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3 Committee for Medicinal Products for Veterinary Use (CVMP)

4 Monoclonal antibodies for veterinary use: specific 5 questions to be addressed by ADVENT

6 Draft

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Background

Monoclonal antibodies (mAbs) are immunoglobulins (Ig) with a defined specificity derived from a single clone of cells. Their biological activities are characterised by a specific binding characteristic to an antigen and may be dependent on immune effector function such as antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

Monoclonal antibodies may be generated by recombinant DNA (rDNA) technology, hybridoma technology, B lymphocyte immortalisation or other technologies (e.g. genetically engineered animals).

The range of clinical indications with potential for treatment with mAbs is very wide. Currently, in human medicine, a number are authorised for use as anti-cancer medicines and in medicines against diseases affecting the immune system, such as rheumatoid arthritis.

To date, the CVMP and its Scientific Advice Working Party (SAWP-V) have addressed a limited number of scientific advice requests concerning mAb products. This activity indicates that mAbs for use as veterinary medicinal products are in development.

Following a review of the scientific advice provided by CVMP relating to mAbs, ADVENT identified a number of areas that would benefit from further consideration by relevant experts and, where appropriate, the elaboration of specific guidance in the form of question and answer (Q&A).

Three specific questions for further consideration have been identified by ADVENT relating to quality and safety aspects. These questions, together with a brief comment outlining the background to each question, are presented below.

Questions

Quality

Characterisation / specification setting: Specifications should be set and take into account relevant quality attributes identified in characterisation studies. When it comes to the setting of specifications for monoclonal antibodies (mAbs) for veterinary use, the Veterinary International Conference on Harmonisation (VICH) GL 40 could/should be taken into consideration as a basic document which is in general relevant for biological/biotechnological substances and related finished products. To address the specificities of mAbs for veterinary use, in the absence of any veterinary specific guidance, applicants could be advised to consider the CHMP Guideline on production and quality control of monoclonal antibodies and related substances, (EMEA/CHMP/BWP/157653/2007), specifically the sections relating to identity, purity and impurities, and potency, and the provisions of the Ph.Eur. general monograph on human mAbs for quantity and standard tests 01/2012: 2031.

Question: For the characterisation/setting of specifications for mAbs, is currently available guidance appropriate and sufficient for mAbs intended for veterinary use?

If no, and it is considered that there would be benefit in elaborating specific guidance, what would be considered appropriate requirements for mAbs for veterinary use?

Safety

Target animal safety: Target animal safety tests should include an evaluation of potential risks to the target species under the proposed conditions of use. For mAbs, the safety evaluation should also

include an investigation of immunogenic potential and effects on immune function or other indirect effects. For example, eliciting effects due to direct/indirect interactions with the antigen or related antigens at the target site(s) or non-target site(s) (when considering a mAb directed at a specific target, it is possible that the target is expressed in tissues other than the tissue of interest with the potential for unwanted treatment-related effects in tissues other than the tissue of interest). While certain parameters can be evaluated in the context of conventional target animal safety studies (haematology, tissue histopathology, bone marrow evaluation, lymphocyte populations), there is no clear guidance on the approach to or the required extent of evaluation of indirect effects.

Question: In the context of safety of mAbs for the target animal, what data need to be generated to characterise the potential for indirect effects:

- Adverse effects on the immune and other physiological systems,
- Effects due to interaction of the mAb with the target antigen at non-target site(s), or
- Effects due to interaction of the mAb with related antigens at the target/non-target site(s)?

For functional rather than histopathological/lesional abnormalities, would it be considered sufficient, in general, to rely on clinical findings in a well conducted target animal safety study or should more specific investigations be conducted?

Reproductive safety: In accordance with existing veterinary guidance, reproductive safety studies are required for systemically absorbed pharmaceuticals or immunologicals when data suggest that the starting material from which the product is derived may be a risk factor intended for use in breeding animals (VICH GL 43 and VICH GL 44, respectively). The goal of reproductive safety studies is to identify any adverse effects of the VMP on male or female reproduction or on offspring viability. A number of mAbs developed for use in humans are known to have (potential) effects on fertility and foetal development.

Question: Should an applicant wish to develop a mAb for use in breeding/pregnant animals, what safety data would be considered adequate to characterise the risk (or confirm the absence of a risk)?