ANNEX I

NAME, PHARMACEUTICAL FORM, STRENGTH OF THE VETERINARY MEDICINAL PRODUCT, ANIMAL SPECIES, ROUTES OF ADMINISTRATION, WITHDRAWAL PERIOD AND APPLICANT/MARKETING AUTHORISATION HOLDER IN THE MEMBER STATES

Member State	Applicant or Marketing Authorisation Holder	Invented name	Pharmaceutical form	Strength	Animal species	Frequency and route of administration	Recommended dose	Withdrawal period
Slovak Republic[1]	Pharmagal Bio, s.r.o. Murgašova 5 949 01 Nitra Slovak Republic	APPM Respipharm	Suspension for injection	Strains of *Actinobacillus pleuropneumoniae* producing Apx I, ApxII and ApxIII toxins: *Actinobacillus pleuropneumoniae* serotype 2 .≥ 4'8 $\log_2$ (*) *Actinobacillus pleuropneumoniae* serotype 9 ≥ 5,2 $\log_2$ (*) *Actinobacillus pleuropneumoniae* serotype 11 ≥ 4'9 $\log_2$ (*) *Pasteurella multocida* serotype A ≥ 2'1 $\log_2$ (*) (*) Mean titre of agglutination antibodies after vaccination in rabbits	Pigs	Intramuscularly deep into the neck muscle. <u>Pregnant sows:</u> Primary vaccination: First injection 4-5 weeks before expected farrowing. Second injection at least 2 weeks before expected farrowing. Booster: One injection 2-3 weeks before each farrowing. <u>Weaned piglets:</u> First injection: At the age of 6-8 weeks. Revaccination: After 14-21 days.	<u>Pregnant sows:</u> Vaccine dose: 3 ml <u>Weaned piglets:</u> Vaccine dose: 2 ml	Zero days

[1] Marketing Authorisation granted

Member State	Applicant or Marketing Authorisation Holder	Invented name	Pharmaceutical form	Strength	Animal species	Frequency and route of administration	Recommended dose	Withdrawal period
Spain	Pharmagal Bio, s.r.o. Murgašova 5 949 01 Nitra Slovak Republic	APPM Respipharm	Suspension for injection	Strains of *Actinobacillus pleuropneumoniae* producing Apx I, ApxII and ApxIII toxins: *Actinobacillus pleuropneumoniae* serotype 2 .≥ 4'8 $\log_2$ (*) *Actinobacillus pleuropneumoniae* serotype 9 ≥ 5,2 $\log_2$ (*) *Actinobacillus pleuropneumoniae* serotype 11 ≥ 4'9 $\log_2$ (*) *Pasteurella multocida* serotype A ≥ 2'1 $\log_2$ (*) (*) Mean titre of agglutination antibodies after vaccination in rabbits	Pigs	Intramuscularly deep into the neck muscle. Pregnant sows: Primary vaccination: First injection 4-5 weeks before expected farrowing. Second injection at least 2 weeks before expected farrowing. Booster: One injection 2-3 weeks before each farrowing. Weaned piglets: First injection: At the age of 6-8 weeks. Revaccination: After 14-21 days.	Pregnant sows: Vaccine dose: 3 ml Weaned piglets: Vaccine dose: 2 ml	Zero days

Member State	Applicant or Marketing Authorisation Holder	Invented name	Pharmaceutical form	Strength	Animal species	Frequency and route of administration	Recommended dose	Withdrawal period
Poland	Pharmagal Bio, s.r.o. Murgašova 5 949 01 Nitra Slovak Republic	APPM Respipharm	Suspension for injection	Strains of *Actinobacillus pleuropneumoniae* producing Apx I, ApxII and ApxIII toxins: *Actinobacillus pleuropneumoniae* serotype 2 .≥ 4'8 $\log_2$ (*) *Actinobacillus pleuropneumoniae* serotype 9 ≥ 5,2 $\log_2$ (*) *Actinobacillus pleuropneumoniae* serotype 11 ≥ 4'9 $\log_2$ (*) *Pasteurella multocida* serotype A ≥ 2'1 $\log_2$ (*) (*) Mean titre of agglutination antibodies after vaccination in rabbits	Pigs	Intramuscularly deep into the neck muscle. Pregnant sows: Primary vaccination: First injection 4-5 weeks before expected farrowing. Second injection at least 2 weeks before expected farrowing. Booster: One injection 2-3 weeks before each farrowing. Weaned piglets: First injection: At the age of 6-8 weeks. Revaccination: After 14-21 days.	Pregnant sows: Vaccine dose: 3 ml Weaned piglets: Vaccine dose: 2 ml	Zero days

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR REFUSAL OF THE GRANTING OF THE MARKETING AUTHORISATIONS AND FOR THE SUSPENSION OF EXISTING MARKETING AUTHORISATION

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF APPM RESPIPHARM

1. Introduction

APPM Respipharm is a multi-component formaldehyde inactivated whole-cell bacterial vaccine containing three strains of *Actinobacillus pleuropneumoniae* (Serotypes 2, 9 and 11) and one strain of *Pasteurella multocida* (Serotype A), and includes aluminium hydroxide gel as adjuvant.

The product is indicated for use in pigs (sows and weaned piglets) from 6 weeks of age, intended to induce active immunization of sows and piglets against pleuropneumonia caused by *Actinobacillus pleuropneumoniae* and against secondary infection by *Pasteurella multocida*. The onset of immunity is stated as 14 days and the duration of immunity as 6 months.

Administration is by two intramuscular injections separated by 2-3 weeks. For immunization of sows the first dose (3ml) should be given 4-5 weeks before the expected farrowing date, with the second injection (3ml) at least 2 weeks before the expected farrowing date. For immunization of piglets the first dose (2ml) should be given at age 6-8 weeks, followed by a second dose (2ml) 14-21 days later.

The product has been authorised in the reference Member State (Slovak Republic) for 7 years. The present referral follows an application for mutual recognition of the product in Poland and Spain. At the conclusion of the assessment phase of the procedure the concerned Member State Poland was prepared to grant an authorisation. Spain raised objections which have led to the present referral procedure as it was considered that the authorisation of this veterinary medicinal product may present a potential serious risk to human or animal health or to the environment on the grounds of concerns over Quality and Efficacy.

In brief, concerns were raised that the composition of *Actinobacillus pleuropneumoniae* serotypes in the vaccine (2, 9 and 11) were not based on the epizoological situation in Spain, where the most prevalent serotypes are 2, 4 and 7. In addition, Spain considered that an adequate justification had not been provided for including the different serotypes of *A.pleuropneumoniae* and *P. multocida* into the same vaccine. In addition to these quality points Spain also considered that the permitted level of residual formaldehyde was too high. Due to concerns related to correlation between serological response against *P. multocida* and protection, Spain considers that because of a lack of correlation there is also no proven correlation between the batch potency test in rabbits and efficacy in pigs for this antigen. Consequently, there were concerns that batch to batch consistency could not be ensured.

Concerns over *A.pleuropneumoniae* efficacy related to a lack of confirmation of Apx toxins in the finished product and absence of specific challenge studies with APP serotype 11. In addition, it was considered that the field studies were not adequate and lacked direct confirmation of the presence of APP or appropriate monitoring of clinical signs or other efficacy parameters. The lack of convincing data in support of the efficacy of *P.multocida* was considered a particular weakness.

2. Assessment of Quality and Efficacy issues

Quality issues:

The applicant has provided data which confirm that the APP serotypes contained within the product are present in the Member States involved. In addition, argumentation has been presented which supports the importance of Apx toxins as important antigens in mediating protection, which is also supported by the requirements of the specific Ph. Eur. monograph (2008/1360). The Apx toxins present in the product (Apx I, Apx II and Apx III) are appropriate to providing protection against the serotypes present in the Member States where the product is intended to be used. Consequently it was agreed that the APP serotypes in the product are relevant and therefore inclusion of the APP components in the vaccine was adequately justified.

The applicant provided field data, supplemented with bibliographical data, to indicate that *P.multocida* causes frequent co-infections with APP in pigs with respiratory disease. In addition, field data were presented comparing the clinical outcome in pigs with respiratory disease on farms where APP and *P.multocida* are simultaneously present, and which have been vaccinated with either APPM Respipharm or a competitor product incorporating APP only. However, in view of the deficiencies in these data (see below) a justification for inclusion of PMA in the product could not be accepted.

The Ph. Eur. (0062) allows levels residual formaldehyde above 0.5 g/L provided the level has been shown to be safe. The applicant has shown that product containing the proposed upper limit of formaldehyde has not given rise to significant adverse reactions during single, repeated and overdose studies or during field use, nor during safety studies in pregnant sows. Since formaldehyde is listed in Annex II of the MRL Council Regulation (EEC) No 2377/90 it has been accepted that it is not necessary for the protection of public health to establish a maximum residue limit. Consequently, there do not appear to be additional safety concerns relating to the levels of formaldehyde that may result from administration of product containing formaldehyde at the levels proposed. Consequently it was agreed that the level of formaldehyde included in the product was acceptable.

There had been initial concerns related to whether the control parameters in place during production and on the finished product could ensure consistency of production. The Applicant/Marketing Authorisation Holder (MAH) had developed additional in-process tests to control antigen levels after inactivation. These tests (Modified Agglutination Test for APP and optical density at 540nm for PMA) had been validated, however further questions were raised concerning the link between the initial antigen levels before inactivation (CFU/ml for all components), the post inactivation specifications (MAT for APP and OD540nm for PM) and the serological potency assay. The Applicant/MAH had conducted further analysis and validation in support of the in-process and finished product testing specifications, which could be considered adequate, provided some points of clarification were adequately addressed.

There are two points for particular discussion, firstly that challenge has not been done with APP Serotype 11, and secondly that because efficacy of the *P.multocida* component is based principally on field data there are no information on the precise specifications of the batches used.

Concerning the absence of challenge with APP serotype 11, part of the applicant's view is that all three Apx groups are represented in the vaccine. The significance of toxigenic group is supported by the specific monograph (2008/1360) which states (Section 2.2.2 Immunogenicity) that "The challenge strain for the following test is chosen to ensure challenge with each Ap toxin produced by the serotypes to be stated on the label…". In view of the fact that Serotypes 9 and 11 belong to the same toxigenic group (Group 1, producing Apx1 and Apx2) and Serotype 2 belongs to Toxigenic Group 2, producing Apx2 and Apx3, then this Ph. Eur. requirement was considered met by challenge studies with serotype 2 and 9. The applicant has provided supporting opinions from EDQM and the Chairman of Group 15V which supports this interpretation.

Concerning the link to the efficacy of *P.multocida* the Applicant/MAH was requested to provide further information on the batches of vaccine used during the field studies and further clarification on the details of the studies sufficient to substantiate a claim for the efficacy of the *P.multocida* component. The data provided was not considered adequate to support a claim for the *P.multocida* component (discussed below) therefore a link between production parameters and efficacy for PMA could not be accepted.

Efficacy issues:

Specific challenge studies had not been conducted using APP serotype 11 as challenge, therefore Spain had requested confirmation of efficacy of the APP 11 component. It was noted that all three Apx toxigenic groups are represented in the vaccine. The significance of toxigenic group is supported by the specific monograph (2008/1360) which states (Section 2.2.2 Immunogenicity) that "The challenge strain for the following test is chosen to ensure challenge with each Ap toxin produced by the serotypes to be stated on the label…". In view of the fact that Serotypes 9 and 11 belong to the same toxigenic group (Group 1, producing Apx1 and Apx2) and Serotype 2 belongs to Toxigenic Group 2, producing Apx2 and Apx3, then this Ph. Eur. requirement was considered met by challenge studies with serotype 2 and 9. This opinion was supported by opinions gathered by the Applicant/MAH from EDQM and the Chairman of Group 15V.

It is considered that the principle requirements for the demonstration of efficacy are laid down by the Ph. Eur. Based on an interpretation of the specific monograph that is supported by EDQM it was considered that the applicant has met these requirements through the use of the challenge strains used. Additional information supporting the close antigenic relationship between APP Serotype 9 and 11 have also been presented. Therefore, in view of the fact that APPM Respipharm has met the efficacy requirements of the Ph.Eur. and considering the additional data in support of a close antigenic relationship between APP Serotypes 9 and 11 it is considered that a request for further challenge studies is not justified. In addition, it is considered that on animal welfare grounds, additional challenge studies with APP Serotype 11 are unnecessary and should not be requested.

Regarding justification of the *P. multocida* component in the vaccine the Applicant/MAH has provided field data from a surveillance study, supplemented with bibliographical data, to indicate that *P.multocida* causes frequent co-infections with APP in pigs with respiratory disease. In addition, field data have been accumulated comparing the clinical outcome in pigs with respiratory disease on farms where APP and *P.multocida* are simultaneously present, and which have been vaccinated with either APPM Respipharm or a competitor product incorporating APP only. The data have been collected over a number of years (at least 2004-2008) and included a total of 163,061 pigs, of which 93,460 had been vaccinated with APPM Respipharm, 37,541 had been treated with an APP vaccine without *P.multocida*, and 32,060 pigs had not been vaccinated. The analysis had looked at the frequency of mortality and lung confiscations at slaughter (indicative of the presence of lesions) caused by either APP or *P.multocida* in pigs vaccinated with APPM Respipharm. The justification to include the *P.multocida* component in the vaccine had been accepted by the Committee during the referral procedure.

The Note for Guidance on requirements for combined veterinary vaccines[2], states *"Deletion of challenges is only acceptable in rare cases and must be fully justified."*, and in addition Annex I to Directive 2001/82/EC as amended (Part 4 Efficacy tests, Field trials), which states that *"Where laboratory trials cannot be supportive of efficacy, the performance of field trials alone may be acceptable."*. The Applicant/MAH had justified the absence of specific challenge studies with *P.multocida* on the basis that there are recognised difficulties in conducting meaningful challenge studies. In addition, published literature was presented to support the view that *P.multocida* is involved in worsening of disease caused by APP. In principle the Applicant/MAH's justification for the absence of specific challenge studies was accepted. However, the committee had significant concerns related to the quality and validity of the field studies provided in support of the efficacy of P.multocida.

In view of the fact that the Applicant/MAH proposed to support the efficacy of the *P. multocida* component with data from the field the Applicant/MAH was requested to clarify whether animals vaccinated with APPM Respipharm, competitor vaccine and unvaccinated controls had been housed together on each site, which could have allowed a valid comparison of the efficacy of the respective vaccines. The Note for Guidance on field trials with veterinary vaccines[3] indicates "*The environment in which the two groups of animals are housed shall be as equivalent as possible (i.e. same farm/barn/batch) or at least as similar as possible (e.g. same farm/different barn/same batch)*." It was confirmed that according to the study protocol the groups of pigs vaccinated with the different vaccines had been housed at the same farm in different halls (barns) which is acceptable.

There were concerns as to how the results had been assessed, in particular how mortality and lung confiscations had been definitively assigned to *A.pleuropneumoniae*. or *P.multocida*. This was considered important as pathological changes caused by *P.multocida* are not specific for infection with this organism. The Applicant/MAH confirmed that the diagnosis was conducted by experienced veterinary practitioners based on previous clinical history and on post mortem findings in cases of mortality. The Applicant considers that the pathological changes seen in the lungs are different due to *Actinobacillus pleuropneumoniae* compared to *Pasteurella multocida*. This differentiation is based on identification of characteristic lesions by experienced veterinary staff at slaughterhouses. Whilst these lesions are not specific for the pathogen in question they provide a basis for differentiation in terms of the specificity of respiratory lesions which have different pathology and are supported in questionable cases by bacterial isolation. The frequency of isolations of each organism in unvaccinated pigs provided some indication of the prevalence of the agent at the site and, taken in association with experience of pathology, could be considered to provide some support for the classification process.

Furthermore, there was a need to clarify the relevance of the APPM Respipharm vaccine batch(es) used in the field studies. In particular the Applicant/MAH should clarify to what extent they could be considered to meet the criteria of minimum potency for *P.multocida*. The Applicant/MAH provided information on the antigen content of the batches of vaccine used in the field studies. Some of the field data presented by the Applicant/MAH confirmed that the antigen levels were in those studies at or below the antigen levels proposed as the product minima. However, in these particular studies a serological response was induced but a correlation between efficacy (clinical signs) and potency could not be shown. Concerning the surveillance field study the Applicant/MAH gave additional data about the batches used, which were by mistake omitted. According to the provided data only batches clearly above the minimum potency were used.

[2] CVMP Note for guidance: Requirements for combined veterinary vaccines - http://www.emea.europa.eu/pdfs/vet/iwp/005297en.pdf

[3] CVMP Note for guidance: Field trials with veterinary vaccines - http://www.emea.europa.eu/pdfs/vet/iwp/085299en.pdf

In view of the fact that the Applicant/MAH intended to demonstrate the efficacy of the PMA component by comparison of the efficacy of APPM Respipharm compared to comparator products there was a need to clarify the composition of the other vaccine (containing *A. pleuropneumoniae* only). In particular, it was requested to confirm that this vaccine covered the whole range of Apx toxins. The Applicant/MAH clarified the composition of the other comparator products and confirmed that they had been administered according to the recommended schedule. It was shown that all comparator products contain the same range of Apx antigens as the current product, therefore a comparison could be justified on this basis.

There were no details of the statistical methods used, nor were there full reports of the field trials. The Applicant/MAH provided the requested clarification, which confirmed the statistical analysis that had been applied. In addition, reports of the field studies were provided. However, whilst these provided more detailed information than had been previously available these were not sufficient to confirm the validity of the studies for the purposes of supporting a efficacy claim for *P.multocida*. It was noted by the Committee that the lack of compliance with the GCP requirements weakened the content of the surveillance study essentially. Notwithstanding the committees reservations concerning the deficiencies in the studies it was also noted that the Applicant/MAH had not provided data in support of the claimed onset and duration of protection for *P. multocida.*

The major point of refusal related to the lack of evidence to support the efficacy of the *P.multocida* component. The field data were deficient and it was not clear that the presence of PMA in the vaccine had any specific benefit. This was in part supported by the view that since *P.multocida* is a secondary infection that any possible benefits seen could equally well be attributed to a reduction of incidence of disease caused by the primary agent (*A.pleuropneumoniae*) afforded by vaccination against APP. In view of these facts the Committee concluded that the efficacy of the *P.multocida* serotype A component was not adequately demonstrated, therefore in the absence of any demonstrated benefit any risk-benefit analysis must necessarily be negative.

GROUNDS FOR REFUSAL OF THE GRANTING OF THE MARKETING AUTHORISATIONS SUSPENSION OF THE MARKETING AUTHORISATION

Whereas:

- the CVMP considered that there are significant deficiencies in the data provided by the Applicant in support of the efficacy of the *Pasteurella multocida* serotype A component.
- the CVMP considered that these deficiencies are such that it is considered that no data have been provided in support of the efficacy of the *P. multocida* serotype A component.
- consequently, the CVMP considered that in the absence of any demonstrated benefit of this component the risk-benefit analysis for the *P. multocida* serotype A component must be negative, therefore presenting an unacceptable serious risk to human or animal health or to the environment.

the CVMP has recommended the refusal of granting the Marketing Authorisations and the suspension of the existing Marketing Authorisation.

The conditions for lifting the suspension are set out in Annex III.

ANNEX III

CONDITIONS FOR THE LIFTING OF THE MARKETING AUTHORISATION SUSPENSION

The National Competent Authority of the Reference Member State, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holder:

The efficacy of the *P.multocida* component should be demonstrated through the provision of appropriate controlled studies clearly demonstrating that the presence of PMA in the vaccine has a specific benefit. The potency test for *P. multocida* should be able to distinguish potent and subpotent batches.