EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Need for MRL evaluation for biological substances

Veterinary Info Day SMEs

Presented by Sebastien Girault on 28 October 2021

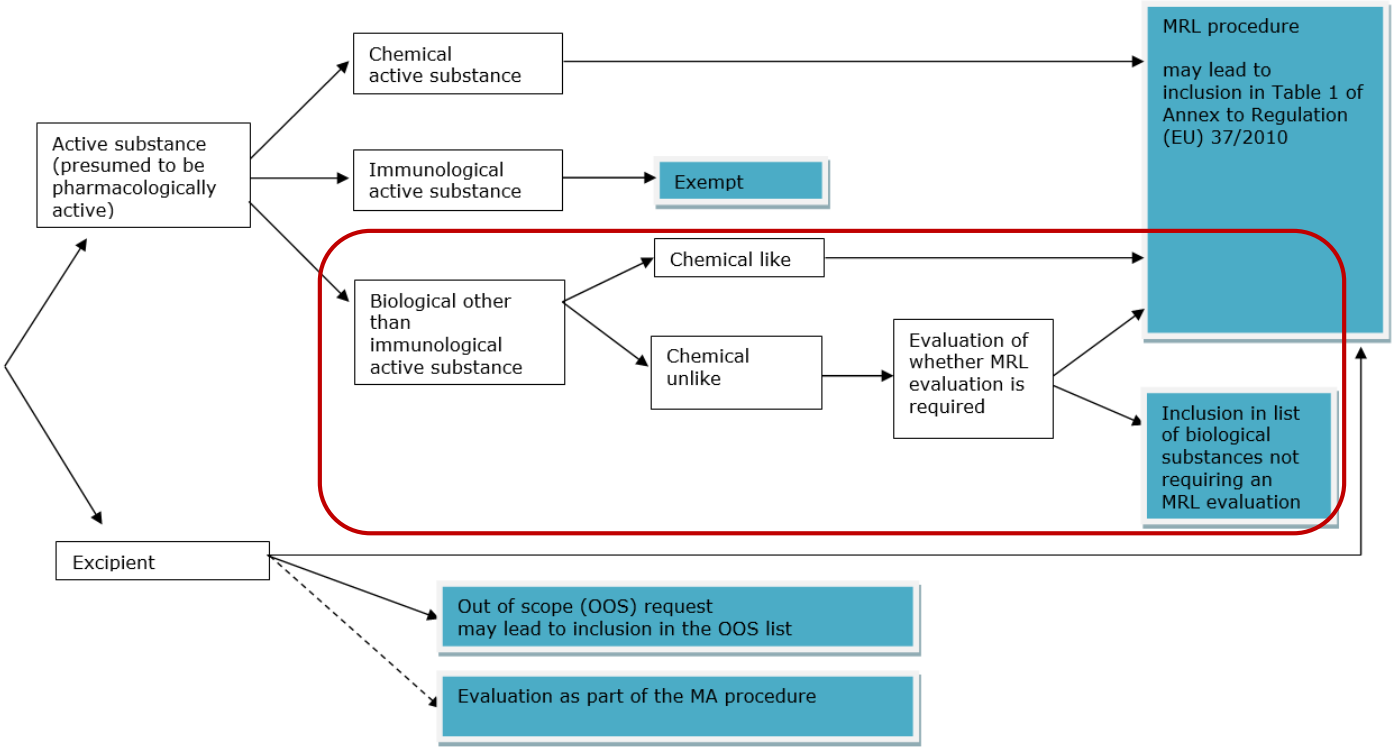
Context

- VMPs for food producing animals: pharmacologically active substances need to be allowed regarding MRLs (except "active principles of biological origin intended to produce active or passive immunity or to diagnose a state of immunity, used in immunological VMPs" as stated in 1(2)(a) of Regulation 470/2009)

- The standard MRL procedure has been used for both 'chemical' and biological (non-immunological) substances: Table 1 of Annex to Regulation 37/2010 includes biological substances.

  - However, there was a need for a lighter procedure to be used for some biological substances

Ways to address the MRL status



Legal basis: Regulation 2018/782 (I.6 and I.7 of Annex I)

30.5.2018 EN Official Journal of the European Union L 132/5

COMMISSION REGULATION (EU) 2018/782

of 29 May 2018

establishing the methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) No 470/2009

Legal basis: Regulation 2018/782 (I.6 and I.7 of Annex I)

I.6. Biological substances other than those identified in Article 1(2)(a) of Regulation (EC) No 470/2009 of the European Parliament and of the Council [1] shall be:

(a) subject to a normal MRL where the biological substance is chemical-like insofar as it could be produced by chemical synthesis and so presents similar concerns to chemical substances and can be expected to leave residues in the same way as chemical substances (e.g. cytokines, hormones);

(b) evaluated on a case-by-case basis where the biological substance is chemical-unlike insofar as being more complex than chemically synthesised pharmacologically active substances and so may contain multiple chemical types whose residues may generally be cells, amino acids, lipids, carbohydrates, nucleic acids and their breakdown products.

Legal basis: Regulation 2018/782 (I.6 and I.7 of Annex I)

I.7. For chemical-unlike biological substances, a report describing the scientific basis for the request on whether a full MRL evaluation is required or not shall be required together with the following information:

(a) the nature of the biological substance (e.g. cell, tissue, live or killed organism) and a comparison with similar biological substances to which consumers are known to be routinely exposed;

(b) a description of the mechanism of action underlying the substances therapeutic effect and, if available, information on its potency;

(c) the fate of the substance in the treated animal (i.e. is it bioavailable, are residues expected in food commodities);

(d) any activity that the substance may have in the human gut (are the residues inactive or do they produce local effects);

(e) the systemic availability of residues following ingestion of residues by consumers, along with a worst case consumer exposure estimate.

Legal basis: Regulation 2018/782 (I.6 and I.7 of Annex I)

I.7.

The information provided above shall be evaluated in accordance with the guidance published by the European Medicines Agency ('Agency') in order to determine whether there is the need for a MRL evaluation. Biological substances for which it is concluded that a MRL evaluation is not required shall be published by the Agency in a list of such substances.

List on EMA website

EUROPEAN MEDICINES AGENCY
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10 December 2020
EMA/CVMP/572629/2019–Rev.1
Committee for Medicinal Products for Veterinary Use

Biological substances considered as not requiring an MRL evaluation as per Regulation (EU) No. 2018/782, with regard to residues of veterinary medicinal products in foodstuffs of animal origin

1. Background information

[…]

List on EMA website

2. Biological substances considered as not requiring an MRL evaluation as per Regulation (EU) No. 2018/782

Bovine casein hydrolysate (bCNH), produced from sodium caseinate hydrolysed with trypsin, heat treated, for intramammary use in cows

Probiotic components including bacteria and yeasts

Recombinant bovine IL-8 (His-tag) for intrauterine use in cattle at a dose of up to 1,000 µg per animal[i]

Stem cells

[i] Entry adopted at the December 2020 CVMP plenary meeting

Administrative process in place

- Applicant to notify EMA that they intend to apply
- Application: report and supporting documents explaining the scientific basis of the request, along the points in I.7 of Annex I to Regulation 2018/782
- Fee established (see Explanatory note on general fees payable to the European Medicines Agency)
- Evaluation by CVMP in 60 days /90 days (if LoQ) timetable
- Where CVMP concludes that no MRL evaluation is necessary:
    - Opportunity for applicant to comment re CCI on the wording to be published (entry in the list, summary of assessment)
    - Publication of the updated list of biological substances and of the summary of assessment

Next steps: towards a scientific guideline

- "Guideline on determination of the need for an MRL evaluation for biological substances"
- Objectives of the guideline
  - Provide a structured approach on how to determine the need for an MRL evaluation for these biological substances
  - Clarify some terms (e.g. chemical-like/unlike)
- Concept paper: public consultation completed 15 July - 30 September 2021
- Guideline: currently under development, public consultation on the draft guideline planned in January – April 2022

EMA webpage on MRLs

Biological substances not requiring an MRL evaluation

Biological substances other than active principles of biological origin used in immunological veterinary medicines can be either 'chemical-like' or chemical-unlike'.

'Chemical-like' substances present similar concerns to chemical substances and are subject to a full MRL assessment.

'Chemical-unlike' substances are more complex substances that may contain multiple chemical types whose residues can be cells, amino acids, lipids, carbohydrates, nucleic acids and their breakdown products. The CVMP decides on a case-by-case basis whether 'chemical-unlike' substances require a full MRL assessment.

For full details, see Annex I.6 of Commission Regulation (EU) 2018/782.

Applicants who consider that a biological substance is 'chemical-unlike' can submit an application to vet.applications@ema.europa.eu for the CVMP to evaluate the need for an MRL assessment.

The application should include a report and supporting information explaining the **scientific basis** for the request. It should also address the points in Annex I.7 of Commission Regulation (EU) 2018/782.

Applicants should notify EMA that they intend to apply at least two months before submitting their application, by emailing the following information to vet.applications@ema.europa.eu:

- active substance;
- intended use;
- target species;
- intended submission date.

The evaluation has a:

- 60-day timetable if the CVMP does not require further information from the applicant;
- 90-day timetable if the CVMP requires further information from the applicant and adopts a list of questions.

EMA charges a fee for evaluating the application. It invoices the fee to the applicant's address after it has validated the application.

When the outcome of the assessment is that the biological substance does not require a full MRL evaluation, EMA publishes a summary of the CVMP's assessment and includes the substance in the following list:

Biological substances considered as not requiring an MRL evaluation as per Regulation (EU) No. 2018/782, with regard to residues of veterinary medicinal products in foodstuffs of animal origin (PDF/102.24 KB)

First published: 29/05/2020
Last updated: 17/12/2020
EMA/CVMP/572629/2019 Rev. 1

Summaries of CVMP assessments to determine whether a substance may be included in the list of biological substances considered as not requiring an MRL evaluation

Bovine casein hydrolysate : Summary of assessment undertaken to determine whether the substance may be entered into the list of biological substances considered as not requiring an MRL evaluation (PDF/123.84 KB)

Adopted

First published: 29/05/2020
EMA/2278/2020

Recombinant bovine IL-8: Summary of assessment undertaken to determine whether the substance may be entered into the list of biological substances considered as not requiring an MRL evaluation (PDF/166.86 KB)

Adopted

First published: 01/02/2021
EMA/CVMP/608257/2020

Conclusion

- New procedure, lighter than full MRL evaluation (dossier, timetable), better fit than standard MRL procedure to some biological substances. No impact on immunological active substances (still exempt).
- Administrative process in place
- First assessments completed
- Information available on EMA website
- Scientific guideline under development

Any questions?

Further information

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