Veterinary Drugs Directorate Peer Review of Veterinary Drug Submissions

Policy Guidance Document - PPD-POL-001

Purpose

Consistent with Health Canada's Decision-Making Framework, this policy is intended to ensure that veterinary drug submission reviews are subjected to a rigorous, transparent, science-based peer-review1 process. This provides consistency in the application of scientific judgement required by submission evaluation2 and subsequent review outputs, and effects measures of quality control of the submission evaluation process.

Background

There is a long history of second and subsequent reviews in the veterinary drugs program, but there has been no formal written policy guiding the existence and application of peer reviews. The need for a formal and explicit policy enunciating the objectives, scope, application parameters, and outcome quality measures expected for the conduct and structure of peer reviews has been identified as a priority. Peer reviews are consistent with the philosophy and guiding principles of the Health Products and Food Branch Quality Management Framework. Standard Operating Procedures outlining the specific procedural steps of the peer review process, further defining roles and responsibilities associated with its implementation for each concerned Division will complement this policy.

[1] Peer Review: consists of a quality control system for the evaluation or subsequent reviews of a veterinary drug submission. It may comprise one or more review steps that could be required to ensure validation of the evaluation outcome.

[2] Evaluation: For the purpose of this policy, evaluation consists of the initial assessment of a drug by a drug evaluator with respect to its pharmaceutical quality, its target animal safety and efficacy, its human safety when used in food producing animals and its proposed labelling. This evaluation includes the examination and analysis of all data (including raw data) submitted in the veterinary drug submissions for completeness, accuracy and acceptability to support label claims. This initial component of the process normally results in the submission of a detailed Evaluation Report including recommendations with respect to the acceptance, rejection or generation of additional data required to ensure compliance of a veterinary drug product with the *Food and Drug Regulations.*

Scope

This policy is applicable to the scientific review of all New Drug Submissions (NDS), Supplemental New Drug Submissions (SNDS), Abbreviated New Drug Submissions (AbNDS) and Investigational New Drug Submissions (IND) - See Appendix for definition of these submission types. Experimental Study Certificates (ESC), Drug Identification Number Submissions (DINs), Emergency Drug Releases (EDRs) and associated activities are excluded from the scope of this specific policy.

Policy Statement

It is the policy of the Veterinary Drugs Directorate (VDD) that a comprehensive peer review process is applied and implemented as part of an overall quality control management system in the evaluation of veterinary drug submissions.

1. Guiding Principles

1.1 Complete and accurate documentation of all activities associated with the evaluation and subsequent peer-review steps supported by an appropriate document management system.

1.2 Integrity of the contents of the peer review reports, summaries, minutes of meetings and other records of decision-making and associated documents at each step at which they are produced.

1.3 Documentation of all decision-making steps of the peer-review process with scientific, regulatory, or administrative rationale or justification.

1.4 Opportunity for dissenting opinions to be voiced, expressed and documented at all levels of the peer-review process hierarchy.

1.5 Comprehensible decisions and their documentation with supporting rationales of decision-making at all levels of the peer-review process hierarchy.

1.6 Exhausting all internal peer review processes, systems and venues of the VDD to the extent possible before allowing outside peer reviews of the evaluation of a veterinary drug submission.

1.7 An external peer review is considered advisory in nature and the final stage of decision-making rests with the Director General of VDD.

1.8 Internal peer review processes and systems should be monitored periodically for their effectiveness, quality of the decision-making outcomes and suitability to address the program's needs.

1.9 Flexibility should be incorporated in the implementation of the peer-review policy and

process to accommodate operational and scientific needs.

2. Triggering Factors

2.1 Specific operational requirements, such as the Division Chief not having sufficient time to conduct Phase I peer- reviews.

2.2 Requests from Drug Evaluators to clarify or resolve problematic or contentious issues associated with the drug product(s) under review.

2.3 Training needs: a submission done by a junior evaluator could be reviewed by a more senior evaluator for the purpose of training.

2.4 Differences between the Drug Evaluators and the Division Chief(s) in the interpretation of the evaluation or peer-review outcomes.

2.5 Safety and/or efficacy profile of a drug product is equivocal or not clear.

2.6 Guidance needs of Drug Evaluators when there are knowledge gaps in addressing data requirements.

2.7 New veterinary drug entities or products requiring new review criteria (such as methodologies and assessment tools) or criteria which have not been established by the VDD.

2.8 Multi-disciplinary evaluation and review approach along with horizontal integration of evaluation components are required.

2.9 Internal or external operational, legal, and scientific considerations.

Policy Requirements/Proceedures

Each Division involved in submission evaluations per se will develop intra- and inter-Divisional Standard Operating Procedural Guidelines (SOPs) for evaluation issues requiring horizontal integration within and across Divisions, ensuring that peer reviews are handled using a consistent, coordinated approach in accordance with this policy. The peer review process is not a substitute for ongoing routine intra-Divisional and inter-Divisional dialogue prior to or during the evaluation process.

The objective of the peer review process is to achieve a scientifically sound evaluation outcome. It consists of a hierarchically-tiered approach, based on the depth, nature and complexity of the drug submission; nature and seriousness of the triggering factors; and the degree of expertise required for reviewing the initial evaluation. It may vary from a simple verification of some of the scientific components of the initial evaluation to a more formal in-depth review of the original or additional data, an audit validating the evaluation approach, and/or a combination of one or more of the above.

This multi-layered process is outlined below:

Phase I Peer-Review: The review of the Evaluation Report could be performed by the Division Chief, but it is normally delegated to another evaluator (designated here as a first reviewer) within the Division. The first reviewer proceeds to a review of the Drug Evaluator's Report and a determination of its scientific soundness and completeness, the suitability and validity of the evaluation process followed and determines whether satisfactory evidence requirements have been met to proceed or not with the approval of the product. This first step of the peer review process normally consists of the review of the Evaluation Report, discussions with the Drug Evaluator, consultation of scientific literature and/or related submission material. It should ideally achieve a mutually agreeable consensus position on the acceptability, need for the submission of additional data on the part of the manufacturer or rejection of the submission.

Phase II Peer-Review: It consists of a more in-depth review of the veterinary drug submission by a Review Panel when no consensus position can be achieved among the Division Chief, the Drug Evaluator and the Phase I reviewer or alternatively, when the Division Chief considers this approach to be the most valuable and effective way to resolve evaluation interpretation or scientific differences. The Evaluation Report and the Phase I Review Report must be available on file at the time a Review Panel is established and must serve as the foundation on which future peer reviews will be built. The most simple form of ReviewPanel could consist of the Division Chief, the Drug Evaluator and the Phase I reviewer, but may also include additional Drug Evaluators from the same Division contributing specific evaluation or scientific expertise identified as necessary for the resolution of the submission evaluation outcome.

Once this panel review is established, it should function as any official peer review structured organization. Minutes of meetings and decisions resulting from the deliberations of the Review Panel should be documented in writing. The panel should review the two documents mentioned above and adopt a process to resolve conflicting opinions between the Drug Evaluator and Phase I reviewer. Depending on the complexity and nature of the submission being examined, this review may consider and opt for a more in-depth evaluation/review approach including, but not restricted to, the review of the initial submission or recently submitted raw data with respect to problematic components, an audit of the evaluation, a review of additional data from other regulatory authorities, industry, academia, etc.

Phase III Peer-Review: When a Review Panel cannot reach unanimous consensus or no consensus at all, the Division Chief may decide to appoint a Divisional Panel for peer review that would include additional or all members of his/her whole Division i.e. a Divisional Review Panel. The same modus operandi, decision-making approach and outcome products as for Phase II ReviewPanel would prevail for the conduct of peer review activities at this level. If there is unanimous consensus, the Division Chief proceeds with the final decision-making, and if not, the matter may be referred to the next phase(s) of the peer-review hierarchy or directly to the Science Issues Review Committee (SIRC) of VDD.

Phase IV Peer-Review: This consists of an Inter-Divisional Review Panel which is a more formal, in-depth peer review structure, where the panel is comprised of selected participants from more than one Division. Its purpose is to specifically review a particularly complex and

possibly contentious submission or aspects of such a submission impacting on the overall safety, efficacy or quality of the drug product e.g. Chemistry and Manufacturing evaluation with respect to purity and quality of the formulation. The modus operandi, decision-making approach and decision outcome products should follow a systematic approach as for Phase III Divisional Review Panel, however, this higher level of peer review reports directly to VDD's SIRC.

Science Issues Review Committee (SIRC): Wherever an evaluation outcome cannot be agreed upon by one or more of the preceding peer-review levels, it should be brought to the attention of the SIRC. SIRC's mandate is to ensure sound science-based risk assessments and in instances when scientific consensus has not been reached within VDD, it is responsible to ensure a forum for discussion aimed at achieving scientific consensus (Reference: VDD - SIRC Terms of Reference, December 05, 2001)

Branch Risk Management Committee (HPFB-RMC/BEC-RMC): This route may be chosen by the SIRC members/Chair to seek advice concerning risk management issues at various stages.

Departmental Risk Management Committee (DEC-RMC): This route may be chosen by BEC-RMC in dealing with issues that involve other Branches.

Quality Assurance: As part of ongoing quality assurance monitoring, there will be periodical quality audits of this peer-reviewpolicy and its associated processes and systems.

Effective Date

This Directive comes into effect as of July 2002.

Appendix - Glossary of Terms and Working Definitions

This policy makes reference to the following terms for which legal and/or working definitions are provided to establish a common understanding of the different terminologies that may be used in the application of the peer review process:

Abbreviated New Drug Submission (AbNDS)

An AbNDS contains information to demonstrate that the generic product is pharmaceutically equivalent as well as bio-equivalent with the Canadian reference product. In the case of food-producing animals, the AbNDS must confirm that the withdrawal period is identical to that of the Canadian reference product.

Canadian reference product:

"Canadian reference product" is a drug in respect of which a Notice of Compliance has been issued and which is marketed in Canada by the innovator of the drug. Where the innovator's product is no longer marketed in Canada, Canadian reference product may be a drug acceptable

to the Minister for the purpose of demonstrating bioequivalence between the generic and the innovator's products.

Drug:

A substance or a mixture of substances manufactured, sold or represented for use in the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state, or its symptoms, in human being or animals, restoring, correcting or modifying organic functions in human beings or animals, or disinfection in premises, in which food is manufactured, prepared or kept.

Drug Evaluator:

See Evaluator.

Evaluation:

See footnote 2, on page 1 of this document.

Evaluation Report:

See footnote 2, on page 1 of this document.

Evaluator:

A scientist responsible for the evaluation of a drug submission and/or appointed to the position of a Drug Evaluator.

Label:

Any legend, word or mark attached to, included in, belonging to, or accompanying, any food, drug, cosmetic, device, or package. The labels for a drug must specify adequate directions for use, including withdrawal periods for drugs intended for use in food-producing animals.

Investigational New Drug Submission (IND):

contains information to support the investigational use of a new drug for determining its efficacy in Canada. This type of submission normally contains information for manufacturing and quality control, target animal safety, human safety, investigational labelling and detailed experimental protocol.

Manufacturer:

A person who under his own name, or under a trade, design or word mark, trade name or other

name, word or mark controlled by him sells a food or drug and includes a firm, partnership or corporation.

New Drug:

A drug that contains or consists of a new substance, or is a new combination of two or more drugs or has a recommendation for a new condition of use, and that has not been sold as a drug in Canada, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of its use a drug.

New Drug Submission (NDS):

NDS contains sufficient information and material to assess the safety and effectiveness of the subject new drug. It includes details of manufacturing and quality control as well as results of toxicity, pharmacology, residue and clinical studies, and proposed labels for the new drug.

Notice of Compliance (NOC):

A Notice of Compliance is the document that is issued to the manufacturer of a drug when an NDS, AbNDS or SNDS complies with the Food and Drug Regulations. It includes the name, the medicinal ingredient(s), therapeutic classification(s) of the medicinal ingredient(s) and the Drug Identification Number (DIN) of the product. In the case of an AbNDS, the NOC states the name of the Canadian reference product referred in the submission.

Peer-Review:

See footnote 1, on page 1 of this document.

Raw Data:

Raw data includes worksheets, records, memoranda, notes, photographs, microfilm, microfiche, computer printouts, magnetic media records and recorded data from automated instruments, or exact copies, all of which are the result of original observations and activities of a study.

Sell:

The term "sell" includes offer for sale, having in possession for sale, and/or distribution, whether the distribution is made for consideration or not.

Supplemental New Drug Submission (SNDS):

An SNDS contains sufficient information and material with respect to the matters that are significantly different from those contained in the NDS previously accepted in compliance with the Food and Drug Regulations, to assess the safety and effectiveness of the new drug.