



MINISTERIO
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productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

DRAFT PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

ENTERICOLIX, emulsion for injection for pigs

CORREO ELECTRÓNICO

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HH_INF_PUB_001_001.docx

F-DMV-25-01

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0228/001/DC
Name, strength and pharmaceutical form	ENTERICOLIX, emulsion for injection for pigs
Applicant	CZ Veterinaria, S.A. P.O. Box 16 PORRIÑO (Pontevedra) SPAIN
Active substance(s)	<i>Escherichia coli</i> strain P4 inactivated (F6 adhesins), <i>Escherichia coli</i> strain P5 inactivated (F18ab adhesins), <i>Escherichia coli</i> strain P6 inactivated (F4ac adhesins), <i>Escherichia coli</i> strain P9 inactivated (F18ac adhesins), <i>Escherichia coli</i> strain P10 inactivated (F5 + F41 adhesins) beta toxoid of <i>Clostridium perfringens</i> Type C (CZV13)
ATC Vet code	QI09AB08
Target species	Pigs (sows and gilts)
Indication for use	<p>Vaccination of sows and gilts for the passive immunization of piglets against colibacillosis caused by enteropathogenic and enterotoxigenic <i>E. coli</i> strains expressing F4ac, F5, F6, F18ac and F41 adhesins, against oedema disease caused by <i>E. coli</i> strain expressing F18ab adhesin and against necrotic enteritis caused by <i>C. perfringens</i> type C.</p> <p><u>Neonatal piglets</u></p> <ul style="list-style-type: none"> - The vaccine reduces mortality and clinical signs (severe diarrhoea) due to colibacillosis. - The vaccine reduces mortality and clinical signs due to necrotic enteritis caused by <i>C. perfringens</i> type C. <p><u>Weaned piglets</u></p> <ul style="list-style-type: none"> - The vaccine reduces mortality and clinical signs due to oedema disease - The vaccine reduces clinical signs (severe diarrhoea) of colibacillosis



	<ul style="list-style-type: none">- The vaccine reduces clinical signs of chronic enteritis due to <i>C. perfringens</i> type C <p>Duration of immunity:</p> <ul style="list-style-type: none">- 21 days for infections caused by F4ac, F18ac, (colibacillosis) and <i>Clostridium perfringens</i> type C (necrotic enteritis)- 21 days for antibodies against F5, F6 and F41, however the protective efficacy of the antibody levels was not established- 28 days for infections caused by F18ab (oedema disease)
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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	Decentralised application in accordance with Article 12.1 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	27/01/2016
Date product first authorised in the Reference Member State (MRP only)	----
Concerned Member States for original procedure	RMS: ES CMS: AT, BE, BG, CY, CZ, DE, DK, EL, FR, HU, IE, IT, NL, PL, PT, RO, SI, SK, UK

I. SCIENTIFIC OVERVIEW

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

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 slight reactions observed are indicated in the SPC.

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

Active substances:

Escherichia coli strain P4 inactivated (F6 adhesins), ≥ 1 RP*
Escherichia coli strain P5 inactivated (F18ab adhesins), ≥ 1 RP *
Escherichia coli strain P6 inactivated (F4ac adhesins), ≥ 1 RP *
Escherichia coli strain P9 inactivated (F18ac adhesins), ≥ 1 RP*
Escherichia coli strain P10 inactivated (F5 + F41 adhesins), ≥ 1 RP*
beta toxoid of *Clostridium perfringens* type C (CZV13) ≥ 10 IU** of β
antitoxin/ml of rabbit serum

*RP: Relative potency for each antigen according to a reference vaccine with satisfactory result in the immunogenicity test (Ph. Eur. monograph 0962)

**IU: International units of beta toxin (Ph. Eur. monograph 0363)

Adjuvant:

Light mineral oil
Montanide 103
Sorbitan oleate

Excipients:

Thiomersal

The container/closure system is a multi-dose high-density polyethylene bottle of 50 ml (25 doses) with a perforable nitrile rubber stopper and aluminium seal. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the adjuvants, vaccine strains, formulation, inactivating agent and the presence of preservative are justified.

The inactivation process and the detection limit of the control of inactivation are correctly validated.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

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.

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



C. Control of Starting Materials

The active substances are *E. coli* and *C. perfringens* type C, an established active substances described in the European Pharmacopoeia. The active substances are 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 guideline.

Starting materials of non-biological origin used in production comply with indicate pharmacopoeia monographs or in-house specifications.

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. and Guidelines; any deviation was adequately justified.

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

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.

E. Control tests during production

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

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



The demonstration of the batch to batch consistency is based on the results of 3 batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

G. Stability

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

The in-use shelf-life of the broached vaccine is supported by the data provided.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life: 1 year

In use shelf life: 10 hours

Store and transport refrigerated (2°C – 8°C). Protect from light. Do not freeze.



III. SAFETY ASSESSMENT

Laboratory trials

A series of GLP safety laboratory trials were carried out in the target species, being the vaccine batches employed in these trials representative of the production process detailed in the registration dossier.

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal as well as the safety of the administration of a booster dose was demonstrated. The trials were performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

The results obtained in these trials were included in the SPC, in section 4.6 Adverse reactions, as follows: "A transient increase in body temperature (maximum 2°C) can be observed between 4-24 hours after vaccination, this event is very common. Temperatures return to normal values within 24–48 hours. The vaccine can produce short term apathy between 1 and 2 days post-vaccination, this event is common. Apathy may last for up to 7 days after vaccination, however this event is uncommon."

Safety of the administration of one dose and repeated administration of one dose

The objective of this study was to determine the safety in pregnant sows after intramuscular administration of two standard doses of 2 ml, following the recommended vaccination schedule and was carried out in accordance with the safety test detailed in monograph 0962 of Eur. Ph. The acceptance criteria of Eur. Ph. monograph 04/2013:0962 "Neonatal piglet colibacillosis vaccine (inactivated)" and monograph 04/2013:0363 "Clostridium perfringens vaccine for veterinary use" were met, ie: none of the gilts showed abnormal local or systemic reactions or death as a result of the vaccination, the mean increase in the temperature of all gilts does not exceed 1.5°C and no animal showed an individual increase higher than 2.0°C. No adverse effects on gestation or offspring were detected.

Safety of the administration of a booster dose

The safety of the administration of a booster dose 4 weeks before farrowing in sows vaccinated with 2 doses in their previous gestation period was demonstrated. No abnormal or systemic reactions were observed after the administration of the two standard doses, nor after the administration of the third dose. In addition, the administration of the two doses and a third dose, did not affect gestation or cause abortigenic or teratogenic effects nor induced significant increases in the number of animals born weak or dead, nor did it affect survival of piglets

Safety of the administration of an overdose and repeated administration of one dose

The objective of this study was to assess the safety in gestating gilts of administering a double dose followed by a standard dose according to Eur. Ph. monograph 01/2008:0962. To achieve this objective, pregnant gilts previously unvaccinated against *E.coli* were divided into two treatment groups (vaccinated and control). The vaccinated group received a double dose 7 weeks before farrowing and a second standard dose 21 days later.



The double dose did not cause any adverse local or systemic effects excepting for a temperature increase that it is detailed in section 4.10 of the SPC . It didn't affect gestation or cause abortifacant or teratogenic effects, or affected survival of piglets after birth.

Results obtained in this study were included in section 4.10 of the SPC as follows: "After administration of a double vaccine dose, a slightly higher transient temperature increase may be observed compared to that after a single vaccine dose (e.g. temperature increase of up to 2.5 °C after a double dose)"

Examination of reproductive performance

This was studied as part of the trials detailed above under headings "Safety of the administration *one dose and repeated administration of one dose*" and "Safety of the administration of an overdose and repeated administration of one dose". Evidence from the field study – see below- is also provided in respect of the reproductive safety. It is concluded that the use of **ENTERICOLIX** is safe to pregnant sows and the health and performance of their offspring. The following wording is included in the SPC: "the vaccine can be used during pregnancy. The vaccine should not be given in the 4 week period before the expected farrowing date".

Immunological functions

No adverse effects on immunological functions are foreseen after the administration of such inactivated bacterial vaccine.

In addition to this, the immune response was studied in several trials and it was observed that the immunisation of pregnant gilts induced a systemic immune response, with the production of high levels of specific antibodies against all *E. coli* fimbria. The statistical differences in the mean serum titres between vaccinated and control gilts were detected at 21 days after the first dose, at farrowing and in colostrum, which permitted the transference of passive immunity to piglets in the first hours of life, detectable when 24 hours of age, which remained elevated at 21 days of age.

Vaccination with **ENTERICOLIX** also induced a high specific humoral response against β -toxin of *C. perfringens* and therefore the high titres in colostrum also permitted the transference of passive immunity to piglets in the first hours of life, at 24 hours of life and these titres remained elevated at 21 days of age.

Additionally, revaccination of sows previously vaccinated in their first gestation showed a strong humoral response at second parturition and the mean titres detected in colostrum were significantly higher for the vaccine antigens. Also piglets born from revaccinated sows showed significantly higher serum titres than those born from non revaccinated dams.

Special requirements for attenuated vaccines

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

User safety

The vaccine is administered by IM injection in the target species by syringe from sealed plastic containers. Since antigenic components of the vaccine are fully inactivated by validated processes in accordance with GMP, these bacteria/toxoid do



not represent a hazard to the user. The vaccine excipients include the adjuvants, marcol oil, montanide 103 and sorbitan oleate. Accidental self-injection by the user is a recognized hazard when vaccinating animals and therefore an appropriate warning is included in the SPC in relation to this. ENTERICOLIX is safe for the user provided that explicit instructions on the product leaflet in relation to hazard of self-injection are followed.

Study of residues

All excipients used in the manufacturing of the vaccine require no maximum residue limit as set out in Regulation 37/2010/EU. Based on this information, no withdrawal period is proposed.

Interactions

No specific assessment of the interaction of this product with other medicinal product was made. Therefore, an appropriate warning in the SPC is included.

Field studies

The main objective of this trial was to evaluate the safety and efficacy under field conditions of **ENTERICOLIX** against diarrhoeal processes in suckling pigs produced by enteropathogenic/enterotoxigenic (ETEC) *E coli* and *C. perfringens* type C.

The trial was conducted in three gestation sites on a single farm with a history of diarrhoeal processes against ETEC *E coli* and necrotic enteritis. The trial was blinded, stratified and with 2 uniform treatment groups: nulliparous pregnant gilts vaccinated and non-vaccinated. The vaccinates received a single 2 ml dose of **ENTERICOLIX** im, 7 weeks before farrowing and a second dose 4 weeks before farrowing. Non-vaccinates were injected in the same way with PBS at the same times. The vaccine batch was representative of the manufacturing process detailed in the registration dossier.

Under field conditions, intramuscular administration of two doses of **ENTERICOLIX** showed to be safe. No local adverse effects at the injection site nor serious systemic adverse reactions were observed – only a short term apathy-. Neither, adverse effects on gestation or on offspring were observed. Further to this, no animal showed a temperature increase higher than 2°C and the mean increase did not exceed 1.5°C.

Results obtained in the above study were included in section 4.6 of the SPC as follows: “A transient increase in body temperature (maximum 2°C) can be observed between 4–24 hours after vaccination, this event is very common. Temperatures return to normal values within 24–48 hours. The vaccine can produce short term apathy between 1 and 2 days post-vaccination, this event is common. Apathy may last for up to 7 days after vaccination, however this event is uncommon”

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 no risk associated with the administration of **ENTERICOLIX** has been identified.





IV. EFFICACY

Laboratory Trials

The efficacy of the product has been demonstrated in several GLP challenge laboratory studies in accordance with the relevant requirements which show that vaccination of sows and gilts allows the passive immunization of piglets against colibacillosis caused by enteropathogenic and enterotoxigenic *E. coli* strains expressing F4ac, F5, F6, F18ac and F41 adhesins, against oedema disease caused by *E. coli* strain expressing F18ab adhesin and against necrotic enteritis caused by *C. perfringens* type C.

Neonatal piglets

- The vaccine reduces mortality and clinical signs (severe diarrhoea) due to colibacillosis.
- The vaccine reduces mortality and clinical signs due to necrotic enteritis caused by *C. perfringens* type C.

Weaned piglets

- The vaccine reduces mortality and clinical signs due to oedema disease
- The vaccine reduces clinical signs (severe diarrhoea) of colibacillosis
- The vaccine reduces clinical signs of chronic enteritis due to *C. perfringens* type C

Duration of immunity:

- 21 days for infections caused by F4ac, F18ac, (colibacillosis) and *Clostridium perfringens* type C (necrotic enteritis)
- 21 days for antibodies against F5, F6 and F41, however the protective efficacy of the antibody levels was not established
- 28 days for infections caused by F18ab (oedema disease).

Challenge strains were fully characterized and experimental infection models were developed to be applied during the performance of the laboratory studies. Vaccine batches representative of the manufacturing process were employed in all studies and the estimation of antibody levels was carried out using validated methods for all *E. coli* fimbria as well as for *C. perfringens* type C beta toxin. Only animals that do not have antibodies against the vaccine antigens to be assessed were selected for these studies.

Studies in support of *E. coli* antigens claim

Neonatal piglets

The vaccine reduces mortality and clinical signs (severe diarrhoea) due to colibacillosis as it was observed in the studies detailed below.

Two studies were carried out following the recommendations of the Eur. Ph monograph 04/2013:0962 "Neonatal piglet colibacillosis vaccine (inactivated)" and met the immunogenicity test requirements in relation to the minimum number of piglets challenged for each inocula and treatment group and in relation to the experimental



challenge. The control piglets showed mortality $\geq 40\%$ and morbidity $\geq 85\%$ for adhesins F6, F4ac and morbidity $\geq 70\%$ for F5, F18ac and F41.

A significant reduction in mortality and severity of clinical signs after challenge was observed in the piglets born to vaccinated dams, in comparison with the piglets from unvaccinated control mothers for all the inoculated *E. coli* strains. Furthermore, a significant higher body weight was observed on day 8 p.i. in the vaccinated piglets.

In addition to this, the vaccine induced a significant serology response against F4ac, F5, F6, F18ac, F18ab, F41 and β -toxoid, and a negative correlation was found between serum titres in piglets at 24 h after farrowing and clinical scores.

Weaned piglets

The vaccine reduces mortality and clinical signs due to oedema disease (STEC-F18ab strain) as detailed in the challenge laboratory study carried out to assess the efficacy and immunogenicity of **ENTERICOLIX** in weaned piglets. Results showed a significant reduction in mortality and clinical signs due to oedema disease after challenge 28 days in piglets from vaccinated gilts compared with the group of piglets from the unvaccinated controls. The test was considered valid since more than 60% of the control piglets developed clinical signs (Bosworth *et al.* 1996; Cornick *et al.*, 2000).

The serological status of the selected piglets was also assessed against F4ac, F5, F6, F18ac, F18ab, F41 and β -toxoid after parturition, at weaning (21 days) and before infection (28 days) and a significant immune response was found.

In addition to this, the vaccine also reduces clinical signs (severe diarrhoea) of colibacillosis as demonstrated in two further challenge laboratory studies that were carried out to assess the duration of the immunity (d.o.i.) against the development of the clinical signs caused by *E. coli* F4ac and *E. coli* F18ac respectively in weaned piglets (21 days old). For this purpose, an infection model of *E. coli* ETEC expressing F4ac fimbria and expressing F18ac fimbria in weaned piglets were developed. A significant reduction in the colibacillosis clinical signs (severe diarrhoea) was demonstrated in vaccinated animals in comparison with controls at 21 days of life. A negative significant correlation between serum titres and clinical signs was found for both fimbrias.

In addition to this, the immunological response was also estimated in sows, and in piglets during the post weaning period, against F5, F6, F41, F18ab and beta toxin.

Studies in support of *C. perfringens* type C claim

Neonatal piglets

Two studies were carried out following the recommendations of the Eur. Ph monograph 04/2013:0363 "*Clostridium perfringens* vaccine for veterinary use" to assess the efficacy of **ENTERICOLIX** against the necrotic enteritis caused by *C. perfringens* type C in neonatal piglets by experimental challenge. Unvaccinated pregnant sows seronegative against *C. perfringens* beta toxoid were selected and randomly divided in two treatment groups. Vaccinated group was subjected to 2 standard doses of **ENTERICOLIX** and the controls group was injected with PBS. After parturition and after colostrum intake, piglets



born to vaccinated sows and piglets born to control sows were randomly selected and experimentally challenged with a virulent *C. perfringens* type C by oral route

After challenge, all the piglets were daily observed during 8 days after infection (d.p.i.) and the development of clinical signs was scored. The test was considered valid if at least 65% of the control piglets developed clinical signs (N.E. and/or diarrhoea) and at least 35% died caused by the experimental challenge. Clinical scores, mortality and morbidity were statistically compared between treatment groups at the end of the study.

Results demonstrated that, the vaccine reduces mortality and clinical signs due to necrotic enteritis caused by *C. perfringens* type C.

A significant serology response was induced by the vaccine and it was demonstrated that a negative significant correlation was found between serum titres in piglets at 24 h after farrowing and clinical signs.

Weaned piglets

A challenge laboratory study was carried out to assess the duration of the immunity against the development of the clinical signs caused by *C. perfringens* type C in weaned piglets (21 days old, 3 days after weaning). For this purpose, an infection model of *C. perfringens* type C in weaned piglets was developed. A significant reduction in clinical signs of chronic enteritis was demonstrated in vaccinated animals in comparison with controls at 21 days of life. In addition to this the serological response was estimated using validated methods and a negative significant correlation between serum titres and clinical signs was found for both fimbrias.

Duration of the immunity

Duration of immunity:

- 21 days for infections caused by F4ac, F18ac (colibacillosis) and *Clostridium perfringens* type C (necrotic enteritis) was demonstrated as detailed in the studies detailed under headings “weaned piglets” for *E. coli* and *C. perfringens* type claims.
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- 21 days for antibodies against F5, F6 and F41 was demonstrated as detailed in previous sections. However the protective efficacy of the antibody levels was not established.
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- 28 days for infections caused by F18ab (oedema disease) was demonstrated as detailed under heading “weaned piglets” for *E. coli* claim.
- The administration of a third dose (booster dose) was fully supported in subsequent gestation periods by the study carried out to estimate the immunogenicity by serological assessment. Revaccination of sows previously vaccinated in their first gestation induced a strong humoral response at second parturition in comparison with non-revaccinated sows for all vaccine antigens. The mean titres detected in colostrum of the revaccinated sows were significantly higher for the entire antigen tested and either piglets born from



revaccinated sows showed significantly higher serum titres than those born from non revaccinated dams.

Field Trials

The main objective the trial was to evaluate the safety and efficacy under field conditions of **ENTERICOLIX** against diarrhoeal processes in suckling pigs produced by enteropathogenic/enterotoxigenic (EPEC) *E coli* and *C. perfringens* type C.

The trial was conducted in three gestation sites on a single farm with a history of diarrhoeal processes against EPEC *E coli* and necrotic enteritis. The trial was blinded, stratified and with 2 uniform treatment groups: nulliparous pregnant gilts vaccinated and non-vaccinated groups. The vaccinates, received a single 2 ml dose of **ENTERICOLIX** im, 7 weeks before farrowing and a second dose 4 weeks before farrowing. Non-vaccinates were injected in the same way with PBS at the same times. The vaccine batch was representative of the manufacturing process detailed in the registration dossier.

The results showed that the vaccination of gilts were associated with a significant reduction in the clinical signs due to colibacillosis and mortality

The vaccine also induced a significant humoral response in vaccinated sows, colostrum and piglets born to vaccinated dams.



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.

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>

or

Complete this section for extensions to the same VPA range or defined, significant variations, using the table shown below.

Some examples of significant changes in safety or efficacy data are:

- *Changes to pharmacokinetic data leading to a change in the SPC*
- *Changes to toxicological data leading to a change in the SPC*
- *Changes to user safety warnings*
- *Changes to ecotoxicological information as given in the SPC or changes to disposal warnings*
- *New residue studies in new target species or tissues*
- *Reassessment of residue data or new studies resulting from changes to MRL*
- *Changes to withdrawal period*
- *Changes to target species*
- *Changes to target species tolerance data leading to change in warnings/precautions for target species*
- *New or changed indications*

Significant changes in administrative or quality data include any Type II change, which affects the initial report. The following Type IA or IB changes may also apply:

- *Name of product [Type IA: 2]*
- *Name of active substance [Type IA: 3]*
- *MAH [Type IA: 1]*
- *Composition of the medicinal product [Type IB: 18, Type IA/B: 25, 34, 35, 39]*
- *Container/closure system [Type 1/B: 26, 28, 29, 36, 41, 43]*
- *Method of preparation [Type 1B: 33]*
- *Active substance specification [Type IB: 25]*
- *CEP [Type IA/B: 15]*
- *Re-test period or storage conditions of active substance [Type IB: 17]*
- *Excipient specifications [Type 1A/B: 25]*
- *Packaging materials [Type 1A/B: 28, 29, 36, 41, 43]*
- *TSE [Type 1A: 16, 22]*
- *Shelf-life or storage conditions of the finished product [Type 1B: 42]*



Quality changes

Summary of change (Application number)	Section updated in Module 3	Approval date
<Example: Change to active substance specification> (MS/V/XXX/X/IB/XX)	N/A	

Safety/efficacy changes

Summary of change (Type; application number)	Section updated in Module 3	Approval date
<Example: Addition of target species - pigs> (MS/V/XXX/X/II/XX)	<IIIA> <IIIB> <IV>	