European Medicines Agency
Veterinary Medicines and Inspections

London, 22 September 2008
EMEA/CVMP/439633/2007

CLARIFICATION NOTE ON THE REQUIREMENTS FOR THE STARTING MATERIALS OF BIOLOGICAL ORIGIN

Position of the problem

In March 2006, the CMD(v) published the position paper CMD(v)/POS/001 on "Requirements For Starting Material Of Biological Origin", supporting the need for the Marketing Authorisation Holder (MAH) to declare the geographical origin of starting materials of biological origin. In October 2006 IFAH-Europe informally expressed concerns on this position at an Interested Parties meeting with the CMD(v), on the basis that it would lead to a significant increase in the number of variations needed to maintain products on the market.

In January 2007, at the CDMv-Interested Parties meeting the CMD(v) reported that the they had considered IFAH-Europe's feedback but the requirement could not be relaxed due to the relevant statements in the Annex of Directive 2001/82. On March 2007, IFAH-Europe sent a letter to the CVMP Chairman formally re-iterating their concerns on the CMDv Position Paper and requesting that the issue is resolved at CVMP and European Commission level, given its scientific nature and major regulatory implications.

IFAH-Europe raised a number of issues related to the scope of the CMD(v) Position Paper and challenge the interpretation of the requirements in Directive 2001/82/EC, as amended, and the European Pharmacopoeia. Specifically, clarification is sought as to biological vs. animal origin; the requirements for substances of milk origin; and, whether details of the origin are required for all substances of biological origin or only those that have not been subjected to a validated inactivation procedure.

In light of the issues raised by IFAH-Europe, the CVMP asked the IWP to consider how requirements in terms of traceability are best met i.e. through the marketing authorisation procedure, through GMP or through a combination of both.

Current legal requirements

In section C.2.1 "Starting materials of biological origin" of part 6 of Annex I of the Directive 2001/82/EC as amended, it is indicated :
"The origin and history of starting materials shall be described and documented" and "Information shall be provided on all substances of biological origin used at any stage in the manufacturing procedure. The information shall include : details of the source of the materials,…."

In chapter 5.2.5 of the Ph. Eur., it is indicated under "Requirements/Source" :
"The risk related to the animal diseases occurring in the country of origin of the substance and to the potential infectious diseases occurring in the source species, in relation to the proposed recipient species must be carefully evaluated."

The chapter 5.2.5 of Ph. Eur. is currently under revision. The revised draft will be published in the next issue of Pharmeuropa 19.4. It mentions two steps to guarantee the quality of the substances of animal origin: a risk assessment and a risk management.

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The risk assessment must take account of the animal diseases occurring in the country of origin of the animal used as a source of the substance. The risk assessment may need to be repeated and revised in order to take account of changes in the incidence of diseases occurring in the country or countries of origin of animals used as the source for the substance, including emerging disease (new pathogens).

For each of the potential extraneous agents identified by the risk assessment and taking into account the proposed use of the substance, the risk must be managed by using one or a combination of the followings:

- placing of restrictions on the source of the material and auditing this;
- using validated inactivation procedures;
- demonstrating the ability of a production step to remove or inactivate extraneous agents;
- testing for extraneous agents.

The control measures indicate that all substances of animal origin used in the manufacture of IVMP must be from a known and documented source (including species of origin, country of origin of source animals and tissue).

CVMP approach

From a practical point of view, the concern of IFAH about the impact of the addition or modification of the country of origin of a starting material has to be taken into account. In particular, the variation procedures as laid down in COMMISSION REGULATION (EC) No 1084/2003 of 3 June 2003 are not sufficiently flexible in this context, and would indeed lead to a non-manageable situation in practice.

Nevertheless, the goal is to have substances free of extraneous agents at disposal, and all measures intended to ensure freedom of extraneous agents have to be considered. This includes details of the geographic origin for substances of animal origin whatever the species of origin (bovine or not). As milk is included in the starting material of animal origin, the same type of data might be requested for this component.

In particular, the addition of a new country as source for a given substance can dramatically change the initial risk assessment, as the initial restrictions, the inactivation/removal procedures and/or the absence of testing for some extraneous agents (because these were exotic to the initial list of sourcing countries) might become insufficient or inadequate.

Conclusion

In order to guarantee the correct assessment of the quality of the immunological veterinary medicinal products, the details of the geographic origin and validated methods of inactivation for all starting materials of animal origin whatever the species of origin (bovine or not) or the tissue (milk included) have to be provided, unless it can be proven that the geographical origin of the substance has no impact on the risk assessment with regard to extraneous agents.

In particular, any change of the geographical origin for a substance of animal origin has to be declared, unless it was already proven in the initial dossier that the geographical origin of the substance has no impact on the risk assessment with regard to extraneous agents.

Further consideration still needs to be given to defining the most appropriate regulatory mechanism for ensuring adequate traceability of relevant materials used in veterinary medicinal products authorised at national and centralised level.