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Veterinary Medicines Division

Joint EMA/HMA Veterinary Vaccine Availability Action Plan

Analysis of industry recommendations

1. Background

A "Joint EMA/HMA Workshop on requirements for the authorisation of veterinary vaccines in the EU" took place on the 25 March 2015. A key question addressed at the meeting was if requirements for marketing authorisation of vaccines in the EU were considered to be proportionate to the benefits and risks of this type of product.

A report of this workshop was published on the EMA website that contains a number of recommendations. These recommendations have been placed within the context of the wider Network Strategy in preparing an action plan (the HMA/EMA action plan on veterinary vaccine availability) with the objective of ensuring efficient and effective cooperation between all of those involved in making vaccines available within the EU (including marketing authorisation holders, regulatory authorities and the European Commission).

To provide strategic oversight on the implementation of the Joint EMA/HMA Action Plan on Availability of Veterinary Vaccines the HMA in its February 2016 meeting established a Steering Group (SG). In March 2016 the CVMP also established the CVMP ad-hoc expert group on veterinary vaccine availability (CADVVA) to identify, prioritise and monitor the implementation of actions within the Action Plan for which the CVMP is responsible.

One of the recommendations included in the Joint EMA/HMA Action Plan was to review the list of recommendations provided by industry in March 2015 on veterinary vaccine requirements. The objective of this review was to identify and prioritise actions arising from this list that can be implemented within the current legal framework and which the SG considers will improve the availability of veterinary vaccines.

The aim of this document is to follow up the above recommendation of the action plan in the form of a review of industry's recommendations, providing a summary analysis of these recommendations, identifying and prioritising possible actions and main implementers.

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Methodology:

Forty three (43) recommendations were submitted by IFAH-Europe in relation to promoting veterinary vaccine availability in Europe. To analyse them a qualitative methodology was followed.

In the first instance, recommendations were grouped in main categories under five (5) overarching themes, then split further into subgroups and then these subgroups were prioritised by taking into account the prioritisation ranking provided by industry. Industry ranked priorities from 1 to 12 in descending order (highest ranked as 1 and lowest as 12).

An assessment of the potential impact of each proposed recommendation on the availability of veterinary vaccines in Europe was conducted by EMA.

The following were considered for each recommendation:

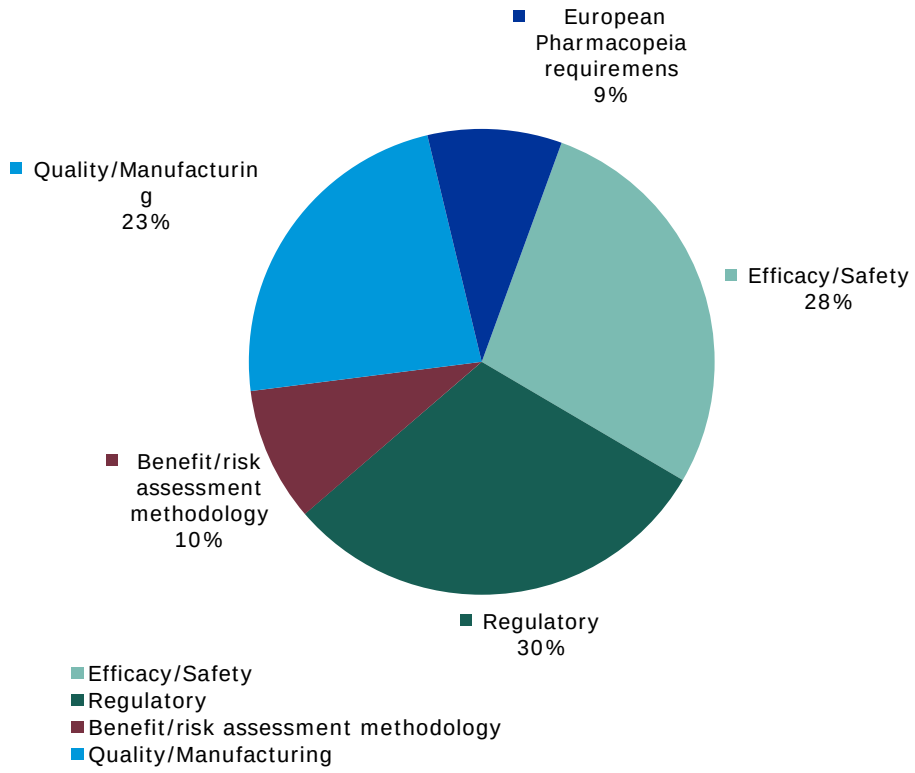
- The potential increase of the availability of veterinary vaccines if the action were to be implemented for each individual recommendation. For the purposes of the analysis, the definition of availability, as agreed by CADVVA, was used i.e. timely and adequate access to the market of suitable new and/or improved veterinary vaccines, to improve the health and welfare of animals, increase production of livestock in a cost-effective manner and prevent animal-to-human transmission from both domestic animals and wildlife, as well as to significantly impact on public health through reductions in the use of antibiotics and other veterinary pharmaceuticals and their residues in the human food chain1 (Parameters such as an improvement in the speed to market, extend of claims2 and product quantity were considered).
- The type of impact on veterinary vaccine availability, including a reduction of financial or development time burdens, an increase in predictability of requirements or a positive impact on the 3Rs principle.
- The feasibility of implementing all necessary actions, where feasibility was defined as the level of practicality for the technical implementation of the proposed actions. Recommendations requiring changes to relevant legislation or Ph. Eur. monographs/texts were assigned as low feasibility, whereas those requiring revision or drafting of new guidelines or position papers were considered of moderate or high feasibility depending on the complexity and extent of the change necessary. For changes to the legislation that are already under discussion as part of new veterinary regulation (NVR) in Council and Parliament the feasibility was considered high.
- The likelihood of success in terms of whether or not it is likely that proposed actions would be achievable in a realistic timeframe.
- The impact on increasing the level of risk for animal or public health in the EU by implementing each proposed recommendation.

Finally an analysis on the basis of the proposed main actors/ implementers has also taken place. Those considered were: the HMA Steering Group (SG), CVMP, CVMP/IWP (CADVVA), European Pharmacopoeia (EDQM), industry, CMDv.

The expected outcome of each proposed action was defined on the basis of the time needed for its implementation, following the finalisation of this report, and was categorised as follows: short term: 6-12 months, medium term: 12-24 months, long term: 24+ months.

[1]The availability of existing veterinary vaccines is also recognised as a concern in some EU markets but is not considered appropriate for the scope of this group.
[2] Based on the assumption that data of acceptable quality were provided to regulatory authorities to support proposed claims.

Distribution of industry recommendations according to main categories (5 overarching themes)



Main categories (Overarching themes)	Main topics of subgroups *(as proposed by industry)*
Efficacy and Safety requirements (Parts 3 and 4)	**Field trials:** role and importance of field trials in the authorisation of veterinary vaccines –why, when, how and from where
	Serology: role of serology as surrogate marker for efficacy, necessary level of correlation with protection
	Better use of **PhV data:** • support efficacy, • replace efficacy trials, • replace safety studies, • amend safety warnings
	Laboratory studies and GLP compliance
Regulatory	**Mutual Recognition Procedure (MRPs) and repeat MRPs:** re-evaluation of older dossiers
	MUMS: reductions to be clearly indicated in writing and applicable to all; better applicability of MUMS requirements

	SPC simplification
	Autogenous vaccines
	Step-wise submission: regulatory requirements alignment with US regulator, conditional licencing
	Miscellaneous: i) simplification of requirements for strain replacement, ii) abandoning of sunset clause, iii) grouping of production transfers variations
Benefit / Risk assessment methodology (Part 5)	Increasing of consistency of assessments
	Acceptance of data from geographical regions outside EU in particular on safety and efficacy (part 3 and 4) and inclusion in B/R
	Increasing flexibility in assessment of alternative approaches
	Different level of requirements for companion versus food producing animals (individual vs herd immunity)
Quality / manufacturing (Part 2)	Possible (restricted) extrapolation of inactivation kinetics for setting maximum pre-inactivation titre
	GPM issues: • Clarify the space that belongs to inspectors and the one that relates to assessment, • exclude IVMPs from QP Declaration requirement
	Stability issues: • Acceptance of R&D batches
	New platforms for quality dossier: Vaccine antigen master file and Vector vaccine platform
	Miscellaneous : • Extraneous agents testing only on starting materials, • Reduced safety and efficacy requirements for cell line replacement if Final Product Control (FPC) test results remain within specification
European Pharmacopoeia (Ph. Eur.) requirements	To subject the development of sections of Ph. Eur. monographs to review and evaluate as some are exceedingly demanding such as salmonella, fowl pox, coccidiosis, etc.
	Sterility issues: • Amended sterility requirements for non-injectables (e.g. products administered by spray, oral & web wing vaccination routes), • Reduced sampling requirements for sterility test (Ph. Eur. 2.6.1), • Stability issues: Real time stability data to be provided for actual shelf life, not for shelf life + 3 months

2. Analysis

2.1. Safety and efficacy (Parts 3 and 4) recommendations

2.1.1. Field efficacy trials

It has been a longstanding view of the industry that field trials pose considerably difficulties when compared with the added value they bring to the final dossier and in particular with regard to the efficacy claims. Reproducing the challenge model under field conditions is claimed to be particularly difficult to achieve as often there is inadequate circulation of infectious agent for an effective challenge. The incidence of disease may also be limited due to overall improvements in biosecurity on farms identified for the field trial. In contrast, challenge can overwhelm the protection afforded by the vaccine when the disease is not under control.

It is important to note that Council Directive 2009/9/EC states that: "unless *justified, the results from laboratory trials shall be supplemented with data from field trials; when efficacy cannot be demonstrated by laboratory trials, field efficacy trials alone may be acceptable*". The Directive therefore provides already some space for flexibility. The CVMP note for guidance on field trials with veterinary vaccines (EMEA/CVMP/852/99) provides a good justification for the requirement of field trials on vaccine applications but also allows for deviations should there be a scientifically acceptable justification.

On the basis that this is one of highest industry's priorities the proposed action is to organise a focus group to explore the specific challenges faced by industry and how these might be overcome whilst still obtaining an adequate assurance of the expected efficacy of a vaccine under field conditions. Such a focus group could bring together stakeholders, including industry and experts from EU and other regions to reflect if there is a need to revise the CVMP guidance on field trials.

Proposed action: Focus group[*]*, Responsible actors: SG, CVMP (CADVVA/IWP) , Outlook: Short term*

[*]*(Proposed priority: High)*

2.1.2. Serology

Accepting serology more readily in the EU as a marker of efficacy is the second highest priority for industry. Challenge trials are usually required to support onset of immunity, duration of immunity, the effect of maternally derived antibodies (MDA) and claims for compatibility between vaccines.

The need to conduct challenge studies to demonstrate efficacy becomes a particular concern when companies want to introduce new combination products and/or want to demonstrate compatibility with another product. This adds cost and possibly translates to an almost a complete re-development of an existing product in the case of demonstrating compatibility with another.

The development of clear guidance on when serology can be accepted as a marker surrogate for efficacy to replace challenge in efficacy studies has therefore become a long standing priority for industry.

Reducing requirements for challenge experiments where appropriate is compatible with the 3Rs principle. Directive 2010/63/EU states in Article 13.2 that "… in choosing between procedures, those which use the minimum number of animals shall be selected" (European Commission, 2010). Furthermore, "The Member States of the Council of Europe have decided that it is their aim to protect live animals used for experimental and other scientific purposes to ensure that any possible pain,

suffering, distress or lasting harm inflicted as a consequence of procedures being conducted upon them, shall be kept at a minimum."

This is a challenging issue for regulators. For some diseases there is no recognised correlation between serology and protection and for such diseases challenge studies are pivotal for demonstrating efficacy. For diseases where there is a good correlation serology can, and has, been used to replace challenge studies e.g. Foot–and-Mouth disease (FMD) vaccines. Moreover the technique used can play a significant role on results and how they are interpreted. It may be possible to define more clearly acceptance criteria and principles in order to direct industry towards the type of work that they need to undertake in order to justify substitution of challenge by serology or other surrogate markers for efficacy.

On the basis that this is one of industry's highest priorities the proposed action is for industry to provide a specific problem statement and their expectations with specific examples if possible, then invite CVMP/IWP to review it against current guidance and whether there is space for flexibility in approach and then form a focus group to review the general principles to which serology (including methods of analysis) can reasonably be or not be used as a correlate or marker of anticipated efficacy and provide a scientific analysis. Stakeholders and experts from regulatory and academic backgrounds will be invited to present evidence in this focus group with the aim for CVMP to produce a guidance document on acceptance criteria taking into account the recommendations of the focus group.

Proposed action: Industry to provide a problem statement, CVMP/IWP and Focus group Responsible actor: Industry, CVMP (CADVVA/IWP), SG,*

Outlook: Medium term

**(Proposed priority: High)*

2.1.3. Use of Pharmacovigilance (PhV) data

A number of industry recommendations make reference to the better use of pharmacovigilance data in authorisation and post authorisation procedures. It should be noted that this type of data may be available for a product undergoing a (repeat) MRP procedure but already authorised in some EU countries or a product undergoing a post authorisation assessment. In particular a request was made that when available, regulators should consider PhV data as valid field data that could support not only the safety of a product (including a reduction of safety warnings) but also its efficacy (replace field efficacy data when possible). Industry is invited to provide their specific concerns and proposals (including specific examples if possible) regarding the validity of PhV data in the context of an authorisation dossier to the Steering Group and to CADVVA at first instance with a view to be decided by these groups whether further action is necessary and in which form.

Proposed action: presentation by industry of specific concerns and proposals, Responsible actor: industry, CVMP (CADVVA/IWP), SG, Outlook: Medium term

2.1.4. Laboratory studies - GLP compliance and other study related recommendations

Remaining efficacy and safety recommendations relate mainly to laboratory studies and a couple specifically make reference to GLP requirements for safety studies. In these recommendations a relaxation on the application of GLP requirements in particular for safety studies as is the case in the USA is proposed. Specifically the applicability of GLP requirements only for single dose, overdose, and

repeat dose studies, virulence and dissemination studies is requested. In the same context it is also proposed that GLP standards are not absolute requirements when assessing safety studies.

Other recommendations relate to design issues of laboratory studies such as the:

i) Acceptance of the principle that a single booster vaccination should suffice without the need to demonstrate a specific booster effect of one dose by performing a long term study (Duration of immunity (DOI) + Booster effect).

ii) Acceptance of one method of administration to support different routes of vaccination - mainly relevant for poultry products-. For example the administration of poultry vaccines via respiratory, oral and ocular (nebulization) routes to be considered as equivalent routes of administration and therefore any of these three can be used in studies to support the other routes in the final SPC.

It should be noted that GLP compliance is a basic legal requirement in European legislation and therefore there is little space to accommodate significant deviations. However there is allowance for some flexibility in the context of the MUMS guideline.

2.1.5. Proposed action: *CVMP (CADVVA/IWP)* Field studies

Finally another recommendation of this subgroup relates to field studies in one day old chicks and a request to waive the requirement that broilers and layer/breeders are both studied in field studies. There is scope for some flexibility regarding this issue depending on the objectives and duration of the studies.

For the various issues raised above it is proposed that they are discussed at CADVVA level, and the group can decide whether any will be taken forward and in what format.

Proposed action: discussion at CADVVA level, Responsible actor: CVMP (CADVVA/IWP), Outlook: Short term

2.2. General regulatory recommendations

Besides safety and efficacy concerns there a number of issues of a general regulatory nature are raised as high priorities. These issues either impact all parts of a dossier (i.e. strain replacement) or are of purely regulatory nature i.e. MRP procedures, phased submission etc.

2.2.1. Mutual Recognition Procedure (MRPs) and repeat MRPs

Re-evaluation of older dossier, increased requirements, reduction of claims.

A repeat theme here is the fact that in MRPs and repeat use procedures many additional questions are asked besides those already queried by the reference Member State (MS) and/or other concerned MSs. A proposal is to provide PhV data to support the safety and possibly efficacy of products undergoing (repeat) MRP procedures. It is recognised that the new legislation is largely addressing the problem with Article 57 of the new draft regulation allowing an administrative repeat use MRP for products registered from its date of entry into force. However the problem remains for the older products authorized before that date of entry of the new regulation. As a result industry is requesting that the all above are considered by national regulators with a view to improve the above described problems during (repeat) MRP procedures.

Given that the MRP is under discussion as part of the new veterinary regulation in Council and Parliament, no specific action is proposed. It would be however useful for CMDv, to investigate to what

extent problems have been experienced with vaccines going through an MRP repeat use procedure and how these were resolved – how many such procedures over the past 24 months, how many resulted in significant changes to indications, how many required generation of new studies, where post-authorisation commitments required for positive opinion, how many ended up with refusals/referrals and withdrawals. It should be noted that CMDv is already doing an exercise in the above context where 40 authorised products are reviewed.

Proposed action: No specific action, CMDv analysis, Responsible actor; MDv, Outlook: N/A

2.2.2. MUMS: reductions to be clearly indicated in writing and applicable to all; better applicability of MUMS requirements

The requirements for MUMS products also feature high in the ranking of the industry priorities. What is emerging as a specific topic is the need for predictability thus a request for applicability of reductions on requirements to all MUMS products rather than a case by case decision. Moreover reduced requirements should be requested to act as final reductions in order to work as incentives and not to be translated in post authorisation follow up actions, increasing this way the cost for developing the product and therefore rendering it financially non-viable given the small market.

The revised MUMS guideline for immunologicals was open for consultation until July 2016 and industry provided extensive comment currently considered by IWP. In the longer term, the new veterinary legislation (Art. 21) will provide information for authorisation of products for 'Limited Markets', thereby giving the legal certainty that industry is seeking.

Proposed action: IWP to consider comments provided during consultation of revised MUMS, Responsible actor: CVMP (CADVVA/IWP), Outlook: Short term

2.2.3. SPC simplification

This is a stand -alone recommendation that features high in the priorities for industry. Concerns were raised that the SPC provides too many details on the basis of the results of laboratory and field studies leading often to complex claims. It was proposed that the Duration of Immunity and Onset of Immunity (DOI and OOI) information remain the most necessary information to be provided in the SPC. However there is a CVMP position on indications of veterinary vaccines (EMEA/CVMP/042/97-Final. 1) that could serve as a discussion basis. Industry will be invited to provide specific concerns and proposals on SPC simplification, with specific examples, in the form of a concept paper with a view for the SG to evaluate whether there is a basis to consider a need for the revision of the position paper by CVMP and possibly drafting of a relevant guideline. Following industry's presentation, the SG will decide on appropriate follow up.

Proposed action: Industry to present specific concerns and proposals, follow up to be decided by SG
Responsible actor: Industry, SG, CVMP (CADVVA/IWP)
Outlook: Medium term

2.2.4. Autogenous vaccines

The need to better regulate the production of autogenous vaccines (custom vaccines that consist of herd specific (homologous) antigens) in Europe was highlighted as priority by industry, in view of the different level of requirements in the different MSs in the EU. Given that autogenous vaccines are exempt from relevant Union legislation (Article 3, Para. 2 of Directive 2001/82/EC) the CMDv is the

appropriate body to address this; however as CMDv is already working on this issue on request of HMA no further action is proposed.

Proposed action: None further action required as CMDv is already working on this issue, Responsible actor: CMDv, Outlook: Medium term

2.2.5. Step wise submission, regulatory requirements alignment with US regulator, conditional licencing

A number of industry requests placed relatively high on the priority list, relate to industry's view that regulators in Europe should adopt a closer approach to what is followed in the USA. In this context recommendations such as a step wise submission, conditional licencing and overall regulatory alignment with the US approach appear in the list of recommendations.

It is clear that in Europe the legislation is based on the principle that the dossier is provided when completed with minor amendments that can be follow up after the authorisation. However in recent years significant assistance is provided to industry by providing advice at early stages of development at national level or through the Innovation Task Force (ITF), the Ad Hoc Expert Group on Veterinary Novel Therapies (ADVENT), scientific advice and pre-submission meetings for centralised applications. There is currently no support within the EU regulatory system to move to a formal process of phased submission and as a result no further action is considered appropriate by the SG.

Proposed action: No action; Responsible actor: N/A, Outlook: N/A

2.2.6. Miscellaneous: i) simplification of requirements for strain replacement/additions, ii) abandoning of sunset clause, iii) production transfers variation, iv) 3Rs

i) The simplification of requirements for substituting or adding strains in vaccines was raised as a concern with reference to the Guideline on data requirements for changes to the strain composition of authorised equine influenza vaccines in line with OIE recommendations EMA/CVMP/IWP/97961/2013, published in 2014.

Given the relatively recent publication of the guideline it is proposed not to take further action until a revision is required.

Proposed action: No further action, Responsible actor: N/A, Outlook: N/A

ii) Sunset clause: The so-called "sunset clause" is a provision leading to the cessation of the validity of the marketing authorisation if the medicinal product is not placed on the market within three years of the authorisation being granted or, where a medicinal product previously placed on the market is no longer actually present on the market for three consecutive years. The European Commission or Competent National Authority may grant exemptions on public health grounds and in exceptional circumstances if duly justified. In the draft new veterinary legislative proposal the sunset clause is not foreseen and so discussion on this proposal will take place in Council and Parliament in the context of the new veterinary legislation.

Proposed action: No further action required, Responsible actor: N/A, Outlook: Long term

iii) Industry request that all changes that relate to the change of a site of manufacture are grouped as one variation, instead of generating separate ones leading to significant costs. Although it has been clarified that this is mainly a problem encountered in non-centralised procedures it is recognised that there is a need for a harmonised approach between procedures involving similar type of changes. It is

therefore proposed to be followed up by CMDv by bringing the issue to the Joint CMDh/CMDv/EMA variation working group.

Proposed action: CMDv to consider the scope for administrative efficiencies within its Joint CMDh/ CMDv/EMA Variation working group, Responsible actor: CMDv, Outlook: Medium term

i**v)** Industry has indicated that despite the 3Rs initiatives (i.e. draft Guideline on regulatory acceptance of 3R (replacement, reduction, refinement) testing approaches, (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)) the impact that the guideline has had on data requirements in particular for safety and efficacy demonstration remains minimal. Training is considered the best approach to address the issue and best practice in 3Rs will form part of training curricula being prepared by the Network Training Centre. It should be noted however that the main responsibility of regulators is to ensure that vaccines are of good quality, safe and effective. In order to get the assurances needed, in vivo studies are a necessary requirement and, a reduction in animal use cannot be used as a justification for not presenting (or requesting) a 'needed' study'.

Proposed action: EMA to provide training to assessors on 3Rs principle, Responsible actor: EMA, Outlook: Short term

2.3. Benefit/Risk recommendations

Recommendations under this category directly relate to the assessment of the benefit / risk of vaccines and feature relatively high in the priority list (priority levels range from 3 to 7). They are grouped as follows:

2.3.1. Consistency of assessment

The improvement of consistency among assessors appears to be a significant concern. Consistency is also recognised by regulators as important element of assessments that provides a fair evaluation of the product. To ensure that assessors are assisted in this context, EMA has initiated a revision by CVMP of the template and guidance used by assessors for the reporting of the scientific overview and List of questions (LoQ) during immunological assessments (revision of template guidance of scientific overview and LoQ for immunological products). The revision is aiming to provide common approaches as much as possible in the way that assessments are presented so that they become more comparable, clear and consistent. It is aimed that the revision will be concluded by January 2017 and relevant training for assessors will commence. Training for immunological assessors accommodated by the Network Training Centre may also promote consistency by providing a common understanding on scientific and regulatory developments across EU assessors. It has also been suggested that the inclusion of experienced assessors and the establishment of multi-national assessment teams may be ways to promote consistency.

Proposed action: Revised version of the template guidance of scientific overview and LoQ for immunological products, Training for immunological assessors, Responsible actor: EMA, CVMP (CADVVA/IWP), *Network Training Centre, Outlook: Short term*

2.3.2. Acceptance of data from geographical regions outside EU in particular on safety and efficacy (part 3 and 4) and inclusion in the Benefit/Risk (B/R) part

The acceptance of data from other geographical data outside the EU appears to be a recurring topic that was considered best to be placed under the Benefit/Risk section as it is important for both

industry and regulators to investigate its impact on the overall B/R. It should be noted that such data may already be accepted if clinically relevant and if of appropriate quality standards. However because of its repeated nature throughout the list of recommendations and its relative significance it is proposed that industry provide specific concerns and possibly examples and proposals on this issue to SG and CADVVA that can reflect whether there is merit for further action.

Proposed action: Industry to provide specific concerns, examples and proposals, Responsible actor: Industry, SG, CVMP (CADVVA/IWP) to review industry proposal, Outlook: Medium term

2.3.3. Increased flexibility in assessment of alternative approaches

Flexibility in assessing different approaches that are not laid out in guidelines seems to be important by industry. Training for assessors on new developments may be the most appropriate way to accommodate novel approaches and their assessment. It should also be noted that the role of the Scientific Advice Working Party and the possibility for applicants to receive Scientific Advice is an important one on issues that are not specifically included in guidelines.

Proposed action: Training of assessors, Responsible actor: Network Training Centre, Outlook: Short term

2.3.4. Different level of requirements for companion versus food producing animals (individual vs herd immunity)

During the 2015 workshop on veterinary vaccine requirements and as reflected in this recommendation industry raised concerns on the current levels of requirements for demonstrating efficacy for veterinary vaccines. They have specifically emphasised the need for regulators to make provision for the differences in demonstrating herd immunity relevant for vaccines for food producing species and individual immunity applicable to small animal vaccines. In recognition of these concerns the CVMP when adopting the Terms of Reference for its ad hoc expert group on veterinary vaccine availability (CADVVA) has included a commitment for IWP to reflect on how best to take into account such differences as part of guidance on the benefit-risk assessment of veterinary medicinal products. Establishing a common definition for herd immunity from which the definition of efficacy can be established is one of the points raised by CADVVA when discussing this recommendation and the best ways to address it.

Proposed action: CVMP/IWP to reflect how best to take into account differences between individual vs herd immunity as part of guidance on the benefit-risk assessment of veterinary medicinal products. Actor: CVMP (CADVVA/IWP), Outlook: Medium term

2.4. Quality recommendations

Recommendations under this section relate directly to the Quality (Part 2) of the authorisation dossier. With the exception of one issue most appear to cover very specific and technical aspects.

2.4.1. Possible (restricted) extrapolation for setting maximum pre-inactivation titre

Extrapolation of inactivation kinetics requires data to demonstrate a linear/log correlation with the inactivant. For some inactivants such as BEI there may be sufficient data to extrapolate due to inactivation following first order kinetics and therefore the principle could be applied. For inactivants such as formaldehyde no such extrapolation is possible. IWP has published a questions and answers

document in 2009 (effective since 2013) confirming that no extrapolation to higher titres is considered safe. It is therefore suggested that the IWP is invited to consider whether to follow up this point further or not (e.g. invite industry to provide further examples of when and how extrapolation could be used).

Proposed action: CVMP/IWP to decide whether follow up is required. Actor: CVMP (CADVVA/IWP), Outlook: Moderate

2.4.2. GMP issues

There are a number of GMP related recommendations by industry highlighting the competence of GMP inspectors as the appropriate people to discuss GMP issues. On the other hand GMP issues affect the quality of a vaccine and therefore the assessors have a legitimate involvement in this section too. It would therefore be useful for all involved to prioritise GMP related training and possibly a joined workshop between assessors and inspectors would enable better understanding of GMP issues in the context of an authorisation dossier. Industry would also be asked to provide a list of GMP issues for which they encounter difficulties in addressing during the authorisation process.

Regarding the request made by industry to GMP inspectors to exclude immunological veterinary products (IVMPs) from the QP declaration requirement, on the basis of legal constrains and lengthy past discussions the SG considers that it cannot be supported, especially in view of the relatively small impact on availability.

Proposed action: Industry to provide a list of GMP issues where they encounter difficulties, Training on GMP issues (e.g. joint workshop), Responsible actor: Industry, GMP inspectors/SG, Outlook: Medium term

2.4.3. Stability issues: i) acceptance of R&D batches for providing stability data during at assessment time, ii) Real time stability data to be provided for actual shelf life, and not for shelf life + 3 months

i) There was a request by industry that information regarding vaccine stability in the authorisation dossier is based on research and development batches rather than only on routine production batches. The Directive requires only that a sufficient number of batches manufactured using production process is used thus there is no current requirement for full scale production batches in legislation. On the other hand *Ph. Eur. 62* (representative batches) and relevant IWP guideline (3 consecutive batches, pilot scale) provide specific reference on the type of these three batches that need to be used for providing stability. However from the EU Directive perspective there is an opportunity for flexibility on the number and size of batches used for stability studies and whether they are manufactured to GMP.

The CVMP/IWP could be invited to reflect if sufficient guidance is available on this topic.

Proposed action: CVMP/IWP to reflect if sufficient guidance is available on this topic, Actor: CVMP (CADVVA/IWP), Outlook: Medium term

ii) Currently the *Ph. Eur.* Monograph 062 for Veterinary Vaccines states: "*Stability. Evidence of stability is obtained to justify the proposed period of validity. This evidence takes the form of the results of virus titrations, bacterial counts or potency tests carried out at regular intervals until 3 months beyond the end of the shelf life on not fewer than 3 representative consecutive batches of vaccine kept under recommended storage conditions*". Although industry considers that there is no legal constrain to their request to use real time stability data for the actual shelf life this (data from 3 months beyond shelf life) is a requirement included in the above monograph.

As this a requirement of the monograph it is proposed that at first instance IWP/CVMP are invited to review the concerns expressed by industry. Following such review the SG would organise a high level meeting with EDQM to discuss the position of CVMP/IWP regarding industry's concerns and possible ways forward. However it should be noted that as proposals for change to EP monographs involve preparing a dossier of evidence to support the need for each change proposed it would probably fall to industry to coordinate the work required for the compilation of such dossier with EDQM being the responsible body for the final decision.

Proposed action: IWP/CVMP to review, SG to organise meeting, Industry to support change, EDQM to decide. Actor: CVMP (CADVVA/IWP), SG, Industry, EDQM/15V, Outlook: Unknown

2.4.4. New platforms for quality dossier

i) Vaccine antigen master file: The legislation provides for the concept of vaccine antigen master files. Likewise, given the fact that this concept has not been successful when applied to vaccines for human use, it is considered that as a first step industry provides a proposal of how they envisage to use the vaccine antigen master file (with specific examples if possible) and then the CVMP/IWP assess whether this can represent a basis for initiating the drafting of a guideline. It would also be useful to investigate and clarify the reasons why the concept was not successful for vaccines for human use.

Proposed action: Industry to provide proposals for CVMP/IWP to assess, EMA to investigate reasons why the concept not successful for human products, Actor: CVMP (CADVVA/IWP), EMA, Outlook: Medium term

ii) Vector vaccine platform: Industry is requesting to establish a regulatory platform/depository for vector vaccines that use the same vector but have different inserted gene(s). There is no legal constraint to stop considering this request; however as a first step to consider such concept it is best for industry to provide a clear proposal on how they envisage this platform (with specific examples if possible) with a view for CVMP/IWP to review and reflect on how best to follow up. It should be noted that it would require the IWP substantial work to develop a guideline on assessment of vector vaccine 'families' rather than viewing each new construct as a new (GMO) organism, if it was considered appropriate At the same time it is also noted that such a concept may not have significant impact in data needed for a new vaccine application but may simplify the level information needed on the dissemination of the vector.

Proposed action: Industry to provide proposals on vector vaccine platform at first instance and CVMP/IWP to follow up; IWP to include it in their work plan, Actor: Industry, CVMP (CADVVA/IWP), Outlook: Long term

2.4.5. Miscellaneous

i) Extraneous agents testing only on starting material: given the GMP controls on starting materials this request can be valid although a risk assessment for each process and each manufacturing site may be needed. The Annex 2 of the Guideline on requirements for the production and control of IVMPs (EMA/CVMP/IWP/206555/2010-Rev.1) and the reflection paper on methods found suitable within the EU for demonstrating freedom from extraneous agents of the seeds used for the production of IVMPs (EMA/CVMP/IWP/251741/2015) are expected to be finalised and published soon, and could potentially address some of the above concerns on extraneous testing on starting materials.

Proposed action: CVMP/IWP finalise documents on extraneous agents, Actor: EMA, CVMP (CADVVA/IWP), Outlook: Short term

ii) Acceptance of cell-culture-derived antibiotic residues in vaccines: antibiotic residues in vaccines have not been posing a concern so far among regulators given the negligible residue amounts that may be found in such products. Therefore further clarification may be required in order to fully understand the problem raised. It is proposed that industry provides a clear description of the problem to the SG that can decide who is best to follow up.

Proposed action: industry to provide clarification document to SG to decide best follow up, Actor: industry, SG, Outlook: Short term

iii) Reduced safety and efficacy requirements for cell line replacement if Final Product Control (FPC) test results remain the same: Industry makes reference to the reflection paper on the replacement of cell lines used for the production of immunological veterinary medicinal products (IVMP) (EMEA/CVMP/IWP/37620/2014). Given that the paper was only adopted in September 2015 and given that such cell line replacement is a relatively rare occasion it would be reasonable to request CVMP/IWP to take into account industry's request in the next revision but no further action should be envisaged in the meantime unless IWP considers a Q&A to the guideline appropriate.

Action: CVMP/IWP to consider industry's view on the issue in the next revision of the reflection paper on the replacement of cell lines used for the production of immunological veterinary medicinal products (IVMP) (EMEA/CVMP/IWP/37620/2014), Actor: CVMP (CADVVA/IWP), Outlook: Long term

2.5. European Pharmacopoeia (Ph. Eur.) recommendations

A small number of recommendations are directly relating to European Pharmacopoeia requirements and therefore the main actor for such changes is EDQM/Group 15V.

The first such recommendation is to subject the 'Development' sections of Ph. Eur. monographs to evaluation as industry considers that some are exceedingly demanding.

The second subgroup of recommendations that fall within the remits of EDQM/Group 15V relates to sterility issues. Industry is requesting in this recommendation for reduced sterility requirements for non-injectable & web wing vaccines respectively (presumably amended sterility test requirements on oral, spray and wing web administered vaccines). Reduced sampling requirements for sterility test (2.6.1) are also recommended for consideration.

A last point that falls under EDQMs competency is the request for reduced stability data (e.g. not 3 months beyond proposed shelf life, as described in the quality section under stability).

While recognising the competence of EDQM/Group15V (and for some sterility requirements Group 15 and other groups responsible for sterile products) to consider and resolve the above issues it is proposed that at first instance the IWP/CVMP will be invited to review the concerns expressed by industry. Following such review the SG would organise a high level meeting with EDQM to discuss the position of CVMP/IWP regarding industry's concerns and possible ways forward. It should be noted however that as proposals for change to EP monographs involve preparing a dossier of evidence to support the need for each change proposed it would probably fall to industry to coordinate the work required for the compilation of such dossier with EDQM being the responsible body for the final decision.

Proposed action: IWP/CVMP to review, SG to organise SG-EDQM meeting, Industry/EDQM to follow up Actor: CVMP (CADVVA/IWP), SG, EDQM/15V, Outlook: Long term

3. Summary conclusion

In order to assist with the processing of all the above information the following parameters are summarised in this section: a) Main priorities and actions arising from addressing industry recommendations, b) main responsible actors.

The highest industry priority that covers more than one specific recommendation relates to the role of efficacy field trials in the authorisation of veterinary vaccines and is proposed to be addressed by organising a high level focus group. In this context and in order to allow an in depth discussion and exchange of views between stakeholders, including external experts it is proposed that this focus groups will address the issues surrounding efficacy field trials and will review the need for revision of the CVMP guidance on field trials with veterinary vaccines .The conclusions of the group would be included in a report and could form the basis for points to be considered when reviewing the relevant CVMP guidance. This focus group should form the main priority for the SG for 2017.

It is also clear that the role of industry will be important in addressing some of the availability issues. This is because it is critical for regulators to have a clear understanding of the exact problems that industry faces and their proposed solutions. As a result industry is asked to present their specific ideas (with specific examples where possible)on a number of high priorities for which further clarification is necessary including among others the specific problem statement with regards to the role of serology, the proposed use and validity of PhV data in the context of an authorisation, the simplification of SPC requirements for vaccines and validity of data from geographical regions outside EU in particular on safety and efficacy (part 3 and 4) and inclusion in B/R, envisaged use of the antigen master file and vector vaccine platform. It is possible that following the presentation by industry on the above issues the SG may decide to follow up some of those issues by establishing new focus groups.

CVMP and in particular IWP are invited to consider a range of recommendations as listed in the table below. The CVMP ad hoc group on veterinary vaccine availability (CADVVA) will be the group that will be invited at first instance to review all CVMP related actions and involve CVMP/IWP as considered appropriate. Given its technical expertise IWP will be most likely be invited to review most quality issues and also provide a view on the proposals made by industry on European Pharmacopoeia monograph changes. CVMP/IWP is expected to provide an opinion on industry's proposals and clarifications for the issues which have been identified as requiring further input by industry.

CMDv is mainly tasked with addressing the autogenous vaccine issue, whereas EMA has been allocated actions relating to coordinating training with the Network Training Centre and the revision of templates for immunological products.

Issues related to change proposals to European Pharmacopoeia monographs by industry will need the input of a number of actors such as IWP/CVMP to provide a position on industry's proposals, the SG to organise a high level meeting with EDQM to discuss the IWP/CVMP position, industry to coordinate and support the change process and ultimately EDQM who will make the final decision as to whether these changes can be accepted or not.

Finally the SG is expected to prioritise and coordinate the implementation of all proposed actions, to monitor and track their progress.

Responsible Actor	Action
Steering Group	The SG is expected to prioritise and coordinate the implementation of all proposed actions, monitoring and tracking their progress. The SG is also expected to take the lead in organising any focus groups that have been agreed to be organised i.e. efficacy field trials and in deciding on appropriate participants for such groups. SG is also expected to lead in to organising a high level meeting with EDQM to discuss industry's concerns and CVMP's position and in communicating with industry the progress of the agreed priorities and actions.
EMA	EMA has been allocated a number of actions, namely related to the following: • coordinating with the Network Training Centre on training of assessors to improve better flexibility on alternative approaches, • revision of template and guidance of scientific overview and LoQ for immunological products, • training on 3Rs, • Investigate and clarify the reasons why the Vaccine Antigen Master file concept was not successful for human products.
CVMP (CADVVA / IWP)	The CVMP and at first instance CADVVA (the CVMP ad hoc group on veterinary vaccine availability) is invited to work on a number of issues and involve IWP as considered most appropriate. It is expected that IWP will be directly involved on all quality issues. In this context recommendations for CVMP actions relate to: • proposal to review industry's problem statements on serology as a surrogate marker of efficacy and proposals on the validity of PhV data when used in the context of an authorisation, • safety and efficacy laboratory studies - GLP issues, • proposal to review industry's proposals on SPC simplification.
	• Training of assessors.
	• Difference in efficacy demonstration for companion vs small animal vaccines - reflect how to take into account in B/R guideline.
	• Possible extrapolation of inactivation kinetics: IWP to reflect how best to address.
	• Stability issues: IWP to reflect how best to address.
	• Vaccine antigen master file and Vector vaccine platform: review industry's proposed use and recommend whether to initiate guideline drafting. Include drafting of guideline in IWP work plan.
	• Extraneous agents testing: IWP is providing already input at the

Responsible Actor	Action
	VICH paper on extraneous testing, • review industry's comments on changes to European Pharmacopoeia monographs and provide CVMP/IWP position on proposed changed.
CMDv	CMDv is invited to consider the recommendations relating to: • autogenous vaccines, • grouping of changes relating to production transfer, • MRP & repeat MRP procedures: investigate what extent problems have been experienced with vaccines going through an MRP and repeat use procedure and how these were resolved.
EDQM(Group 15V)	EDQM (Group 15V), is the appropriate body to implement issues directly relating to their area of competence: • subjecting the development of some sections of Ph. Eur. monographs to evaluation that are considered excessive or confusing, • specific sterility issues raised by industry, • reduced stability data (up to shelf life and not +3).
Industry	Industry itself is required to provide: • specific problem statement and examples on use of serology as a surrogate marker of efficacy, • proposals and examples on the validity of PhV data when used in the context of authorisation, • proposals and examples on SPC simplification, • proposals and examples on validity of data form non EU countries, • list GMP issues where problems are encountered, • proposals and examples on vaccine antigen master file and vector vaccine platform envisaged implementation, • clear description of the antibiotic residue concerns, • compile necessary evidence dossier and co-ordinate with national representatives to implement changes to European Pharmacopoeia monographs following CVMP/IWP's review (i.e. provide required supporting material for each proposed change).