EDQM reflections on aspects of the current legal framework for veterinary medicines which merit review

ARTICLE 82 OF DIRECTIVE 2001/82/EC AS AMENDED BY 2004/28/EC (OCABR)

This article gives the possibility and sets the operating rules for independent laboratory control of batches of immunological veterinary medicinal products by Official Medicines Control Laboratories (OMCLs). The process is referred to commonly as Official Control Authority Batch Release (OCABR).

Current application in the EU – shared use of resources

Although the development and initiation of the codified application of article 82 through a balanced, risk-based approach was sometimes difficult, the system of OCABR, coupled with official batch protocol review (OBPR) based on application of article 81, is now being applied in a successful manner by many members of the OMCL Veterinary Batch Release Network (VBRN). Mutual recognition of both OCABR and OBPR is improving and expanding and the increased communication and cooperation between Member States is a testament to the importance the Member States give to this activity. Training sessions, both on an individual exchange level between OMCLs and on a larger scale as organised by EDQM in dedicated workshops, have also helped to ensure that all OMCLs work at the same high standard. In addition, the VBRN is dedicated to finding ways to reduce the use of animals in the context of OCABR and they were a major contributor to the development of an alternative assay for rabies vaccines (inactivated) for veterinary use. All of these practices are helping Member States to make best use of the resources in the EU while still providing a thorough surveillance of IVMPs lot to lot.

OCABR an important tool

The possibility to apply OCABR remains an important tool for regulatory authorities to monitor the quality of IVMPs. This can be attested by the fact that OMCLs continue to detect out of specification (OOS) lots that are submitted to control authorities via the OCABR and OBPR procedures. As such we would recommend that the possibility to perform independent testing on IVMPs be kept as part of the future legislation.

Areas for Improvement

Nevertheless there are some elements that could be improved which would help to streamline and reduce further the difficulties sometimes encountered with full mutual recognition of OCABR.
• **Common specifications for the same products in different Member States**

In particular, the differences in specifications for the same product in different Member States can be problematic. This is especially true for older products and can pose difficulties for both OBPR and OCABR. We note that the authorisation process and harmonisation of already authorised products are key points in your on-line survey. We would strongly encourage measures that help to harmonise the specifications for the same product in different Member States. A fully centralised procedure for new products could be a solution provided there are sufficient resources. It should of course remain possible for Member States to prohibit a product from their market due to specific animal health reasons and this would have to be built into the procedure. Accelerated harmonisation of older products would also be most welcome.

• **Access to up to date MA quality details for Member States/OMCLs**

It is very important that individual Member States and their OMCLs have rapid and full access to the details of marketing authorisation dossiers (at least the quality part) in order to correctly assess the manufacturers’ protocols for OCABR and OBPR and to carry out OCABR testing where relevant. Should there be a fully centralised procedure for authorisation (and variations) of veterinary medicines, a mechanism to ensure that Member States have access to this up to date information should be considered.

• **GMP and oversight**

It has been noted by network members that the manufacturers themselves seem sometimes unaware internally if batches have been submitted to more than one control authority. This coupled with the frequent errors (transcription/omissions) observed during protocol review and significant shortcomings in standard operating procedures provided to OMCLs by some manufacturers during method transfer suggests that more attention could be paid to their GMP systems. While it is not the goal to make the process heavier than it already is, a rigorous documentation of batch data and SOPs in a controlled QA environment is not an exaggerated requirement and we recommend that care be taken when re-evaluating the needs in this area.

• **Responsibility for single OCABR submission**

In general we feel that the main elements of article 82 are relevant and appropriate and should be maintained. It could however be considered to change the emphasis in paragraph 2; specifically in the second subparagraph. It should indeed be the responsibility of the competent authority to inform all others of its intention to control batches of a given product (as now noted in subparagraph 2 of section 2) and this could be noted in paragraph 1, however in paragraph 2 it should be made the responsibility of the manufacturer to ensure that they do not send a batch to more than one OMCL for review under article 82 as they should be the best placed to know this. If this were applied correctly it would reduce considerably the repeat evaluation of batches by authorities and ultimately reduce the delays to market for the manufacturer.
ENCOURAGING 3R (REDUCTION, REFINEMENT, REPLACEMENT) IN ANIMAL USE

As it appears that the authorisation procedure for veterinary medicines is under scrutiny during this consultation it would be a welcome step to consider how revisions to the procedure might encourage manufacturers to update their practices to more 3R friendly test methods. This is particularly relevant for the IVMP field where many of the potency assays used still require heavy animal use. Perhaps mechanisms could be built in which would provide incentive to apply for variations that would improve animal welfare.

Finally, we recognise the difference in environment between the human and veterinary field and the special difficulties faced by the veterinary industry which requires a different balance on the regulatory level in comparison to the counterparts in human medicines. We would however wish to plead caution against sweeping changes that could directly or indirectly weaken the requirements for safe, high quality veterinary medicines in the EU.
CENTRALLY AUTHORISED PRODUCTS (CAP)

Regulation (EC) No 726/2004 of the European Parliament and of the Council of the European Union lays down a centralised Community procedure for the authorisation of human and veterinary medicinal products - clearly defining the eligible products for this type of Marketing Authorisation - for which there is a single application, a single evaluation and a single authorisation allowing direct access to the single market of the Community (all EU/EEA Member States).

In order to control the quality of these products a coordinated approach became necessary. In June 1999, a contract governing an annual CAP Sampling & Testing Programme was signed by the European Medicines Agency (EMA) and the European Directorate for the Quality of Medicines & HealthCare (EDQM). The EMA is the sponsor and has overall responsibility of the programme; whereas the EDQM coordinates the sampling and testing operations performed by the EU/EEA national authorities. This includes reporting the results and proposing follow-up actions, if necessary, to the EMA.

Regulatory Background

According to Directive 2001/82/EC, Title 3, Chapter I, Article 12, paragraph 3 (i):

“The following particulars and documents shall accompany an application in accordance with Annex I: (…) description of the control testing methods employed by the manufacturer (qualitative and quantitative analysis of the constituents and the finished product, specific tests e.g. sterility tests, test for the presence of pyrogens, for the presence of heavy metals, stability tests, biological and toxicity tests, tests on intermediate products).”

In addition, in accordance with Directive 2001/82/EC, Annex I, as amended in Directive 2009/9/EC:

- For Veterinary Medicinal Products (VMP) other than Immunological Veterinary Medicinal Products (IVMP) (Directive 2009/9/EC, Annex I, Title I, Part 2):

“All test procedures shall fulfil the criteria for analysis and control of the quality of the starting materials and the finished product and should take account of established guidance and requirements. The results of the validation studies shall be provided.

All the test procedure(s) shall be described in sufficiently precise detail so as to be reproducible in control tests, carried out at the request of the competent authority; any special apparatus and equipment, which may be used shall be described in adequate detail, possibly accompanied by a diagram. The formulae of the laboratory reagents shall be supplemented, if necessary, by the method of preparation. In the case of test procedures included in the European Pharmacopoeia or the pharmacopoeia of a Member State, this description may be replaced by a detailed reference to the pharmacopoeia in question.”

“All test procedures shall fulfil the necessary criteria for analysis and control of the quality of the starting materials and the finished product and shall be validated procedures. The results of the validation studies shall be provided. Any special apparatus and equipment which may be used shall be described in adequate detail, possibly accompanied by a diagram. The formulae of the laboratory reagents shall be supplemented, if necessary, by the manufacturing method.

In the case of test procedures included in the European Pharmacopoeia or the pharmacopoeia of a Member State, this description may be replaced by a detailed reference to the pharmacopoeia in question.”

Nevertheless, in the guidance published by the European Commission in The rules governing medicinal products in the European Union, Volume 6 B, Notice to applicants, Veterinary medicinal Products, Presentation and Contents of the Dossier it is stated that:

• For VMP other than IVMP (Part 2 F – Control Tests of The Finished Product, 1.2 Control Methods) “1.2.1 Test procedures for identification and quantitative determination for the active substance(s) (...) must be described in detail (including biological and microbiological methods where relevant), together with other tests which include those in the appropriate general monograph for the type of dosage form in the European Pharmacopoeia(…)” should be provided;

• For IVMP (Part 2 F – Control Tests Of The Finished Product, Paragraph 1.4) a “Brief description of the test, including details of the samples used for the test (The detailed description of each test should be given in an annex to this part of the application dossier, together with the details and results of the validation studies, which have been undertaken.)” should be provided.

10 years of testing Veterinary Medicinal Products – EDQM experience

Since 1999, 61 Veterinary Medicinal products have been tested by national control laboratories (Official Medicines Control Laboratories Network) in accordance with the protocols established in the Marketing Authorisation (MA) dossiers, among which 24 Immunological Products (IVMP) and 37 Chemical Products (CVMP).
Figure 1 - Testing of Veterinary Medicinal Products within CAP programme

The 10 years experience of coordination of the annual CAP Testing Programme enables EDQM to highlight the issues most frequently encountered by the OMCLs involved in the testing. The outstanding problem when testing VMP, especially IVMPs, is the quality of the test procedures provided by the Marketing Authorisation Holders (MAH). Hereafter is an overview of the most frequently encountered issues:

- Unclear and/or insufficiently detailed description for carrying out the testing procedure;
- Level of detail not sufficient to perform method transfer, namely concerning System Suitability (SST) and Assay Acceptance criteria;
- Demonstration by actual testing that the method is not suitable for the intended purpose;
- Level of detail not sufficient to perform the necessary calculations, where applicable;
- Discrepancy between the specification and test procedures in the MAH dossier and MAH in-house Standard Operating Procedures.

As a result, OMCLs are often not in a position to be able to adequately control the quality of these products on the basis of the SOPs currently provided.

With respect to IVMPs, it should be noted that about 2/3 of the major issues encountered have required extensive work and exchange between involved partners to find a solution or were impossible to solve and required particular action. It should be noted that the causes for such issues are mainly connected to the MAH method and SST criteria sections. This reflects the conclusions presented in CAP individual product reports transmitted to EMA, where the poor quality of the SOPs provided by the MAH was regularly highlighted.
In extreme cases, these issues have resulted in concerns regarding the final results provided by the testing OMCLs, as it becomes unclear whether the quality of the product (confirmed OOS) is compromised / reliable or whether it is the information provided by the MAH in the dossier that is inaccurate / incomplete / misleading.

**Areas for Improvement**

The requirements concerning the level of detail required for test procedures for IVMPs and non-IVMPs should at least be similar. Comprehensive procedures should be established allowing any independent laboratory to perform the testing without any assistance from the MAH. Furthermore, it should be clearly stated that suitable SST criteria should be part of these test procedures.

In particular, the guidance published by the European Commission in *The rules governing medicinal products in the European Union, Volume 6 B, Notice to applicants, Veterinary medicinal products, Presentation and Contents of the Dossier* should be harmonised with the Directives in force.

Despite the modification of the wording specifically referring to the quality of the test procedures in *Directive 2009/9 EC*, the following reference still exists “test procedures shall fulfil the necessary criteria for analysis and control”. This wording is open to interpretation and therefore it is the regulators responsibility to define and clarify the level of these “necessary” criteria since Marketing Authorisation files are intended to be used throughout the entire life of the product and to serve regulators in multiple domains (assessment, control, supervision,...).

Overall, the discussion promoted by the European Commission between the pillars of the supervision system and all stakeholders is greatly welcomed as it favours development of synergies and reinforcement of the partnership between Assessors, Inspectors and OMCLs. It should also be ensured that industry meets the expected level of information requested by the current legislation for these products and that authorities have a harmonised approach with respect to the level of information requested.
EUROPEAN PHARMACOPOEIA RELATED COMMENTS

The European Pharmacopoeia (Ph. Eur.) is a single reference work for the quality control of veterinary medicines in the signatory states of the Convention on its elaboration, European Union being a signatory member since 1994. Reference to European Pharmacopoeia monographs in European Union Directive 2001/82/EC, as amended, provides the legal basis of Ph. Eur. monographs in the European Union and a scientific basis for quality control of veterinary medicines during the development, production and marketing processes.

As stated in the General Notices of the Ph. Eur.: “The active substances, excipients, pharmaceutical preparations and other articles described in the monographs are intended for human and veterinary use (unless explicitly restricted to one of these uses).” The Ph. Eur. therefore promotes the same quality for veterinary medicines as that defined for human medicines. Exceptions are for substances or products intended for veterinary use only, for example immunological veterinary medicinal products (IVMPs), Premixes for medicated feeding stuffs for veterinary use and a number of substances for veterinary use. At several exceptional occasions, it has been observed that the quality defined for human medicines was not appropriate for veterinary medicine and the Ph. Eur. has been solicited to define new standards for veterinary medicines; for example the microbiological quality requirement for oral dosage forms is considered to be too stringent for premixes, as noted by QWP of EMA. This is being examined by the relevant Ph. Eur. Group of Experts. In those cases discussions between the respective Groups of the two entities (Ph. Eur. and EMA) are beneficial.

Considerable progress has been achieved by Ph. Eur. in the last 15 years for the definition of acceptable quality standards for the development, production and quality control of IVMPs. This has been achieved by the elaboration of a significant number of relevant monographs and general chapters. Work was performed by Experts of Group 15V, whose members are constituted solely of national regulatory authorities. The elaboration of Ph. Eur. texts, together with the revision of Annex 1 to EU Directive 2001/82/EC, as amended, has initiated the revision and/or the suppression of immunological guidelines\(^1\), in the spirit of avoiding duplication of information and of streamlining the legislative framework for IVMPs. The work is underway within the IWP of EMA, in close collaboration with Ph. Eur. This will most probably satisfy Industry, who is often of the opinion that guidance documents in the field of IVMPs are too numerous.

Revision to Annex 1 of EU Directive 2001/82/EC, as amended, has initiated further revision of monographs on IVMPs, such as the deletion of the overdose testing for inactivated vaccines. Its consequence for the batch safety test is being studied by the experts of the Ph. Eur. In the same spirit, Ph. Eur. Group 15V has revised the general monograph on Vaccines for Veterinary Use (0062)\(^2\) in order to allow for reduced testing in the case of vaccines

\(^1\) EudraLex - Volume 7 Scientific guidelines for medicinal products for veterinary use, Volume 7B - Immunologicals, quality (http://ec.europa.eu/health/documents/eudralex/vol-7/index_en.htm)

\(^2\) PA/PH/Exp. 15V/T (08) 23 COM, to be implemented in Supplement 7.2 of the Ph. Eur.
intended for minor species and therefore will favour the application of the recent EMA guideline.

Ph. Eur. monographs on IVMPs include a production section which describes the safety and efficacy tests to be conducted during the development. These tests are usually carried out once in the lifetime of a vaccine. They constitute minimum requirements for the products. This section has often been criticised by Industry, who has suggested to delete this section to allow for entire freedom in development tests. The criticism is often due to the lack of comprehension of pharmacopoeia texts. In response to the need to clarify the mandatory status of parts of the Ph. Eur. monographs, Group 15V has drafted a Technical guide for the elaboration and use for IVMPs. The elaboration of this guide was made in consultation with Industry and close collaboration with IWP.

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1 EMA/CVMP/IWP/123243/2006-Rev.2, Committee for medicinal products for veterinary use (CVMP) Guideline on Data requirements for Immunological veterinary medicinal products intended for minor use or minor species/limited markets