Federal Office of Consumer Protection and Food Safety

Focus group meeting on bacteriophages as veterinary medicines

Part 3: Safety documentation

Federal Office of Consumer Protection and Food Safety

Guideline on quality, safety and efficacy of veterinary medicinal products specifically designed for phage therapy

Safety Part

4.3. Safety documentation – general considerations

documentation shall be presented in accordance with **Annex II of Regulation (EU) 2019/6**

CVMP and VICH guidelines are applicable

- requirements may be adapted if scientifically justified **and** based on the required specific product properties
- risks should be proactively identified  taking into account the quality risk management approaches.
- If, safety risks cannot be excluded control/mitigation measures can be applied

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Safety Part

4.3. Safety documentation – Food producing animals

- withdrawal period(s) should be established (even when withdrawal period is zero) → specific for formulation and dosing regimen

- MRLs status shall be considered in accordance with Regulation (EC) No 470/2009 in advance
  - for active substance(s) and excipient(s)
  - For the concerned species
  - for relevant tissues or products
- EMA should be consulted for the need for an MRL evaluation

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Safety Part

4.3. Safety documentation – Food producing animals

- Two positive outcomes of the MRL assessment will be anticipated:
  1. The inclusion of the substance(s) in the list of (chemical-unlike) biological substances considered as not requiring an MRL evaluation following Annex I of Regulation (EU) No. 2018/782, with regard to residues of veterinary medicinal products in foodstuffs of animal origin.
  2. The inclusion of the substance(s) in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin.

- Excipients can either be included in Regulation (EU) No 37/2010 or in the list of "Substances considered as not falling within the scope of regulation (EC) No 470/2009 with regard to residues of veterinary medicinal products in foodstuffs of animal origin" (EMA/CVMP/519714/2009)

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Safety Part

IIIa.3A. Safety tests

should address user safety, environmental risk assessment and partially target animal safety

Annex II of Regulation (EU) 2019/6, chapter IIIa is applicable

- For TAS study details → efficacy chapter
- Studies (including toxicology and special studies) could be carried out with representative monophage or multiphage preparations
- representative phage preparation should represent worst case scenarios in terms of safety concerns
  - E.g., contain the maximum amount of protein content in any phage combination,
  - or the maximum number of monophage in multiphage preparations

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Safety Part

IIIa.3A. Safety tests

- Extrapolation between
  - comparable strains of bacteriophages,
  - (target animal) species,
  - different route of administrations
- may be possible based on representative/validated *in vitro* or *in vivo* parameters or in well justified cases, based on scientific justification for respective safety studies

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Safety Part

IIIa.3A1. Precise identification of the product and of its active substance(s)

Requirements in Annex II of Regulation (EU) 2019/6 for this point might not be adequate

- The identification of the active substance(s) should be tailored for biological (viruses) entities and based on the requirements for identification used in quality part.
- The formulation of the product should be in line with point 2.A.1. (Qualitative and quantitative composition)

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Safety Part

IIIa.3A2. Pharmacology

necessary to provide pharmacological data for the bacteriophage VMP to characterize mechanism of action and pharmacodynamics relevant for the safety evaluation

- absence of studies in laboratory animals could be justified by reference to existing data and data from target animal species studies

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Safety Part

IIIa.3A2. Pharmacology

conventional ADME studies may not be appropriate/possible

- pharmacological data necessary for the safety could be drawn from studies in the target animal species submitted in part 4 of the dossier, provided that these have been adequately designed to address this evaluation
- information should be provided concerning
  - the absorption from the site of administration
  - dissemination to other anatomical locations
  - expected degradation pathways

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Safety Part

IIIa.3A2. Pharmacology

- situations when the product will be used in target animals without active bacterial infection and when the product will be used for treatment in target animals with presence of the host bacteria of the bacteriophage strain(s)
- data should be derived from appropriate sources
  - e.g., dedicated PK/PD studies,
  - in vitro models,
  - pilot efficacy studies,
  - or a combination of these
- Due to the novel and complex nature of phage products, it is not possible to provide guidance beyond the general principles outlined above

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Safety Part

IIIa.3A3. Toxicology

no mechanism-based concern for toxicity in target animals or humans

- potential presence of microbiological contamination in bacteriophage products, e.g. endotoxins or exotoxins is considered a safety concern
- the control of these aspects is an essential element of the manufacturing process
- in agreement with 3R principles, single-dose toxicity, repeated dose toxicity, and effects on reproduction and developmental toxicity can be addressed by
  - a satisfactorily controlled manufacturing process
  - target animal safety studies (preclinical or clinical)
  - literature data according to the current state of science
- if a specific safety concern is identified, supplementary studies should be submitted

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Safety Part

IIIa.3A3. Toxicology

no direct interaction with DNA or chromosomes expected

no influence on eukaryotic cell proliferation or immunosuppressive effects expected

- for biologics, the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable → standard battery of genotoxicity test can be omitted
- carcinogenicity studies most likely be omitted

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Safety Part

IIIa.3A4. Other requirements

IIIa.3A4.1. Special studies (immunogenicity, immunotoxicity, neurotoxicity, endocrine dysfunction)

- Concerning potential immunogenicity and immunotoxicity of bacteriophage products.
- This risk could be assessed by
  - data from target animal studies,
  - combined with the proposed posology
  - existing knowledge on immunogenicity and immunotoxicity of phages
- For VMPs for which skin and eye exposure may occur, the general requirements in Annex II of Regulation (EU) 2019/6 apply

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Safety Part

IIIa.3A4. Other requirements

IIIa.3A4.2. Development of resistance and related risk in humans

- Direct risk form Bacteriophages for humans unlikely → specific studies might be omitted if appropriately justified
- Over time bacteria most likely develop resistance to bacteriophages. The applicant should reflect upon the risk of developing/spreading resistance in the environment and the related risks to humans associated with the use of the product

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IIIa.3A5. User safety

no specific guidance on user safety is available for biological products other than immunologicals

- to derive appropriate warnings or other risk management measures, general principles on user safety assessment lined out in GL EMA/CVMP/543/03-Rev.1 (hazard identification and characterisation, exposure assessment and risk assessment) should apply to phage products when required.
- The information obtained from the assessment of hazard identification and exposure will be considered for the risk characterisation.
- In cases where no information on dose response relationship is available, a qualitative risk characterisation might be sufficient.

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Safety Part

IIIa.3A6. Environmental risk assessment

IIIa.3A6.1. Environmental risk assessment of veterinary medicinal products not containing or consisting of genetically modified organisms

- Bacteriophages used as VMPs enter the environment either by direct excretion or by application of manure to agricultural land.
- Only limited research has been conducted on anthropogenically released bacteriophages that are non-native to their receiving environments.
- uncertainties about the fate and effects of such bacteriophages in the environment exist

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Safety Part

IIIa.3A6. Environmental risk assessment

IIIa.3A6.1. Environmental risk assessment of veterinary medicinal products not containing or consisting of genetically modified organisms

- Experimental studies indicate that changes in the microbial community composition with effects on the natural ecosystem function are to be expected (Meaden S et al. 2013; Kowalska JD et al. 2020),
- Applicants should reflect upon the environmental impact to soil bacteria and soil function associated with the use of the product.
- The performance of studies in accordance with OECD test guidelines might be required, such as OECD GL 216
- Genetically modified bacteriophages need to be additionally assessed like genetically modified organisms according to IIIa.3A6.2.

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Post marketing authorisation changes

General remarks

Annex II of Regulation (EU) 2019/6 recognizes that phage products will likely need to be updated on a regular basis

- assessment and authorisation of updated phage products can be streamlined → based on some studies conducted with the parental product, **combined with other relevant data** which may have been generated during the commercial lifespan of the parental product
  - improved understanding of commercial-scale manufacturing processes,
  - pharmacovigilance data,
  - supplementary scientific knowledge, to enhance the impact on the quality, safety and efficacy
- the scientific standards for data supporting product updates are the same: it should be demonstrated that the proposed product update will have the intended effect (restored efficacy) without negatively impacting on the quality, safety, efficacy and traceability of the product.

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Post marketing authorisation changes

General remarks

it is not possible to specify exact data requirements for product updates

Recommended to consult with the Agency on a case-by-case basis

- If the results from the risk assessment and initial comparability studies indicate relevant differences between monophage components and/or products, additional studies on quality, safety and efficacy may be required to document comparability
- If comparability of quality, safety and efficacy cannot be concluded based on *in vitro* studies, documentation of safety and efficacy of the updated product by *in vivo* studies in target animal species will be usually required

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Post marketing authorisation changes

Safety documentation – simple updates

Addition of a monophage component which is comparable to a component which is authorised with the marketing authorisation application

- If monophage components are comparable, safety studies are not expected to be required (post-authorisation changes expected to be approvable based on quality data alone)
- In the same line, user and environmental risk assessment is not expected to be required
- It is advised to consult the EMA for the need of a MRL status

Guideline on quality, safety and efficacy of veterinary medicinal products specifically designed for phage therapy

Post marketing authorisation changes

Safety documentation – complex updates

Addition of one or more new monophage components which are not comparable to a component which is authorised with the marketing authorisation application

- If the impurity profile of the product is not substantially worsened, safety studies might not be required
- In high level of complexity or lack of alternative evidence, safety data may be required
- New user risk assessment and environmental risk assessment might be needed
- It is advised to consult the EMA for the need of an MRL

Thank you for your attention!