# Divergent position on a CVMP opinion on a referral under Article 82 of Regulation (EU) 2019/6

## Veterinary medicinal products containing procaine benzylpenicillin as a single active substance presented as suspensions for injection

## Procedure EMEA/V/A/145

The undersigned has a divergent position on the CVMP opinion on the maximum treatment duration of products concerned by this referral procedure, for the reasons outlined below:

The extension of the maximum treatment period to 7 days for all indications, all target animal species and all veterinary medicinal products (VMPs) included in this referral is not considered necessary or scientifically justified. It is also my belief that recital 22 should be taken into account in article 82 referrals, and that the arguments of involved marketing authorisation holders should be considered fully during referral procedures.

The objection is based on the following.

**No scientific support for a general extension of the maximum treatment duration to 7 days**

No serious risk has been identified by the CVMP to justify a blanket extension of the maximum treatment period for all species and all indications. Please see 'General comments' to further elaborate this issue.

No clinical studies have been presented with the VMPs included in this referral where the treatment period was longer than 5 days.

No relevant literature has been presented whereby a blanket extension of the treatment duration to 7 days could be supported.

A general principle of penicillin treatment for 3-5 days has been applied in Finland for decades. This principle together with a restrictive antibiotic policy has resulted in an overall very good resistance situation in pathogens isolated from food producing animals (Finnish Veterinary Antimicrobial Resistance Monitoring and Consumption of Antimicrobial Agents 2021 https://www.ruokavirasto.fi/globalassets/viljelijat/elaintenpito/elainten-laakitseminen/antibioottiresistenssin_seuranta/finnish_food_authority_publications_6_2022_finres_vet_2021.pdf). Almost 50% (47 % in 2022) of all antibiotic treatments in animals consist of injectable penicillin. There is no signal that the approved treatment length of 3-5 days is too short.

Anecdotal reports and general statements that penicillin only works in Germany when given for 7 days cannot replace robust scientific evidence. It seems that this procedure has its main driver in Regulation (EU) 2019/6 article 106(1), the strict interpretation of which would seemingly prevent use of the concerned VMPs in individual animals for more than 5 days.

Several marketing authorisation holders for the concerned VMPs have provided information that a treatment period of 7 days is seldom needed and not justified scientifically. This further supports currently approved maximum treatment duration of most products included in this referral.

**Risks related to a harmonised maximum treatment period of 7 days**

A general principle applied to the marketing authorisations of VMPs for food-producing animals is that the residue depletion studies should be performed with the maximum treatment duration. This principle has been followed in most dossiers. In this referral procedure no clinical studies with a longer treatment duration than 5 days were presented, and the maximum treatment duration used in residue depletion studies for meat and offal as well as for milk was five consecutive days.

It is agreed with the CVMP that the current withdrawal periods should be considered safe for the currently authorised posology. This is also supported by the fact that no signals have been reported to EU Member States of major penicillin residue violations in food stuffs following use of procaine benzylpenicillin containing VMPs as currently authorised. The current withdrawal periods shall remain unchanged when the currently authorised treatment periods are used.

However, the extended treatment duration to seven days set for all VMPs concerned by this referral procedure is not adequately covered by the available residue depletion studies to ensure the consumer safety related to a treatment period of more than 5 days. As the VMPs in this referral are off-patent and residue withdrawal period studies are costly, there is a real risk that some MAHs may decide to withdraw the MA of their VMP in case additional residue data is requested. This constitutes a serious risk for decreased availability that would hinder prudent and responsible use of antibiotics based on the first line treatment with an AMEG category D antibiotic, procaine benzylpenicillin. This would also jeopardize the national antibiotic policy in Finland, which relies heavily on the use of this category D narrow spectrum antibiotic. Additionally, the requirement for new residue depletion studies would not be according to the 3R's principles.

The CVMP approach to find a pragmatic solution to ensure consumer safety is acknowledged and appreciated. However, the proposed blanket addition of 2 days for edible tissues to adjust the withdrawal periods for an extension of treatment duration does not have a solid scientific justification. No residue depletion studies for milk with a treatment period more than 5 days have been presented and a confirmation is lacking regarding the consumer safety in keeping the same milk withdrawal periods for a 7-day treatment. Milk MRL violations always have tremendous economic consequences for the farmers and cases where the 7-day treatment period and other provisions of the SPC would have been followed might have even bigger consequences as described in the divergent position of Dr Nepejchalová.

On the other hand, an addition of high safety factors for withdrawal periods for edible tissues and milk could lead to the situation where treatment with penicillin is not an economically feasible choice compared to a higher AMEG category antibiotic with a shorter withdrawal period.

It is concluded that no consumer safety risk has been identified with the current posology. Therefore, withdrawal periods shall remain unchanged, when the currently approved posology is used. Withdrawal periods for longer treatment durations should be defined with scientifically agreed principles. However, measures that could lead to the risk of losing currently authorised critical products or promote use of higher AMEG category products instead of penicillin, should be avoided.

General comments

In addition to the divergent position on CVMP's scientific conclusion on this referral I want to present the following regulatory concern:

With a reference to the CVMP discussions during this procedure an evident challenge is pointed out in the interpretation of Article 82 of the Regulation (EU) 2019/6: The Article 82 itself states that "*Where the interests of the Union are involved, and in particular the **interests of public or animal health or of the environment related to the quality, safety or efficacy** of veterinary medicinal products, the marketing authorisation holder, one or more of the competent authorities in one or more Member States or the Commission may refer its **concern** to the Agency for the application of the procedure laid down in Article 83. The matter of concern shall be clearly identified.*"

On the other hand recital (22) states: "*Where a Member State, the Commission or the marketing authorisation holder considers that there are reasons to believe that a veterinary medicinal product could present a **potential serious risk to human or animal health or to the environment**, a scientific evaluation of the product should be undertaken at Union level, leading to a single decision on the area of disagreement, binding on the relevant Member States, and taken on the basis of an overall benefit-risk assessment.*"

According to recital (22) a serious risk is a prerequisite for a Union Interest Referral. My opinion is that where Article 82 does not have enough detail, the spirit of the article should be interpreted based on the recital. According to the Joint Practical Guide of the European Parliament, the Council and the Commission for persons involved in the drafting of European Union legislation "The purpose of the recitals is to set out concise reasons for the chief provisions of the enacting terms…"

As a consistent and legally coherent interpretation of Article 82 and recital (22) have a direct bearing on the legal position of the MAHs, it is considered that further guidance about the prerequisites for Article 82 referrals would be necessary to the competent authorities and to MAHs and would ensure transparent procedures that follow accepted legal principles.

Amsterdam, 7 September 2023

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