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Autogenous vaccines: Quality of production and movement in a common market

Kornelia Grein [a], Carmen Jungbäck [b], Vaughn Kubiak [c]

[a] Veterinary Medicines Consultancy, Frankfurt am Main, Germany
[b] IABS-EU, Germany
[c] IABS, France

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ABSTRACT

An international meeting, held in Munich, Germany, on 14–16 September 2021, explored the expectations and views of different stakeholders regarding the implementation of the new veterinary medicines Regulation (Regulation (EU) 2019/6) in respect to inactivated autogenous vaccines (AVs) in non-notifiable diseases. Guidance documents on specific Good Manufacturing Practice (GMP) for AVs are acheduled to be developed at EU and a wider international level in the future. Presentations and discussions by the experts from regulatory authorities, industry and users made it apparent that their views on the quality requirements for the starting materials as well as quality standards for premises, personnel and manufacturing were broadly aligned for most of the aspects considered. The conclusions and recommendations of this meeting are expected to facilitate the development of urgently needed guidance documents for a harmonised implementation of this element of the Regulation.

1. Introduction

Autogenous vaccines against non-notifiable diseases are a complementary tool in veterinary medicine when a licensed vaccine[1] is not available for treatment and control of infectious diseases in animals. They have gained increased importance over the years in particular due to the efforts to reduce the use of antibiotics. Autogenous vaccines were in the past excluded from the EU legislation [1] and have been regulated independently by Member States leading to differences in approach and requirements. The new veterinary legislation, Regulation (EU) 2019/6 [2], which will enter into force on January 28, 2022, lays down legal provisions on inactivated autogenous vaccines (AVs) including provisions for their manufacturing, control and use. The responsibility for the authorisation of AVs will remain with the national competent authorities. Supportive guidelines, which will ensure harmonised requirements for production and quality of the final product, will be developed in the years 2022–2025 under the mandate of the European Commission by competent expert groups at the European Medicines Agency (EMA). Guidelines will also be prepared in parallel internationally under the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S). The International Alliance for Biological Standardization (IABS), together with the European Manufacturers of Autogenous Vaccines & Sera (EMAV), organised an international Workshop on AVs, which was held on 14–16 September 2021 in Munich, Germany [3], to initiate discussions between competent authorities, manufacturers and users of AVs and facilitate the development of urgently needed guidance documents for a harmonised implementation of the Regulation.

Twenty-seven (27) experts from national authorities, manufacturers and users provided presentations in five different sessions. These experts and meeting attendees participated in roundtable discussions at the end of each session and during a final discussion forum. Many aspects were addressed repeatedly at several points during the meeting but are summarised under the relevant heading instead of addressing them in chronological order.

The meeting was opened by Professor Dr Reinhard Straubinger, the Dean of the Faculty of Veterinary Medicine at the Ludwig-Maximilians-University Munich, highlighting emerging key points for discussion.

2. Legal provisions

Regulation (EU) 2019/6 defines the veterinary autogenous vaccines

E-mail address: info@kgvetmedconsult.com (K. Grein).

[1] The term 'licensed' is used here when referring to authorised veterinary medicinal products according to the EU legislation or other equivalent legislation in place.

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falling under its legal framework as '*inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals in an epidemiological unit and used for the treatment of that animal or those animals in the same epidemiological unit or for the treatment of an animal or animals in a unit having a confirmed epidemiological link*' (Article 2 (3)).

Article 106 (5)) on the use of medicinal products restricts AVs to ' … *only be used in exceptional circumstances, in accordance with a veterinary prescription, and if no immunological veterinary medicinal product is authorised for the target animal species and the indication'*. The provisions for use of a medicinal products outside the terms of a marketing authorisation under Article 112, the so-called 'cascade', are however silent regarding the use of AVs.

The other legal provisions applicable to autogenous vaccines are: Article 94 (obligation for good manufacturing practice (GMP) certification), Article 105 (obligations for veterinary prescriptions), Article 108 (record-keeping by owners and keepers of food-producing animals), Article 117 (collection and disposal of waste), Article 120 (prohibiting advertising for autogenous vaccines), Article 123 (control of manufacturers and importers) and Article 134 (conditions for prohibiting the supply). Clarification is required that GMP compliance of the manufacturing conditions according to Article 94 is only applicable once the specific guidelines for AVs will have been established as inferred in Article 159.

Furthermore, recital No. (70) of the preamble to the Regulation referring to AVs states that ' … *detailed guidelines of good manufacturing practice should specifically be prepared for those products since they are manufactured in a way that is different from industrially prepared products. That would preserve their quality without hindering their manufacturing and availability*.'

3. General considerations and expectations from different stakeholders

The speakers reiterated the necessity for AVs as critical responses to emerging epidemiological situations where no licensed vaccine is available or where it is not efficacious in treating the disease. This specific scenario demands that the AV is manufactured and made available in a very short time, differing considerably from the development timeline for a licensed vaccine.

In order for the veterinarian to identify if a licensed vaccine is available or to obtain more information on its efficacy, the new Union Product Database and Union Pharmacovigilance Database, established under Regulation (EU) 2019/6, will be helpful. If no suitable licensed vaccine is available, the responsible veterinarian is obliged to provide a sound justification for the use of an AV to solve the animal health situation. It was discussed whether or in how far the responsible authority should be involved in this decision. The primacy of licensed vaccines is non-disputed.

AVs can only be manufactured from the pathogens which were obtained within the concerned epidemiological unit or unit having a confirmed epidemiological link and are only allowed to be used by the prescribing veterinarian or under his/her supervision in this epidemiological unit/link. The introduction of the terminology of "epidemiological unit" and "confirmed epidemiological link" in the scope of applicability of AVs is welcomed and recognises husbandry practises, including breeder and hatchery operations and cross-border movement of animals. These terms would benefit from further clarification to provide for consistency in interpretation and use, however.

Further clarification of these terms is particularly needed for aquaculture production systems, as the determination of epidemiological unit boundaries, including confirmation of an epidemiological link between the epidemiological units in aquatic animal husbandry is posing specific practical and regulatory challenges. This is primarily due to the open nature of aquaculture production facilities which frequently share water resources and are in close proximity to wild aquatic animal populations. Such specificities present different risks than the ones commonly addressed in terrestrial or avian animal production. Therefore, concern has been raised that definition of epidemiological units and confirmation of epidemiological links solely based on circumstances relevant to terrestrial or avian livestock could lead to an unequal burden related to prescribing, production, and use/application of aquatic animal specific autogenous vaccine products.

AVs are custom-made products with mostly small batch sizes compared to industrially manufactured vaccines; however, batch sizes for AVs may vary widely. Normally, only one batch for an AV is produced. Manufacturers typically produce many small AV batches, their number ranging from several hundred to several thousand per year (or millions in case of aquatic animals), depending on the manufacturer. The manufacturers often deal with a wide range of pathogens/antigens and need to handle processes with different antigens in the same room during a day. The processes applied are mostly manual. The revenue for small batches, i.e. for companion animals or minor species, is small and AVs need to be affordable.

The introduction of legal provisions for AVs (and their implementation) and the development of harmonised EU-GMP guidelines were welcomed and will ensure that manufacturers produce AVs under uniformly defined and controlled conditions in the future.

Accepted general principles were discussed, including the requirement that no AV shall be produced from pathogens of notifiable diseases. For AVs used in food-producing animals, the materials used need to comply with the current legal requirements concerning residue in food (Maximum Residue Limits (MRL) legislation). Freedom from transmitting animal spongiform encephalopathy agents needs to be confirmed, whenever relevant. The use of antibiotics in the production of AVs should be avoided. If it cannot be avoided, their use should be justified. Antibiotics classified as critically important must not be used in the manufacturing process, and they must not be used as preservatives. The use of preservatives should be justified, and their effectiveness be tested.

The recommendations by the Coordination Group for Mutual Recognition and Decentralised Procedures - Veterinary (CMDv) for manufacture, control and use of autogenous vaccines [4] serve currently as basis for the rules applied by authorities and manufacturers, with additional detailed national rules established by a few Member States. Some presentations from manufacturers described the proposals developed by the EMAV on GMP requirements for AVs [5], which have been developed based on the CMDv document.

The availability of licensed medicines, in particular licensed vaccines, for fish is very limited. At the same time, aquaculture plays an increasing role in the food supply with, beside other reasons, the limitations of capture fisheries. Aquaculture is a highly diverse production and covers a large number of different species produced in a wide range of production systems and conditions (from freshwater to marine, from cold to warm waters). Biosecurity, including epidemiological units/links establishments and vaccination efforts have successfully been used to reduce the use of antimicrobials in salmon aquaculture, and other species/systems are following. Due to the diverse nature of aquaculture, bacterial, parasite and viral AVs for fish are manufactured, with the viral AVs being produced under principles and practices much closer to the ones used in the production of licensed vaccines. The licencing, labelling and cascade provisions are not fully compatible with the needs of veterinary services to act in the best interest of the farmers and farmed aquatic animals. AVs are very important tools for prevention and treatment of different infectious diseases occurring in fish. In order to ensure and secure access to and availability of autogenous vaccines in aquaculture, it will be necessary to acknowledge aquatic animal production specificities in future discussions.

4. Starting materials and seeds

The appropriate selection and standards of the starting materials are

vital to establishing the required quality and safety of an autogenous vaccine, and also have an important role for achieving its desired efficacy. Starting materials were defined as 'all components used in the production of an AV, including active substances/seed materials, culture medium, adjuvants, other excipients and the primary packaging'. The views expressed by speakers and other meeting participants were broadly aligned.

All starting materials, except the active substance(s)/seeds, should comply with the specifications of the relevant European Pharmacopoeia (Ph. Eur.) [6] monographs, and in absence of Ph. Eur. Monographs, with appropriate national pharmacopoeias. Starting materials without pharmacopoeia monographs need to comply with the supplier's specification and be "fit-for-purpose".

Starting material used for food producing animals need to comply with MRL provisions.

An example of a certificate of analysis for each starting material should be provided. For starting materials of animal origin, a certificate of origin for each should be provided from each supplier.

Regarding the certification of suppliers, the level and formality applied to their qualifications should take account of the nature of the material and be commensurate with the risk.

A system of receipt, inspection and release of starting materials should be in place and documented in writing. Testing should only be carried out by the manufacturer where a risk assessment justifies its conduct. Stored starting materials should be appropriately labelled. Reference samples of critical starting materials should be kept for at least three months beyond the expiry date of the last batch of the finished product using them.

Starting materials of animal origin, including cells for production of viral vaccines, shall comply with the relevant Ph. Eur. Monograph as well as general monographs and chapters of the Ph. Eur. They must be free of relevant pathogens and extraneous agents. Testing for extraneous agents is limited to those that cannot be excluded through risk assessment including analysis of purification and inactivation steps. The risk assessment should be comprehensive, justifications robust and relevant, and the supportive bibliography should be relevant. Testing methods for detection of extraneous agents should preferably be *in vitro* methods and be highly sensitive. The methods should be validated and have justified limits of detection (LODs).

The seed material has to be isolated by the prescribing veterinarian, or under his/her supervision, from the concerned epidemiological unit/confirmed epidemiological link. This requires the veterinarian to select the right timing, the right animal(s) and the right organ(s) from which samples are isolated. It was proposed that for viral seeds the sampling should be carried out only by the responsible veterinarian.

The use of the right isolation and identification techniques are vital for the safety and efficacy of the AV. Thus, isolation and identification should be conducted by a competent authorised site according to purpose-fit methods and following established Standard Operation Procedures (SOPs), e.g. by a diagnostic laboratory or licensed manufacturer. For viral AVs the virus isolation and identification should be carried out by an accredited laboratory and follow Ph. Eur. principles.

Viruses and bacteria isolates should be handled in a seed lot system established in accordance with GMP principles. Adequate measures should be in place to avoid mix-ups, and/or contamination with other organisms not intended to be AV's active substance. Where appropriate, cell line seeds used for viral AVs should be placed in a clearly established master cell seed bank (MCS).

All seed material should be pure, i.e. it should contain only the isolated pathogen and no mixed cultures of other organisms. The Ph. Eur. requirements for the relevant pathogen species should be considered.

Starting material originating from animals which might carry transmissible spongiform encephalopathies (TSE) should comply with relevant TSE provisions, in accordance with Ph. Eur. requirements and EU TSE guidance documents.

The re-use of isolates should only be authorised based on a robust justification by the veterinarian and provided it has been verified that they are still relevant for the locality and/or epidemiological link, as applicable to terrestrial, avian and aquatic animal production systems.

The vaccine composition, in particular the choice of suitable adjuvants and their combination, is highly relevant for the efficacy and safety of AVs.

5. Premises and personnel

GMP is designed to minimise the risks involved in any pharmaceutical production that cannot be eliminated purely by testing of the final product. Adherence to GMP principles for manufacturing facilities, processes and personnel adjusted to the need of AVs will ensure that products are consistently produced and controlled according to defined quality standards, thus ensuring the quality of the AVs produced. Deviations from the standard GMP requirements should be based on sound risk assessment and risk management considerations and appropriate measures, e.g. by separating work banks and maintaining clear strategies on airflow. Monitoring procedures should be implemented to support continuous risk assessment.

There was broad consensus that the GMP guideline to be developed for AVs and be tailored for their specific manufacturing conditions and requirements, should be prepared as a stand-alone document, rather than being formulated as deviations from the GMP guideline for industrially produced, licensed vaccines.

The manufacture of AVs should be carried out in clean areas, only accessible through personnel and material airlocks. The premises and equipment should satisfy appropriate hygienic standards, in particular surfaces should be smooth, unbroken or resistant against cleanings material and disinfectants, and constructed to allow easy cleaning.

In order to ensure that no contamination of the AV by dust or microorganisms occurs during production, the layout of the premises should be designed following a logical order considering the sequence of operations (one-way process flow system) and required cleanliness levels. These should include zoning concepts and specific clean areas, separated from other areas/rooms by an airlock system. Separate units should exist for production, quality testing, storage, diagnostics, technical rooms, changing rooms, and other facilities. Diagnostics and isolation facilities should preferably be located in a separate building. The purpose of each area/room should be clearly designated and documented in a master plan together with the flow of people and product. Access to production zones should be only allowed for authorised personnel.

Procedures justifying the production of multiple batches in the same room on the same day based on a risk assessment need to be established and adequate measures to avoid mix-up and/or contamination with other organisms or antigens should be in place; the procedures should also ensure separation of live and inactivated antigens.

Safety work benches or biosafety cabinets with laminar air flow systems should be in place, as appropriate for the operation. Suitable environmental conditions should be ensured on a risk basis with suitable air filtration systems.

A system of 'qualification and validation' of clean rooms derived from the GMP system for industrial vaccine production and adjusted for the needs and specificities of AV production was proposed with environmental air classes derived from the GMP classes A, C and D referring only to particle counts and designating the classes as A*, C* or D*. Environmental air classes for different operations based on risk assessment considerations were proposed [5]. Modifications of specificities of this proposed system and in particular in respect to the environmental conditions were considered as well.

It was recognized that for very small batch sizes the GMP requirements create a challenge that could prevent the ability to produce such vaccines. Therefore, specific considerations would be required to maintain availability of AVs under these circumstances whilst ensuring adequate quality and consideration of risk.

Adequate personal hygiene procedures including protecting clothing and health checking measures need to be in place, where appropriate with increased specifications e.g. breathing masks with own air supply, limited and defined access, for aseptic manufacture.

Personnel should have appropriate skills and qualifications, in accordance with their tasks, and mandatory training schemes should be in place with routinely scheduled training updates. Participation in these trainings should be recorded. For laboratory staff the suitable qualification might be a laboratory assistant trained in an appropriate discipline.

Head of quality control and the Qualified Person (QP) for manufacture and batch release, require a higher level of qualification with an appropriate university degree in a relevant scientific discipline and appropriate experience and training, which is specified e.g. in Regulation (EU) 2019/6 for the QP. The tasks and responsibilities of personnel need to be documented in job descriptions and organisation charts.

The holder of the manufacturing authorisation should have at least one QP for manufacture and batch release at its disposal. Deviations may be granted by the responsible authority.

6. Manufacture and final batch control

The manufacturer should hold a specific authorisation for the manufacturing of AVs specifying the organisms and antigens handled at the site. Manufacturing documentation (SOPs, manufacturing prescriptions) for each type of AV produced should be established. Manufacturing records should be produced and kept on site.

Particular challenges for AV production are the parallel or successive production campaigns. These require the implementation of specific organization and techniques to separate activities and control risks of contamination as described before to ensure that no cross-contamination or mix-up can occur. The measures and processes should be adapted to the risk analysis for the specific AV considering the type of pathogen/antigen.

A cleaning and disinfection management for rooms, materials and personnel should be established. Appropriate testing to detect any cross contaminations may need to be adapted or developed, depending on the risk assessment.

Critical manufacturing steps should be validated. Significant changes to the manufacturing process (e.g. equipment or materials), affecting product quality and/or the reproducibility should be validated. The validation may be carried out with a characteristic representative for a group of pathogens when they are prepared in the same way as the antigen used for production. Using possibly existing data for related organisms for validation requires sound justification. Bracketing design could be justified for validation of products based on extensive process knowledge and ongoing verification programmes. Process validation can be realised as a prospective validation, concurrent validation or retrospective validation, where this is justified. Equipment, facilities, utilities and systems should be qualified, and test methods be validated for the intended use.

To achieve complete inactivation is a highly critical step in the manufacture of AVs as it ensures the absence of both intended organisms and active adventitious agents. The inactivation should be carried out by adding an inactivation agent with sufficient agitation to the product or using another validated method, as described in the CMDv Recommendations [4]. It is important to ensure that all organism-bearing fluids are completely exposed to the inactivating agent, commonly achieved by using a two-vessel approach. Full validation of the inactivation method is required. For viral AVs the inactivation process and validation results are reviewed by the responsible authorities.

Minimum controls for the finished product before batch release are:

- Completeness of inactivation should be tested with at least 2 passages in the relevant culture system, with a validated test and the LOD defined. Residue levels of the inactivating agent should, where appropriate, be controlled as required by Regulation (EU) 37/2010 [7] in accordance with Ph. Eur.
- Sterility should be tested in accordance with Ph. Eur. 2.6.1., for which adaptations regarding sampling sizes or frequencies are proposed in case of small batch sizes, which need to be representative and justified. The sterility test should be performed (not incubated) under laminar flow, with environment air monitoring via settle plates. For the validation of the sterility test, the control strains specified in Ph. Eur. 2.6.1 should be used.
- Other tests may be required to ensure product quality, e.g. the content of endotoxins in endotoxin-producing microorganisms or adjuvant content, where appropriate.
- For viral vaccines, absence of extraneous agents should be ensured in accordance with Ph. Eur. requirements.

Stability testing is not considered mandatory for AVs. Antigen storage times under appropriate conditions for up to 12 months and a uniform shelf-life for finished product AVs of 12 months in appropriate conditions is proposed.

No in-use stability studies are considered necessary with packaging sizes designed for use within one working day.

If crucial controls are not possible to be carried out on the finished product it is proposed that they may be performed at an appropriate earlier stage of production.

Each AV batch should be certified by the responsible QP for batch release and stating the conformity with the specified manufacture and testing requirements.

The requirements for reference sampling have so far been set by the regulatory authorities and may vary. It was pointed out from manufacturers that sampling for AVs is particular challenging due to the large number of batches combined with small batch sizes. EMAV proposed to retain a minimum of one representative container per batch of finished product for at least six months after expiry.

7. Use of vaccines, import, export, surveillance

It was recognized that a wide range of licensed vaccines are available in EU Member States, authorised based on a full set of quality, safety and efficacy data. Development timelines for these are normally 5–10 years. However, the importance and role of AVs in addressing unmet needs of veterinarians in dealing with diseases in many animal species was highlighted. This situation is particularly pertinent in minor species including aquaculture and can occur in major species for diseases caused by a number of pathogens for which no licensed vaccines are available. The reason for the non-availability of licensed vaccines are numerous and include considerations such as variation of strains, or inadequate economic benefits to develop a vaccine.

To compensate for the partial waiving of the data on quality, safety and efficacy for AVs, measures have been put in place. These include, in particular, the limitations to inactivated vaccines, specific GMP requirements, standard processes for the manufacturing, and restriction of their use.

Presentations by representatives from authorities, and comments by manufacturers and users throughout the meeting, showed the differences in regulatory approaches applied at present at national level. The legal provisions and foreseen implementing acts under Regulation (EU) 2019/6 do not address several important aspects, which are expected to become part of national laws. It is however encouraged that harmonised EU approaches are also developed on these aspects, in order to provide for consistency in requirements and interpretation across the EU. In addition, this would allow for import/export of AVs as well as consistency in economics regarding AV production and for the provisions for animal health.

The areas for which these harmonised EU guidance documents are needed include: interpretation of the restrictions of use of AVs and restrictions of use within an epidemiological unit/epidemiological link,

monitoring and control of AVs by the competent authorities, the use of pharmacovigilance data to justify manufacturing and using AVs, standardised labelling of AVs and possibly harmonisation of their distribution, as well as precautionary measures when AVs are used in large groups of animals, such as conducting first a trial/tolerance test in a smaller group with an appropriate number of animals before wide application of the AV. Reporting of manufacture and use of AVs by manufacturers and practitioners on quantities and identity of antigens, but also reporting of any quality defects or adverse events, is envisaged. The establishment of an information system dedicated to AVs to facilitate this reporting was proposed. Furthermore, better interaction between national authorities regarding the control and monitoring of AVs in the future was recommended.

In particular, the terms 'epidemiological unit' and 'unit having a confirmed epidemiological link' require clear harmonised interpretation, as expectations appear at present inconsistent.

Also, the conditions under which the use of a given AV is allowed to be extended require further clarification.

Gathering information on the effects on use of AVs will be highly valuable for the practitioner as well as the manufacturer to optimise treatment results and possibly improve the vaccine. This information might even facilitate developing a licenced vaccine, e.g. an authorisation under exceptional circumstances.

It was also suggested that vaccine manufacturers would benefit from producing both AVs and licensed vaccines, and this could lead to more licenced vaccines eventually becoming available.

Finally, it was also suggested that the future applicability of innovative approaches for vaccines production like platform technologies or RNA techniques for AVs should be explored, recognising that this would require changes to the legislation.

8. Summary and conclusions

The new veterinary legislation, Regulation (EU) 2019/6, includes provisions for the manufacturing, control and use of inactivated autogenous vaccines (AVs). AVs are only allowed to be used in emergency situations, when licensed vaccines are not available due to a number of reasons and vaccinations against non-notifiable diseases are urgently needed. They are manufactured from the pathogens isolated from the concerned epidemiological unit or unit having a confirmed epidemiological link and are only allowed to be used in this epidemiological unit/link by the prescribing veterinarian.

Data on quality, safety and efficacy are partially waived for AVs due the use restrictions and establishing standards for manufacturing and control. The specific guidelines on GMP for AVs to harmonise the quality of manufacture and final product throughout Europe will have to be developed and the current workplan of the European Commission foresees that they are drafted and discussed by the competent expert groups and forums between 2022 and 2025.

It was stressed that the use of AVs contributes to the efforts currently made to manage emerging diseases and reduce the use of antibiotics, especially in food producing animals including aquaculture. AVs are an accepted component in a One Health approach by strengthening the opportunities in prevention of infectious diseases.

The GMP requirements for AVs should be rooted in the GMP guidelines for industrial immunological veterinary medicinal products adapted to the specific characteristics of AVs. These characteristics include a highly variable range of batch sizes and presentations needed for epidemiological units or units with a confirmed epidemiological link in food producing animals as well as for small holdings such as kennels, and the need to produce these vaccines in a short time and for an affordable price. This requires parallel working with different strains for different batches. AVs needed for aquaculture cover a large number of species in a broad range of production systems and will require additional considerations to ensure their availability and critical use. The GMP guideline for AVs should be a stand-alone document.

Quality and choice of the starting material have an important role in the safety of the product. The right combination of antigen and adjuvants enhance the prospects for the vaccine's efficacy. Materials used for AV production need to comply with current regulatory provisions, such as Ph. Eur., MRL legislation or TSE requirements. All materials and suppliers need to be qualified. Isolates used as seeds for vaccine production should be pure. The exclusion of extraneous agents in the starting material and final product should preferably be made by strategic testing and risk assessments, including analysis of purification steps and inactivation. Physical testing should be restricted to extraneous agents which cannot be excluded by risk assessment and ideally should be conducted using *in vitro* tests.

The future requirements for premises and personnel should resemble the GMP approach for licensed vaccines but reflect the specific conditions of the manufacture of AVs. Deviations should be justified by sound quality risk assessment and risk management considerations. The need for parallel or successive production campaigns in one room require implementation of specific measures to separate activities and control risks of contamination, such as zoning or by separating work banks, with clear strategies on airflow and handling of infected waste. The measures and processes should be adapted to the risk analysis for the specific AV considering the type of pathogen/antigen. High importance is given to appropriate qualification, training programmes and clear instructions for personnel.

Critical manufacturing steps should be validated. The validation may be carried out with representative antigens when they are prepared in the same way as the antigen used for production, which would expedite product availability. Complete inactivation is a highly critical step in the manufacture of AVs and full validation of the inactivation method is required. The minimum controls to be conducted for the finished product before batch release were proposed, as well as uniform shelf-life for AVs (12 months) and requirements for reference sampling.

A recording and documentation system for all aspects covered by GMP is required.

Gathering information on the effects on use of AVs will be highly valuable for the practitioner as well as the manufacturer to optimise treatment results and possibly improve the vaccine, and might even allow developing licenced vaccine, including an authorisation under exceptional circumstances. It was also suggested that vaccine manufacturers would benefit from producing both AVs and licensed vaccines, and this could lead that more licenced vaccines become eventually available.

9. Recommendations

Clear guidance for the interpretation of the terms 'epidemiological unit' and 'unit having a confirmed epidemiological link' should be prepared to provide for consistent application. This should include, where possible, the consideration of the diversity and specificity of aquaculture production systems.

The applicability of the 'cascade' system to AVs should be discussed and clarified.

Clarification on the implementation timelines for GMP certification under Article 94 in connection with Article 159 of Regulation (EU) 2019/6 is needed as well.

An information system and reporting mechanisms dedicated for AVs are proposed on:

- manufacture and use of AVs (by manufacturers and practitioners) specifying quantities and identity of antigens
- the movement of AVs and of the animals vaccinated with these products within the European market, and
- observed quality defects or adverse events.

This information is needed by the competent authorities to be informed on manufacture and movement of AVs and allow their

epidemiological surveillance. The interaction between national authorities regarding the control and monitoring of AVs should be strengthened.

Harmonised EU guidance documents should be produced regarding:

- monitoring and control of AVs,
- use of pharmacovigilance data to justify the use of AVs,
- standardised labelling of AVs,
- distribution of AVs,
- Precautionary measures when used in large groups of animals, such as conducting first a trial/tolerance test in a smaller group with an appropriate number of animals before wide application of the AV.

The use of innovative and modern techniques to produce AVs should be allowed and needs to be discussed with the legislators, even if this requires specific changes in the legislation.

Liaison between the expert group that will be mandated with drafting the GMP guidelines for AVs with the CMDv is highly encouraged.

Declaration of interest by the authors

None.

Moderators and speakers

Max Bastian, Secretary to the Standing Committee on Veterinary Vaccines, Friedrich-Loeffler-Institute, Germany.

Klaus-Peter Behr, EMAV, Germany.

Wiebke Bielenberg, AniCon, Germany.

Nancy De Briyne, Federation of Veterinarians of Europe (FVE), Belgium.

Rosario Bullido, Spanish Medicines and Medical Devices Agency, Spain.

Santiago Cabaleiro, Centro Tecnológico del Cluster de la Acuicultura (CETGA), Spain.

Panos Christofilogiannis, Aquatreck Animal Health SL, Spain.

Rory Cooney, Veterinary Medicines Directorate (VMD), United Kingdom.

Sebastien Deville, Airliquide, France.

Jean de Foucauld, CEVA, France.

Maarten De Gussem, Poulpharm, Belgium.

Ernö Horvath, Directorate of Veterinary Medicinal Products (NEBIH), Hungary.

David John, AnimalHealthEurope, Belgium.

Dietmar Katinger, Polymun Scientific Immunbiologische Forschung, Austria.

Ewald Van Kuppeveld, RIPAC Labor, Germany.

Iska Lehmann, LAVES, Germany.

Jordi López-Ramon, Spanish Federation of Aquaculture Health Defense Groups (FEADSA), Spain.

Dries Minne, Federal Agency for Medicines and Health Products (FAMHP), Belgium.

Petra Müllerová, Institute for State Control of Veterinary Biologicals and Medicines (USKVBL), Czech Republic.

Brigitte Othmar-Vielitz, EMAV, Germany.

Dusan Palić, Ludwig-Maximilians-University Munich, Germany.

Dietrich Rassow, Chief Veterinary Officer (CVO), Federal Ministry of Food, Agriculture and Consumer Protection (BMEL), Germany.

Mariette Salery, French Agency for Veterinary Medicinal Products (Anses-ANMV), France.

Peter Schmid, CEVA, Germany.

Ynte Schukken, Royal GP, The Netherlands.

Annie Sigognault-Flochlay, FILAVIE, France.

Alain Schrumpf, Laurent Drouet, CEVA, France.

Jason Todd, Veterinary Medicines Directory (VMD), United Kingdom.

Joris Vandeputte, IABS, Belgium.

Grégory Verdier, French Agency for Veterinary Medicinal Products (Anses-ANMV), France.

Florian Voisin, HYOVET, France.

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References

[1]] European Parliament and the Council of the European Union. Directive (EU) 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-5/dir_2001_82_cons2009/dir_2001_82_cons2009_en.pdf (accessed on 20 November 2021).

[2] European Parliament and the Council of the European Union. Regulation (EU) 2019/6 of the European Parliament and the Council of the European Union of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R0006&from=EN (accessed on 20 November 2021).

[3] International Alliance for Biological Standardization: Autogenous vaccines: Quality of Production and Movement in a Common Market – An IABS-EU and EMAV Workshop. Proceedings available at: https://autogenous-vaccines-munich-2021.iabs.org/index.php (accessed on 20 November 2021).

[4] Coordination Group for Mutual Recognition and Decentralised Procedures - Veterinary (CMDv). Recommendations for manufacture, control and use of autogenous vaccines. 2017. EMA/CMDv/452656/2016. Available at: https://www.hma.eu/fileadmin/dateien/Veterinary_medicines/CMDv_Website/Procedural_guidance/Miscellaneous/Recommendations_manufacture_control_use_inact_autogenous_vaccines.pdf. [Accessed 20 November 2021].

[5] European Manufacturers of Autogenous Vaccines & Sera (EMAV). EMAV Proposal: EU-GMP-Annex for Autogenous vaccines_rev 01. Available at: https://www.emav.be/templates/images/documents/85_1_pdf/EMAV-Proposal_EU-GMP-Annex-for AutogenousVaccines-032021.pdf. [Accessed 20 November 2021].

[6] Council of Europe. European pharmacopoeia. tenth ed. 2019. Strasbourg.

[7] European Commission. Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-5/reg_2010_37/reg_2010_37_en.pdf (accessed on 20 November 2021).