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Veterinary Medicines Division

## Committee for Veterinary Medicinal Products (CVMP)

# CVMP assessment report for Poulvac E. coli (EMEA/V/C/002007/II/0018)

Vaccine common name: Avian colibacillosis vaccine (live)

**Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted**

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# 1. Introduction

## *1.1. Submission of the variation application*

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Zoetis Belgium SA (the applicant), submitted to the European Medicines Agency (the Agency) on 1 March 2021 an application for a type II variation for Poulvac E. coli.

## *1.2. Scope of the variation*

| **Variation(s) requested** | | **Type** |
|---|---|---|
| C.I.4 | Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | II |

To adjust the SPC section 4.7 to highlight that safety of Poulvac E. coli has been demonstrated when administered to chickens during lay.

## *1.3. Changes to the dossier held by the European Medicines Agency*

This application relates to the following sections of the current dossier held by the Agency:

Part 1 and Part 3.

## *1.4. Scientific advice*

Not applicable.

## *1.5. MUMS/limited market status*

Not applicable.

# 2. Scientific Overview

The applicant would like to adjust section 4.7 of the SPC by deleting the exclusion of laying hens (and hens within 6 weeks before the onset of lay) from vaccination with Poulvac E. coli. Furthermore, changes of sections 4.1 and 4.2 of the SPC are proposed to reflect the inclusion of layers for vaccination.

The variation is applied for because of a strong demand to use the vaccine in layers in the face of changing husbandry conditions of laying hens (restricted use cages) and efforts to reduce the use of antibiotic treatment in poultry industry.

Safety

The applicant has presented two GLP compliant, randomised, negatively controlled, blinded laboratory overdose safety studies in SPF laying hens; the second study was performed for further investigation of the safety of the vaccine in layers, since it could not be excluded that some mild findings in necropsied animals of the first study are related to vaccination.

The above-mentioned findings in necropsy in the first study were not reproduced in the second study, indicating that lesions were not related to vaccination in the first study either.

Furthermore, it can be stated that both laboratory safety studies confirmed normal egg laying performance and absence of clinical signs in vaccinated hens with approximately 10-times the maximum dose of Poulvac E. coli.

Another aspect for using the vaccine in layers is the consumer safety, if the vaccine strain is excreted by laying birds and contaminates eggs for human consumption. According to the current SPC, the vaccine strain can be excreted 28 days after vaccination (studies were performed with day-old SPF birds) and can be found in the environment after 5 weeks. Accordingly, the applicant has presented further data on spreading after vaccination of laying hens.

Data on possible recovery of the vaccine strain from the intestinal tract of vaccinated chickens as well as on or in eggs are not presented in a format generally considered adequate for initial applications or variations. Instead of a complete study report, the applicant has presented a summary of a field study, where layer parents were vaccinated with Poulvac E. coli under field conditions. Nevertheless, taking into account that there seems to be a severe and urgent demand to use the vaccine in layers, the publication as a format may be exceptionally accepted and has been assessed accordingly.

No excretion of the vaccine strain could be detected in presented studies, neither in the intestinal tract of laying birds, nor in or on eggs at 3 or 7 days after vaccination. The discrepancy between findings of the new study and the studies in SPF animals provided for the initial registration of the product may be due to differences in several parameters. One major factor among them possibly is the titre used for vaccination (dependency of excretion on the titre was observed in initial studies), which is of the range applicable for commercial batches and may have been too low to initiate detectable excretion. Accordingly, the excretion after vaccination of layers and subsequent contamination of eggs cannot be excluded, based on the data in the provided field study.

However, this possible low contamination after vaccination stands against a probably much higher contamination by natural *E. coli* infection of the laying hens if they stay unvaccinated, or any negative impact by the use of antibiotics instead of vaccination.

As mentioned in the field study, the vaccine strain belongs to multilocus sequence type 23, which already has been isolated in humans. This concern was addressed by the applicant by providing an updated human consumer risk assessment taking into account the additional route of human exposure via contaminated eggs. Several aspects including the auxotrophic, non-zoonotic nature of the vaccine strain, potential sources of faecal contamination of the eggshell at lay and contamination of the reproductive tract and/or egg content, the probability of egg contamination and additional processing which could potentially eliminate contaminating *E. coli* were considered. Strict biosecurity measures as usual in commercial egg production farms serve as additional risk mitigation with respect to reduced transmission to humans.

Additionally, the applicant provided a study report investigating the tenacity of Poulvac E. coli on the surface of embryonated chicken eggs. The eggshell of eggs at 17th day of incubation in this experiment has been 'on ovo' inoculated Poulvac E. coli each. The amount used is considered much higher than the amounts of vaccine *E. coli* that is expected to shed through the faeces. During incubation, the titres on the shell dropped below the detection limit within 29 hours and no *E. coli* was detected in the foetus 1 hour after incubation.

Furthermore, the lack of vertical transmission of the vaccine strain is further supported by a preliminary non-GLP compliant study. The objective of this study was to investigate the dissemination of Poulvac E. coli vaccine strain in eggs, when administered to layers at a 10X

overdose and to evaluate the egg laying performance. A total of ten SPF laying hens at an age of 42 weeks were included in the study. All the chickens were vaccinated by ocular route with an overdose (10X) of Poulvac E. coli. Before vaccination (D0) and at D4, D7 and D14 egg's swabs and contact plates of the eggs were taken and a bacteriological analysis was performed to determine vaccine *E. coli* strain presence. Chickens were observed daily for clinical signs until the end of the study. Two chickens died, one on day 9 and another on day 25 due to reason not related with Poulvac E. coli vaccination (cloacal prolapse). Poulvac E. coli vaccine strain was not isolated from any eggshell up to 14 days post vaccination and was not isolated from the content of eggs laid on D4 post vaccination. No clinical signs were observed, the eggs laid after vaccination had a good quality, and the egg laying performance was normal.

In conclusion, taken all results from the original data and from the supplementary information together and bearing in mind the auxotrophic properties of the attenuated, non-zoonotic vaccine strain, the risk of Poulvac E. coli vaccine strain being a potential disease-causing agent for humans or acting as reservoir for the virulence-associated genes is very low. Based on the data provided, there is no indication for changing the currently registered withdrawal period of zero days, when the vaccine is administered to chickens during lay as recommended.

A severe impact on egg production and body condition was indicated in two cases (pharmacovigilance data). A detailed assessment of the two cases was provided. Based on that, no safety concern regarding laying performance could be concluded.

The statement regarding the demonstrated safety in laying chickens is as follows:

*"The safety of Poulvac E. coli has been demonstrated when administered to chickens during lay at one dose by both coarse spray and drinking water administration. However, the efficacy of Poulvac E. coli has not been demonstrated when administered to chickens during lay. A decision to use this vaccine in chickens during lay should be made on a case by case basis.*

*The safety of Poulvac E. coli has not been investigated in turkeys during lay. Do not use in turkeys in lay and within 6 weeks before the start of the laying period."*

Although the safety of the vaccine when administered to chickens during lay via coarse spray has not been demonstrated either in laboratory or in a field safety study, the wording is considered acceptable as in the safety studies provided the vaccine was given by eye drop to ensure the administration of the full dose. This route of administration is considered as a 'worst case' scenario for both recommended routes, drinking water and coarse spray.

Efficacy

Regarding the aspect of efficacy, it should be pointed out that no supportive efficacy data were provided. The absence of such data might be considered acceptable but needs to be clearly reflected in the SPC.

Although efficacy was consistently demonstrated for the initial registration of the vaccine for chickens vaccinated with one dose at one day of age by coarse spray and with variation EMEA/V/C/002007/II/0006 for chickens administered one dose of vaccine from 5 days of age by drinking water, the efficacy results obtained from those studies cannot be regarded to automatically apply for adult laying hens. Efficacy in laying hens will, more than in very young animals, depend on factors such as level of antibody titres, gained by natural exposure to *E. coli* strains, general immune and health status, as well as housing and keeping conditions. In addition, the changes to come into lay and to keep up laying may lead to a significantly lower efficacy of the vaccine in layers than in the youngest animals chosen for demonstration of the currently authorised routes of administration.

Taking the absence of specific efficacy data for laying birds into account, the applicant proposes to indicate under section 4.7 that the efficacy of Poulvac E. coli has not been demonstrated when administered to chickens during lay and that the decision to use the vaccine during this period should be made on a case by case basis.

Beside of the change in SPC section 4.7, the applicant has applied for changes of sections 4.1 and 4.2 of the SPC to reflect the inclusion of layers for vaccination. The proposed target species 'chickens' without mentioning of any sub-category would imply that the full indication as well as the onset and duration of immunity are valid for all sub-categories, including layers. Those expectations need to be substantiated by supportive data, which are not presented with this variation. Therefore, the proposed changes for sections 4.1 and 4.2 of the SPC are not considered acceptable. Consequently, the applied changes have not been implemented and the currently authorised wording 'Chickens (broilers, future layers/breeders)' has been retained.

In summary, based on the original and complementary data presented in this variation the product is well tolerated by laying hens and presents an acceptable risk for users, the environment and consumers when used as recommended, i.e. one dose administered via coarse spray or by drinking water administration.

However, with respect to pharmacovigilance aspects it is recommended to monitor the incidence in layers in Europe closely following approval of the variation. The results should be discussed by the applicant/MAH with the next yearly signal detection report.

# 3. Benefit-risk assessment of the proposed change

This product is a lyophilisate for suspension for spray vaccination or for use in drinking water authorised for active immunisation of broiler chickens, future layers/breeders and turkeys in order to reduce mortality and lesions (pericarditis, perihepatitis, airsacculitis) associated with *Escherichia coli* serotype O78. The active substance is live aroA gene-deleted *Escherichia coli*, type O78, strain EC34195. Chickens are given one dose of vaccine from 1 day of age by coarse spray administration or one dose of vaccine from 5 days of age by drinking water administration. Turkeys are given one dose of vaccine from 1 day of age followed by a second dose of vaccine 3 weeks later by coarse spray administration. The withdrawal period is zero days.

The applicant would like to adjust section 4.7 of the SPC by deleting the exclusion of laying hens (and hens 6 weeks apart from the onset of lay) from vaccination with Poulvac E. coli. Furthermore, changes of sections 4.1 and 4.2 of the SPC are proposed to reflect the inclusion of layers for vaccination.

The variation is applied for because of a strong demand to use the vaccine in layers in the face of changing husbandry conditions of laying hens (restricted use of cages) and efforts to reduce the use of antibiotic treatment in poultry industry.

Laboratory safety studies confirmed normal egg laying performance and absence of clinical signs in hens vaccinated with approximately 10-times maximum dose of Poulvac E. coli.

According to the current SPC, the vaccine strain can be excreted for 28 days after vaccination (studies were performed with day-old SPF birds) and can be found after 5 weeks in the environment.

Therefore, the applicant provided an updated human consumer risk assessment taking into account the additional route of human exposure via contaminated eggs. Several aspects including the auxotrophic, non-zoonotic nature of the vaccine strain, potential sources of faecal contamination of

the eggshell at lay and contamination of the reproductive tract and/or egg content, the probability of egg contamination and additional processing, which could potentially eliminate contaminating *E. coli* were considered. Strict biosecurity measures as usual in commercial egg production farms serve as additional risk mitigation with respect to reduced transmission to humans. In addition, two further studies investigating the tenacity of Poulvac E. coli on the surface of embryonated chicken eggs and demonstrating the lack of vertical transmission of the vaccine strain were provided.

In conclusion, taken all results from the original data and from the supplementary information together and bearing in mind the auxotrophic properties of the attenuated, non-zoonotic vaccine strain, the risk of Poulvac E. coli vaccine strain being a potential disease-causing agent for humans or acting as reservoir for the virulence-associated genes is very low. Based on the data provided, there is no indication for changing the currently registered withdrawal period of zero days, when the vaccine is administered to chickens during lay as recommended.

Regarding the aspect of efficacy, it should be pointed out that no supportive efficacy data were provided. Consequently, the proposed changes for sections 4.1 and 4.2 of the SPC (omission of the sub-categories broilers, future layers/breeders) have not been implemented and the currently approved wording is retained.

## *3.1. Benefit assessment*

The use of the vaccine in layers can reduce antibiotic treatment in laying hens, reduce contamination of eggs via naturally occurring *E. coli* strains and lead to a better health status and laying performance of vaccinated flocks. However, as long as no efficacy data are available, the benefit is restricted to the safety aspects only.

### Direct therapeutic benefit

The safety of the product is expanded to layers.

## *3.2. Risk assessment*

### Quality:

The quality of the product is not affected by the variation.

### Safety:

Safety, including user safety and environmental safety remains unaffected by this variation. Target animal safety is affected by this variation. However, the safety of Poulvac E. coli has been demonstrated when administered to chickens during lay at one dose, by both coarse spray and drinking water administration. Laboratory safety studies confirmed normal egg laying performance and absence of clinical signs in hens vaccinated with approximately 10-times maximum dose of Poulvac E. coli.

Consumer safety might by affected by the variation but, bearing in mind the auxotrophic and non-zoonotic nature of the vaccine strain, the risk of Poulvac E. coli being a potential disease-causing agent for humans or acting as reservoir for the virulence associated genes is very low. Egg

processing and strict biosecurity measures in commercial husbandry systems serve as additional risk mitigation with respect to reduced transmission to humans.

In summary, based on the original and complementary data presented in this variation, the product is well tolerated by laying hens and presents an acceptable risk for users, the environment and consumers when used as recommended, i.e. one dose administered via coarse spray or by drinking water administration. The current information given under 'Special precautions of use' (SPC section 4.5) provides the user with clear advice on how to use the product.

However, with respect to pharmacovigilance aspects it is recommended to monitor closely the incidence in layers in Europe following approval of the variation. The results should be discussed by the applicant/MAH with the next yearly signal detection report.

### Efficacy

No supportive efficacy data were provided. Therefore, changes proposed for sections 4.1 and 4.2 of the SPC are not considered acceptable and consequently they had not been implemented. The absence of efficacy data for laying hens is properly noted in section 4.7 of the SPC.

## *3.3. Evaluation of the benefit-risk balance*

No change to the impact of the product is envisaged on the following aspects: quality, safety, user safety, environmental safety, consumer safety, target animal safety. The absence of efficacy data has been adequately addressed in section 4.7 of the SPC.

Based on the data presented, the overall benefit-risk remains positive.

The product is well tolerated by laying hens and presents an acceptable risk for users, the environment and consumers when used as recommended, i.e. one dose administered via coarse spray or by drinking water administration.

Appropriate precautionary measures already included in the SPC and other product information are applicable for the vaccination of laying hens, too.

# 4. Conclusion

Based on the original and complementary data presented on safety, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Poulvac E. coli can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows:

- to adjust the SPC section 4.7 to highlight that safety of Poulvac E. coli has been demonstrated when administered to chickens during lay.

However, the following proposed changes have not been sufficiently supported by efficacy data and, therefore, have not been accepted:

- proposed changes of sections 4.1 and 4.2 of the SPC to reflect the inclusion of layers for vaccination.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above-mentioned medicinal product.

With respect to pharmacovigilance aspects it is recommended to closely monitor the incidence in layers in Europe following approval of the variation. The results should be discussed by the applicant/MAH with the next yearly signal detection report.

Changes are required in the following Annexes to the Community marketing authorisation:

I and IIIB

As a consequence of this variation, section 4.7 of the SPC is updated. The corresponding section 12 of the Package Leaflet is updated accordingly.