subsp. *paratuberculosis*, the increase in skinfold always being greater with avian tuberculin than bovine tuberculin. This efficacy is maintained over time, as the yearly repetition of the CITT showed consistent results and always with greater increases in the inoculation site with the avian tuberculin.

The efficacy (sensitivity and/or specificity) of SITT in cattle naturally infected with *Mycobacterium bovis* under field conditions was assessed in two additional trials.

In the first trial a total of 125 samples from cattle that were standard reactors to the SITT were collected and analysed by macroscopic examination, bacterioscopy, microbiological culture (4 cultures performed in parallel), PCR of isolate, and direct qPCR on the biological sample, performing parallel DNA extractions using two different DNA extraction methods (4 simultaneous qPCR per sample in total). Results showed an 88.8% (95% CI) of test sensitivity.

Assessment of the Efficacy (Sensitivity and Specificity) of CZV Bovine Tuberculin PPD in Cattle Naturally Infected with *Mycobacterium bovis* Under Field Conditions
The second trial assessed the sensitivity and specificity of 40 different batches of bovine tuberculin in SITT. In parallel to culture testing (by duplicate), direct molecular detection on all biological samples was performed in duplicate by multiple real-time PCR using oligonucleotides and the TaqMan-MGB probe on the IS6110 region. Anatomopathological examinations were also carried out. The results for the specificity and sensitivity in the SITT were 77,5% (95% CI) and 89,9% (95% CI) respectively.

A report analysing the Safety and Efficacy of the Bovine and Avian PPD produced by CZ Veterinaria, S.A. in the National Bovine Tuberculosis Eradication Programme was included. Both tuberculins have been systematically used in the Spanish Bovine Tuberculosis Eradication Programme since 1986. Post-mortem inspection results (presence of compatible lesions and positive PCR/culture) were established as the "gold standard" for the evaluation of diagnostic results, both for reactors and negative animals. The apparent sensitivity for farms in different epidemiological situations provided values between 81% and 95% for SITT. Similarly, the specificity was between 99.2% and 99.85%. The results gave an estimated sensitivity for the CITT using CZV Bovine and Avian Tuberculin PPD of 100% and a specificity of 92%.

Another report analysing the Efficacy of Bovine PPD in the SITT under field Conditions in two livestock farms was presented. Sensitivity data on cattle undergoing sacrifice of the whole herd and another herd underwent 6 repeated test and culling in 15 months at inervals of 2-3 months was assessed. In the first case sensitivity was 93.3% and in the second the mean value was 82.4% during the different tests and culling.

Pharmacovigilance reports

Several Periodic Safety Update Reports on bovine tuberculin PPD have been provided by the MAH, and after the analysis and evaluation of all the pharmacovigilance information that has been sent we can conclude that the risk-benefit balance of this product remains unchanged and there is no need to change the SPC or to take any regulatory actions due to safety reasons.

Bibliographical studies
The applicant has presented bibliographical studies. Some of these studies were performed with the applicant's product and some others were not performed with it, but due to the standardization of tuberculins, all results have been considered as additional data to demonstrate the efficacy of the product. The studies are summarised and copies of the published studies are presented.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

The quality of the product is adequately demonstrated by the data presented in the dossier and the consistency of the final product is sufficiently documented through out the shelf-life of the product.

The safety and efficacy is supported by the studies presented in the dossier, as well as bibliographically and extensively on pharmacovigilance data as this product has been licensed since 1996.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the veterinary Heads of Agencies website (www.hma.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

None