



WORKSHOP REPORT

5th Global Animal Health Conference 2016

Good Regulatory Practice for the Marketing Authorisation of Veterinary Products in an Asian Context

14-16 November 2016
New Delhi, India

Organising Committee

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Health for Animals
global animal medicines association



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EXECUTIVE SUMMARY

The workshop was held immediately prior to the 5th Global Animal Health Conference (GAHC2016) with the support of the Bill and Melinda Gates Foundation and organized by HealthforAnimals together with partners from the European Medicines Agency (EMA), US FDA, The World Organisation for Animal Health (OIE), GALVmed, Drug Information Association (DIA), and the Indian Industry organisation (INFAH).

Thirty seven participants from India, Philippines, Nepal, Malaysia, Micronesia, Myanmar, Japan, Saudi Arabia, Argentina, Barbados, Peru, Zimbabwe, USA, Belgium, United Kingdom, France and Ireland actively participated in group discussions and presentations, facilitated by a professional moderator and thought provoking questions in the presentations.

The aim of the workshop was to share knowledge and understanding of good regulatory practices and to promote further close cooperation amongst a regional network of regulatory agencies. This serves the wider aim of promoting animal health and contributes to the One Health approach. The close relationship between animal health and access to veterinary products underpins the need to ensure that the regulatory environment works to international standards and enables manufacturers of veterinary products to bring products to the market.

CONFERENCE OBJECTIVES

The specific workshop objectives, built on the outcome from the 4th Global Animal Health Conference (Tanzania, June 2015), were to review and discuss:

- The essential elements of a regulatory system for the marketing authorisation of veterinary products and the opportunities for stimulating the entry of new quality assured, safe and effective products on the market.
- The roles of legislation and guidance documents, and alignment with international standards.
- Good Manufacturing Practices (GMP), authorisation procedures for veterinary products and pharmacovigilance.
- The benefits and hurdles of mutual recognition of marketing authorisation processes from other regions with internationally recognised regulatory systems, including GMP.
- The benefits and hurdles of the formation of regional organisations to pool resources and the advantages of alignment with international standards.
- The processes necessary for market control of veterinary products, including how to tackle falsified products, identification of the critical elements, and where the resources should be focused.

HealthforAnimals opened the workshop and welcomed all participants.

THE WORKSHOP TEAM

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Rick Clayton, HealthforAnimals

Jason Todd, Veterinary Medicines Directorate

Ken Noda, JMAFF

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SESSION 1: GENERAL INTRODUCTION

The General Introduction session was based on identifying the main characteristics of a credible, effective and fair authorisation system for veterinary medicines. The importance of access to veterinary medicinal Products (VMPs) for animal health, welfare and productivity in a One Health perspective was agreed by the workshop.

The benefits of a good regulatory system and good quality control of VMPs were addressed, and it was stated several times during the workshop that alignment to international standards and regulatory harmonisation would be key factors for improving market access. An active communication with stakeholders in the regulatory process was also seen as a cornerstone in an efficient regulatory system.

The discussion on how to develop the national or regional regulation focused on the differences between the human medicines and veterinary medicines sectors. Due to the differences

in size, resources and benefit/risk profile, the workshop concluded with the recommendation that a separate veterinary legislation is preferable in order to take these specific characteristics into account.

Some of the challenges posed by the current state of VMP regulation in several regions are counterfeit medicines in the market place, and the need for consistency in implementation of guidelines and standards. A need for training of both assessors and industry was identified and the benefit of a forum for discussion between collaborating countries, including communication of consensus views, was stressed. Several examples of current and emerging regional collaborations were discussed, e.g. ASEAN, CAMEVET, EU, ZaZiBoNa (for human health only), VICH, and a strong recommendation to join the VICH Outreach Forum was expressed by current VICH members and VICH Outreach Forum members.

SESSION 2: LEGISLATION AND GUIDANCE

The governing structure varies between countries but it was clear from the workshop that the responsibility lies with the ministries of Agriculture and Health, and a good collaboration is needed between these governmental departments, including clear agreements on shared responsibilities. There are many available international standards, such as those from Codex, OIE, VICH, and PIC/S, and they are extensively used. Both local, regional (e.g. ASEAN and CAMEVET) and international guidelines are used and typically implemented via manuals or administrative orders. It was the general understanding that guidelines are normally not legally binding and a different approach can be used if justified by the applicant. The workshop discussed that during the drafting of guidelines, the industry experts may possess very valuable

knowledge and early stakeholder involvement plus public consultation were felt extremely important.

A question was raised on how we can ensure consistent implementation of guidelines. In response, the system of a national council, public consultation, and involvement of the private sector in the Philippines was described. The EU regulatory network training center for regulators was mentioned as a forum for improving a harmonized understanding of the requirements among assessors. Industry associations should be encouraged to provide feedback on areas where disharmonized interpretation of guidelines is causing significant problems.



SESSION 3: GOOD MANUFACTURING PRACTICE (GMP) AND MARKET CONTROL

In all the participating countries, manufacturers are inspected and/or approved. This requires a lot of resources, particularly inspecting manufacturing sites in other countries for imported product. The workshop acknowledged the benefits of cooperation or mutual agreements between regulatory authorities in order to be able to recognize inspection reports or certificates from other countries. The requirements may vary due to differences in GMP-standards, but mutual 'equivalence' agreements might still be possible. A call was made for a veterinary adapted GMP standard, and it was emphasized that countries developing their regulatory systems should not waste resources on drafting their own GMP standard but use an internationally recognized existing text from a well-established regulatory authority or regional organisation.

The workshop had a longer discussion on the resources needed for inspections and an approximate level of 30 sites per inspector was mentioned as a general benchmark figure. It was strongly recommended to collaborate with other countries, and to use a risk-based approach to inspections. However, the risk-based approach sometimes resulted in expiry of the GMP certificate before the subsequent inspection took place, which complicated logistics, particularly for the export of products. A GMP-certificate covers the products and processes in place at the moment of the inspection of the specific site, which means that any new products or processes will not be included on the GMP-certificate until next inspection. This can be a problem when exporting to third countries.

Inspectors must have appropriate education and experience, be impartial and be legally empowered. A clear need for training of veterinary specific inspectors was identified in many countries and several opportunities were put on the table for discussion; OIE-members have access to capacity building activities at collaborating centres, e.g. US-FDA, USDA, FR-Anses, and in Japan. Many agencies are approachable. On-line videos are available from US FDA covering production processes, and some are translated to several languages.

Presentations on GMP control and inspections of manufacturers included several levels, from desktop-assessment of site information, or official testing of VMPs, to a full inspection of

manufacturing sites. A GMP facility needs a Quality Management System, suitably trained staff, suitable premises and equipment, documentation, retention of records to ensure control over the production processes, a batch release process, and potential product defects process. Several countries expressed that this is implemented in their national systems.

The Pharmaceutical Inspection Cooperation Scheme (PIC/S) was discussed and found very useful as an international organisation (49 agencies from all over the world are members), being a non-binding, informal co-operative arrangement between Regulatory Authorities in the field of GMP of medicinal products for human or veterinary use. It is open to any Authority having a comparable GMP inspection system. The topic of a vet-specific GMP guideline was further discussed and an encouragement for more authorities to participate in PIC/S. Specific, appropriate training and guidelines for GMP inspection of vaccine production are necessary. OIE has published new guidelines on this.

One country explained that due to scarce resources, they informally "ranked" countries in 2-3 GMP-levels and made a risk-based evaluation based on where the product originated from.

Batch release of products was mentioned by several countries and is done to an internal standard, QC and occasional retesting in some places, while others use a dedicated person responsible for batch release and checking that the companies have documentation for this.

In relation to medicated feed the point of application of the GMP standard was also briefly discussed (i.e. at the level of the medicine 'pre-mix' manufacture or at the level of the feed manufacture), as well as coordinated inspection programs and the possibility of accepting inspections performed by other countries.

A dedicated event with sharing of practical experience in GMP-inspection and control of veterinary medicinal products is an urgent recommendation from the workshop.

SESSION 4: AUTHORISATION PROCEDURES

Dossier structure in different regions was discussed and most countries have specific requirements for pharmaceutical medicines and biological medicines (e.g. vaccines), and with separate sections on Quality, Safety and Efficacy in each dossier. There was consensus that templates from human medicine are not adequate. Harmonization between countries, and regional cooperation e.g. Gulf states, EAC, ASEAN, EU, is highly beneficial. Electronic submission of dossiers is helpful for industry and

reviewers, and if the systems are secure it can increase the security of the data, but may require investment.

The workshop discussed the use of experts and their qualifications and affiliation with the applicants. Industry often uses external experts to write expert reports or give advice during product development. Governments often use internal (employed) experts for dossier assessment and must pay attention to



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potential conflicts of interests from other/previous employment or affiliation.

The workshop recommended that a list of scientific experts, both from industry and from government/academia, should be publicly available. Some countries noted that direct contacts between experts (assessors and industry experts) facilitate assessment, particularly if the technology is new and the expertise is concentrated with the applicant.

The participants agreed that mutual recognition of authorizations from other countries may avoid duplication of assessment, creates faster availability to more markets/countries, builds trust and leads to more robust assessments. It also brings benefit to animal welfare due to fewer animal studies and increased access to veterinary medicines.

To enable mutual recognition a common format of the application form and dossier is required, such as those used in the EU, USA/Canada and EAC. Post authorization changes (variation/amendment) of a mutually recognized product should also

be harmonized to avoid that industry must have two different manufacturing methods in parallel while waiting for the last country to approve the variation, as occurs where unharmonised individual national authorisations exist.

It was stated that a mutual recognition procedure in principle only needs a harmonized set of requirements, a forum/group for discussion, political will to support it, and a transnational framework to run the procedure. Also Standard Operating Procedures (SOPs), guidelines and templates were felt essential for an efficient regulatory system.

The scientific review process was discussed and from industry's side the most important factors are clear timeframes, predictability, and transparency. A possibility to exchange information/views with assessors was felt very helpful for successful outcomes. A fast-track procedure exists in several regions for exceptional circumstances or emergency vaccines. An appeal process for the applicant was in place in several countries but the timelines and conditions varied.

SESSION 5: LOGISTICS

The workshop discussed experience with application forms and dossier submission related to paper submission versus electronic submission. Paper has lower cost and infrastructure, but is more difficult to share between assessors or countries and requires more archiving space. In some countries, paper versions are required due to the need for official signatures. Moreover, the internet network is not always good enough for electronic transfer. Several countries have paper versions but are in the process of going to electronic systems in the future.

Electronic submission can be a CD/DVD-system and/or cloud/portal-system. It requires agreed templates and IT-structures, so the initial cost and manpower is higher, but accessibility of data is better and security of data can be better if the system is good. The workshop recommended that countries setting up an electronic system should benchmark and exchange with other countries. The secure access by companies was solved by password protection given only to selected persons, or by electronic means. Backup of data in real-time in a remote server and scanning of paper documents prior to destruction was discussed.

Confidentiality is very important for industry to trust that data are kept secure and a confidentiality policy should be in place including signed Conflict-of-Interests declarations from assessors and that no unauthorized persons have access to the work-area of an agency.

Transparency of the regulatory process is necessary with simple and clear requirements. Many countries use a website and documents to show product approvals, and it was recommended that the process-flow, timelines and fees were also published. A healthy balance between confidentiality and transparency has to be struck. Product information to be published on regulators' websites should always be checked with applicants before publishing

A fee system where applicants pay for the assessment procedure existed in most, but not all countries. It was agreed that a fee system makes it possible to hire qualified experts, keep timelines, and be independent of government budgets year-to-year. However, the system must be transparent to ensure that the public perception of an agency's impartiality is maintained (i.e. that assessors are not perceived as "bought" by industry), and the fees should be fair and proportionate to the work and services given.



SESSION 6: POST AUTHORIZATION PROCEDURES AND MARKET CONTROL

Variations to the dossier are a frequent occurrence due to, for example, updates in the manufacturing process, pharmacovigilance, or administrative changes. In most countries, it is a legal obligation to submit a variation application, and the content of the change (major/minor change) decides the assessment procedure, fee and timelines.

The workshop participants felt that applicants generally keep their dossiers up to date. In some countries, a period between authorization and variations is requested, and the fees and timelines vary across the world.

Options to tackle falsified and counterfeit products and illegal import were discussed by the workshop and can be based on three pillars; marketing authorisations, inspections and market/import surveillance. Good Distribution Practice (GDP) guidance helps to handle the distribution chain from manufacture to customer, recalls, complaints, storage, traceability, and controls. Inspectors must be fully empowered to take actions, such as to withdraw a licence or illegal/counterfeit products on the market and even start prosecution. Risk-based inspection and control programs are recommended to efficiently use the available resources, focusing for instance on antibiotics, notifiable diseases,

and high-risk products. Methodologies and equipment to find and identify counterfeit products is strongly needed, including control of internet sales of medicines.

A pharmacovigilance (PhV) system is needed to receive reports on problems with a VMP, and to monitor and act on signals of adverse events. It is a benefit for users to have updated information and improved label warnings, where necessary. Setting up a system requires a legal basis, a responsible agency/body, definition of roles and stakeholders, documentation and information systems. The workshop recommended using international PhV standards and guidelines to avoid reinventing the wheel, and to facilitate the sharing of data. Several countries described their developing PhV systems, and the challenges regarding stakeholder awareness, IT-systems, web-site forms, social media reports, resources, and education of the veterinarians to understand the importance of PhV. Some regional platforms like ZaZiBoNa and Camevet were considered useful in the future to enhance surveillance of VMPs and a lot of work is still needed in this area in many regions. Everyone agreed that for a system to work it should be easy to use.

SESSION 7 PART 1: KEY ENABLING FACTORS

The key enabling factors of a functioning regulatory system were discussed; the small size of the veterinary sector compared to the human sector was noted and the importance of taking into account veterinary-specific aspects was highlighted. Regulators need to provide predictable timelines and consistent, transparent and science-based assessment. In turn, industry needs to provide good dossiers, prompt responses, and the commitment to keep products and dossiers up-to-date. Regulators were encouraged

to allow for the possibility of proportionate timelines and fees for change to the authorisation once granted. Benchmarking of similar agencies, surveys among clients and setting of priorities were mentioned as good options for improvement to achieve regulatory convergence. Predictability can be improved with more collaboration with other agencies. The benefits of early dialogue between the regulators and applicants were stressed in order to clarify expectations on both sides.

SESSION 7 PART 2: RISK MANAGEMENT STRATEGIES FOR CONTAINMENT OF ANTIMICROBIAL RESISTANCE IN FOOD PRODUCING ANIMALS

Risk management strategies for containment of antimicrobial resistance in food producing animals were discussed. The competing use of antimicrobials/antibiotics in food production to enhance nutrient utilization and growth of the animals with the

use of antimicrobials for human health purposes was discussed and should be based on risk-assessment, monitoring, scientific knowledge and should potentially lead to certain restrictions or elimination of use.



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RECOMMENDATIONS AND KEY MESSAGES RESULTING FROM THE WORKSHOP:

All countries should in the future have a legally based system for authorization and control of VMPs.

A good regulatory practice is necessary with the regulatory system based on product authorization, GMP-production and inspection.

A harmonization process for the whole world, which is adapted region-wise, is the long-term goal. A global move towards harmonized guidelines for VMPs is envisaged and training of assessors will be needed.

A strong encouragement to join the VICH Outreach Forum was voiced, and development of regional cooperation was a key to successful progress in several regions.

A VMP-inspectors training with exchange of practical experience is strongly needed.

Regulation and action against counterfeit VMP drugs must be developed.

Human regulatory systems can be used as a starting point, but regulations and requirements must be made proportionate to veterinary resources and to the very different benefit:risk profile of veterinary products.

It is recommended to continue these meetings and workshops because personal relations and contacts are important in the harmonization process. Regulators can reach out and learn from each other and use the existing standards and texts.

Applicants need a channel to be able to approach the regulators in the early phase to know what studies are needed and to make a good quality dossier that enables a robust assessment.

Manufacturers or marketing authorisation holders will only go to countries with their products if it is worth the investment. One of

the decisive factors is the difficulty of the registration procedure. There is an obvious need for clear time-frames, predictability, and transparency. Data security is also important.

Novel products require lots of investments, and regulatory authorities need scientific expertise to assess these. Early communication to understand what the product is may improve the content and assessment of the dossier. Regulators should be brave and accept new technologies. VICH has identified the need for guidelines on biotechnologies. A horizon-scanning activity with open doors in the authorities can be useful to ensure knowledge about upcoming new technologies.

Improved pharmacovigilance systems and communication is necessary in many regions, including education of vets, production of leaflets, training programs, awareness campaigns, strengthened implementation, and talking to industry, vets and farmers.

Government websites should list all relevant information concerning the authorization of veterinary medicinal products for transparency and predictability, and should also house a list of authorised products.

Antimicrobial use and resistance development should be monitored, using internationally agreed methodologies, and new reporting systems should be established particularly in pig and poultry production.

Certificates for export: the model often used is from WHO, and it would be helpful to have an OIE version to certify the product registration and the GMP-manufacturing license.

SPECIFIC ACTION POINTS

Industry is encouraged to send dossiers for establishing maximum residue limits (MRLs) of active substances to JECFA.

ASEAN is encouraged to finalize the work on the development of a Mutual Recognition Procedure.

The regional cooperation of ZaZiBoNa should be extended from human medicines to veterinary medicines.

CLOSING COMMITMENTS

A commitment was made from all participants to (a) take back home their key learnings with a view to implement these into their national regulatory systems and (b) to share the recommendations from this workshop with all stakeholders (vets/farmers/other regulators), and to seek their feedback.

PRESENTATIONS

Presentations, this report and the conference report are available on www.healthforanimals.org

ACCESS PICTURES

Pictures taken at the conference are available online:

<https://www.flickr.com/photos/gahc2016/albums>

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