Chapter 5
Fish Vaccines: The Regulatory Process and Requirements from the Laboratory Bench to a Final Commercial Product, Including Field Trials

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Abstract Vaccines are recognised as important tools for the prevention and control of diseases in fish. The regulatory requirements for registering veterinary vaccines have grown considerably over the last 50 years; nevertheless, they have contributed to a steady increase in the availability of vaccines of high quality with good safety profiles and proven efficacy against many diseases. In the EU, there are stringent requirements for vaccine manufacturers to comply with good manufacturing practice (GMP); consequently, the cost of vaccine production is high. Compared with vaccines for other animal species, the market for fish vaccines is limited in size; however, the cost in meeting the regulatory requirements is similar and the cost of development is equally expensive. Fortunately vaccines for use in small markets may take advantage of the Minor Use Minor Species Limited Market (MUMS) and limited market process for which the regulatory requirements are reduced where a successful application can be made for inclusion in the MUMS listings. Also, the field of animal ethics is constantly changing, leading to some reductions in the regulatory requirements for animal studies performed to generate safety, quality and efficacy data. The pharmaceutical industry needs to keep abreast of such changes and amend product development plans accordingly to remain competitive in the market.

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Introduction

This chapter will explain the EU regulatory requirements to bring a fish vaccine through the basic development stages to the final product, including the registration process leading to the granting of the authorisation to market the product.

Although the registration process itself will be the same for any type of veterinary vaccine, for simplicity, this chapter will focus on the regulatory requirements for a monovalent inactivated bacterial vaccine for fish.

Where appropriate, the text will indicate the locations in the EU registration dossier where the data should be included and will provide references to EU guidelines which explain how to generate data suitable for inclusion in the dossier.

The regulatory requirements for fish vaccines differ slightly for each type of vaccine; however, guidelines (General requirements for the production and control of live mammalian bacterial and viral vaccines for veterinary use WC50004652 Vol 7BIm1a; Requirements for the production and control of inactivated mammalian bacterial and viral vaccines for veterinary use in 1992) are available to assist applicants intending to apply for marketing authorisations for all types of immunological veterinary medicinal products (IVMPs), whilst another guideline is available specifically for fish vaccines (Guideline on the design of studies to evaluate the safety and efficacy of fish vaccines & EMA/CVMP/IWP/314550/2010). The first two of these three guidelines have been superceded by a new, simplified guideline (Guideline on requirements for the production and control of immunological veterinary medicinal products EMA/CVMP/IWP/206555/2010) on the requirements for the production and control of immunological products, which clarifies some aspects of the regulations that applicants had previously been found to be ambiguous.

Vaccine Types

There are several categories of vaccines for use in humans and animals, and vaccines for fish fall within the same categories, namely, viral, bacterial, fungal or parasitic. Within these categories, vaccines can be live, attenuated or inactivated. To stimulate a protective immunity against a disease, the antigenic component of the vaccine may be prepared from whole cells, cell supernatant or parts of an immunising agent, e.g. subunit or vector vaccines.

Antigen Development

Once a market for a vaccine for immunisation against a specific disease has been identified and evaluated, a suitable source for antigen preparation must be found.

Generally, the strain of bacteria (or virus) selected for antigen production will have been isolated from a diseased fish. The strain will have been identified by

genus and species and allocated a strain designation. The strain will be tested to ensure that it is pure rather than a mixture of different bacteria. Its origin, date of isolation, passage history and storage conditions are recorded for presentation in the registration dossier (Part 2. C). If the strain has come into contact with any material of bovine origin during the development process or even in the finished product, a declaration to this effect must be included in the dossier under the section on "Minimising the Risk of Transmissible Spongiform Encephalopathies".

- Master Seed
  Once purity and identity are confirmed, a master seed is prepared. Several vials of the master seed will be produced. Normally these will be lyophilised (freeze-dried) by adding a stabiliser such as lactose, sucrose or bovine serum albumin to the culture. The master seed is a critical part of vaccine development and production. Its stability under the chosen storage conditions is essential to enable a continued supply of batches of the vaccine. The testing required for viral master seeds is far more extensive than for bacterial seeds since the absence of several potential extraneous agents (Table of Extraneous Agents to be Tested for in relation to the General and Species Specific Guidelines on Production and Control of Mammalian Veterinary Vaccines Vol 7BI10a) that could contaminate the seed must be shown. The master cell seeds for viral vaccines also require testing.
- Working Seed
  From the master seed, subcultures are prepared that will be used for development testing and for production. The generation or passage level to be used for production is known as the working seed. Preparation and storage of the master seed and working seed are known as a seed lot system. For bacterial vaccines, the number of passages between the master seed and the working seed is not limited but must be specified. The same passage level must be used for production of all subsequent batches of final product as is used in the batches with which target animal safety and efficacy are demonstrated. In contrast, the passage level for virus vaccine production is limited to five passages from the master seed, as specified in the European Pharmacopeia (Ph Eur) monograph 0062.

Vaccine Development Process

The next step in vaccine development is to determine what form of the antigen is to be selected to provide the best protection whilst remaining safe to the target species and stable in the final vaccine under the proposed storage conditions. This may already be known from previous experience or from the literature. If not, a series of experiments will be required to determine the optimum antigen preparation. Once the most suitable preparation is known, it is necessary to test its efficacy in a proof-of-concept experiment. There are no specific protocols to be followed for such testing, and indeed the results of these tests are not required to be included in the registration dossier. The design of all the tests carried out during this development

phase is the responsibility of the scientists working on the product. Experiments such as those described below may need to be performed several times, with slight modifications each time until a satisfactory outcome has been reached. The types of testing recommended and the parameters to be measured in such laboratory experiments include the following:

- Route of administration – this will depend on the age and species of fish to be vaccinated. For this example, testing for a vaccine to be administered by immersion will be used.
- Optimising the challenge dose – this involves the use of a heterologous strain of the same bacterium species as the vaccine strain and selecting the dose capable of killing 80–100 % of unvaccinated fish. The optimum dose will be measured in terms of colony-forming units (CFU).
- Efficacy – a preliminary efficacy test is performed by setting up, for example, three tanks containing an identical number of young fish (fingerlings) in each one. One tank of fish will remain as untreated controls. To one of the other two tanks, experimental vaccine is added at a high concentration and to the other one experimental vaccine at a low concentration. After a suitable time interval to allow immunity to develop, the optimised challenge dose is administered to each of the three tanks. The number of fish that die in each tank is counted to determine the protective index of the vaccine. This preliminary efficacy test is not a legal requirement. Eventually a controlled challenge test will be performed which is reproducible and supportive of the claim for efficacy.
- Dose – optimisation of the vaccine dose will not only confirm that the vaccine is efficacious but will avoid the unnecessary wasteful cost of using excess antigen for vaccinating fish. Dose optimisation is normally achieved by performing a dose titration study followed by a challenge infection to identify the minimum immunising concentration.
- Safety – unlike other animal species in which vaccines are mostly administered by subcutaneous or intramuscular injection or by intraocular administration, the assessment of safety at the injection site cannot be evaluated if vaccine is to be administered by immersion nor by oral administration with feed. The only practical way to assess safety in this case is to look for and record morbidity and mortality in vaccinated fish in the efficacy test prior to administration of the challenge dose. These tests are part of product development. There are no regulations describing what must be done. The manufacturer decides what to do at this stage and then, based on the results, decides whether or not to proceed with registration studies and apply for a marketing authorisation.

Although none of the results of these proof of concept studies are required to be included in the registration dossier, sufficient supportive information about them should be presented in the quality section of the dossier, “Part 2.4 Product Development”, which requires the applicant to provide an explanation regarding the composition, components and containers proposed for the commercial vaccine, supported by scientific data on product development.

In-Process Testing

During the studies to establish that the antigen is safe and effective, it may become necessary to introduce certain purification steps prior to formulating the vaccine. When this occurs, it will be necessary to introduce additional testing at different stages to ensure the identity, purity and safety of the antigen.

For inactivated vaccines, either before or after any early purification steps, it will be necessary to subject the bacterial culture to inactivation. Agents such as formaldehyde or betapropriolactone (BPL) are commonly used. During the development stages of vaccine production, the kinetics of any inactivation process must be validated. The Ph Eur requires that it be shown that the time required for inactivation shall be not more than 67 % of the duration of the inactivation process, thus allowing a 33 % margin of safety for inactivation during routine production of the vaccine.

Assay Development and Validation

Depending on the type of vaccine under development, one or more assays will be required to test the antigen quality during the in-process stages and in the final product. If the tests are not established ones, such as those included in the relevant pharmacopoeia monographs, it will be necessary to fully validate them. The following aspects of the test method should be demonstrated – specificity, precision, linearity, sensitivity (includes limit), repeatability, reproducibility and robustness.

Ideally, once a vaccine formulation has been developed and batches are being manufactured routinely, the batch release tests will not involve the use of live fish. For all veterinary vaccines, it is a normal practice, once efficacy has been demonstrated by challenge studies in the target species, to develop in vitro assays for batch testing, especially for batch potency testing. If an in vivo potency assay for a fish vaccine can be replaced by an in vitro assay, it is necessary to validate (VICH GL1 Guideline on validation of analytical procedures definition and terminology; VICH GL 2 Validation of analytical procedures methodology) the test and report such validation and its correlation with the in vivo assay in the registration dossier or by means of a post-licensing variation application. All inactivated vaccine potency tests must be validated to show that they are capable of detecting a subpotent batch.

Formulation/Blending of Bulk Vaccine

Some vaccines, particularly live attenuated virus vaccines, are presented in their final containers as lyophilised powder for reconstitution with a diluent. To ensure their stability following lyophilisation, they are usually blended with a stabiliser prior to filling into containers and being freeze-dried.

In the present example of a liquid monovalent inactivated bacterial vaccine, it is normal practice to include one or more adjuvants in the formulation when administered by injection. The advantage of an adjuvant in an inactivated vaccine is that it stimulates the slow release of the vaccine antigen, thereby improving the duration of exposure of antigen to the animal's immune system to improve the stimulation of antibody production. However, for inactivated vaccines administered by immersion, adjuvants are not normally included in the formulation.

Selection of Final Containers

Selection of the vaccine container is important. It must be sufficiently robust to ensure the stability of the vaccine at least until the end of the supported shelf life. It must also be suitable for the user to broach and use under field conditions. Consideration of the volume of the container is important and it is often necessary to select different container sizes to meet the needs of different customers. Details of the containers and closure, together with data to demonstrate the integrity of the closure system, are required in the registration dossier (normally Part 2. A.2). The marketing authorisation (MA) lists the volumes or sizes of all the containers approved for the product on the summary of product characteristics (SPC). Any additional containers required following the granting of the MA must be added by means of a variation to the MA before they may be commercialised.

Development Testing/Preregistration Testing

In parallel with developing the vaccine formulation and validating the assays, the development tests required by EU legislation (Commission Directive 2009/9/EC) can be started. These tests only need to be performed once. They are not the same as the batch tests performed on each batch of vaccine prior to its release.

The timing of these tests is important in the EU since they must be conducted using vaccine produced exactly according to the method that will be described in the registration dossier (Part 2. B.1 and 2. B.2). If any changes are subsequently made to the production process or the formulation of the finished product, the safety and efficacy tests will need to be repeated, prior to submission, using the revised formulation. It is therefore critically important that these studies are not performed too early in the development process.

An important and useful specific EU guideline (Guideline on the design of studies to evaluate the safety and efficacy of fish vaccines & EMA/CVMP/IWP/314550/2010) for testing the safety and efficacy of fish vaccines has been published as a result of the recognition by EU regulatory authorities of the problems faced when conducting safety and efficacy studies in fish compared with other species. This guideline allows for a reduction in the normal requirements for veterinary vaccines under certain cir-

cumstances. For example, for some fish vaccines, it may be appropriate to apply for classification under minor use–minor species/limited markets (MUMS). Once MUMS classification has been obtained, it is possible to register such vaccines in the EU with considerably reduced fees and in some cases with no fees applicable at all.

For inactivated vaccines, there is generally a requirement that the target species safety test is performed using a batch produced at maximum potency, whilst efficacy testing is performed using vaccine formulated at minimum potency. In practice, this means that the minimum potency allowed for batch release is established based on the potency of the batch used to demonstrate efficacy under controlled laboratory conditions. Likewise the batch release limit for safety is established by the antigen content/potency of the batch used for the development safety studies.

- Safety

Details of the target animal safety tests are described in VICH guideline GL44 (VICH GL44 Guideline on target animal safety for veterinary live and inactivated vaccines EMEA/CVMP/VICH/359665/2005). These tests must be conducted according to good laboratory practice (OECD principles on good laboratory practice) (GLP). They are divided into laboratory tests and field trials as follows:

– *Laboratory tests*, in which vaccinated fish are observed with each morbidity/mortality being recorded daily for at least 14 days after vaccination:

  (i) Single dose
  (ii) *Overdose* – (this is no longer required in the EU for inactivated vaccines)
  (iii) *Repeated dose* – if the recommended vaccination schedule requires more than a single dose

– *Reproductive safety,* only if relevant, i.e. if the fish to be vaccinated are to be used for breeding purposes

Omitted from this guideline, but available in its own separate guideline, is the test to be carried out with live attenuated vaccines – VICH GL41 – "Target Animal Safety: Examination of Live Veterinary Vaccines in Target Animals for Absence of Reversion to Virulence".

– *Field safety* – this is achieved by monitoring safety, e.g. weight gains and local reactions, in the efficacy field trials.

- Efficacy

As with safety, the data to be generated to demonstrate the protection afforded by the vaccine, as described on the label, falls into the two categories of laboratory tests and field trials.

– *Laboratory Tests* – these are normally challenge tests in the target species using the recommended route of administration and the proposed vaccination schedule. They must be performed in each category of species for which claims are made. The batches used must be manufactured according to the method described in Part 2 B.1 and 2. B.2 of the dossier, formulated to reach minimum potency.

It is normally required to demonstrate both onset and duration of immunity by challenge infection unless an alternative method is available which correlates with the protection afforded against challenge, e.g. serology. The duration of immunity is used to recommend the interval between the primary vaccination course and any subsequent booster dose if a booster dose is recommended. If duration of immunity is studied in field trials, these should be large-scale research facilities where fish can be taken from holding tanks at different intervals and subjected to challenge infection or specific antibody response if this has been shown to correlate with protection. The conditions in the holding tanks, e.g. water temperature, quality, etc., should be similar to the conditions under which the vaccine will be used naturally in the field.

It should be noted that in the fish vaccine guideline (Guideline on the design of studies to evaluate the safety and efficacy of fish vaccines and EMA/CVMP/IWP/314550/2010), it has been recognised that for some disease situations in fish, no or only poor challenge models exist. The guideline states that in such situations, with appropriate justification, more emphasis may be placed on field studies conducted under conditions which reflect the disease situation in the field. Ideally, duration of immunity (Note for guidance: duration of protection achieved by veterinary vaccines) should be based on the results found in both laboratory studies and field trials; however, it is important to monitor the fish at regular intervals in field trials to detect the occurrence of disease outbreak, so that the recommended time interval between the primary course and booster vaccination can be justified.

– *Field Trials* – as with all veterinary medicinal products, field trials must be carried out in accordance with good clinical practice (GCP) (VICH GL9). The fish vaccine guidelines (Guideline on the design of studies to evaluate the safety and efficacy of fish vaccines & EMA/CVMP/IWP/314550/2010) provide useful information about the design of the trials explaining that they should be carried out in established commercial fish farms; the field studies are to be performed in established commercial farms where the relevant disease is anticipated and should preferably include unvaccinated controls. Allocation of groups should be done randomly, and the prevalence of disease, daily mortality, clinical symptoms and other relevant parameters should be monitored in both vaccinates and controls for comparison. The treatment of the controls, i.e. mock vaccinated, vaccinated with a comparator vaccine or non-vaccinated, should be justified. Studies should be conducted at the time of year when the disease normally occurs.

Field trial permits must be applied for before trials can begin. The method for applying for field trials is not the same in every member state. Advice should be sought from the relevant authority. Informed consent must be obtained from the owner of the fish farm, and consent is usually required from the relevant environmental protection agency.

A GCP (Setting up GCP trials in fish; Note for guidance) protocol of the planned trial must be prepared. Some flexibility in the details of the protocol will be necessary for trials carried out offshore since weather conditions may affect the planned start and end dates of the trial.

At the end of the trials, the results must be collected for the GCP report. The results must be analysed statistically in accordance with EU guidelines.

Reports of the GLP safety studies and GCP efficacy studies are included in Parts 3 and 4, respectively, of the registration dossier.

Final Product Testing

Part 2. E of the registration dossier is where the tests performed for batch release are described, together with the limits of acceptance for each test. The test methods themselves are also included in the dossier, normally in the Annex to Part 2, as standard operating procedures (SOPs). In addition to the descriptive summary of the tests including the stages at which they are performed, it is useful to prepare a tabulated summary of the tests and their acceptance criteria since this serves as the summary of the finished product specification and can be used as a guide to preparing batch certificates.

Samples for these tests are normally taken from filled containers; however, some tests may be performed on samples of bulk vaccine prior to filling. Guidance on this is available in Ph. Eur. (European Pharmacopoeia). Typical tests for an inactivated bacterial vaccine would include:

Test	Limit of acceptance (examples)
Appearance	*For example, pale white suspension*
Purity	Pure
Sterility	Sterile
Identity and assay of active ingredient	*For example, Yersinia ruckeri* 10^6–10^7*/ml*
Identity and assay of adjuvant	*For example, 5 % aluminium hydroxide gel*
Tests on excipients	*As relevant*
Identity and assay of preservative	*For example, thiomersal*
Safety	*Since January 2013* (Guideline on requirements for the production and control of immunological veterinary medicinal products EMA/CVMP/IWP/206555/2010), *this test is no longer mandatory for inactivated vaccines*
Inactivation	Completely inactivated

Batch Consistency

In Part 2. F of the dossier, it is necessary to include the results of tests on three consecutive batches of the vaccine. These will normally be pilot-scale batches that will also be used for stability testing. The purpose of this section is to demonstrate that

the quality of the product is consistent from batch to batch and to demonstrate conformity with the specification. Full batch protocols of these batches should be included in the Annex to Part 2.

Stability

Stability studies need to be set up as soon as possible so that some stability results can be included in the dossier. Samples of each container size should be stored at the recommended temperature. There should be sufficient samples so that testing at intervals of, say, every 6 months can be performed to support the claimed shelf life for the vaccine. Data must be provided for 3 months longer than the proposed shelf life. It is not necessary to carry out the entire list of tests described under Part 2. E controls on the finished product. It is only necessary to perform stability-indicating tests such as potency and any other important parameter that would highlight degradation or a reduction in stability over time. A minimum of 6 months stability data should be included in Part 2. G together with a commitment to provide further data, when available, to support extensions to the shelf life approved initially.

If the vaccine contains a preservative, this must be shown to be efficacious according to the requirements in the Ph. Eur. preservative efficacy test (Ph Eur 01/2005:50103). The preservative must be shown to retain its effectiveness up to the end of the shelf life.

Compiling the Registration Dossier

The regulatory authorities of all EU member states accept the same standard registration dossier, in English (Commission Directive 2009/EC). Depending on the nature of the vaccine, data intended for inclusion in different parts of the registration dossier are usually being generated simultaneously; therefore, it is normal practice to work on each section as the information becomes available rather than progress through the dossier sequentially.

The dossier is divided into five parts:

Part 1 – This is the *administrative* section containing the application form (1A), the SPC and draft packaging (1B) and the expert reports (1C).

Part 2 Manufacture and Quality – There are eight sections in this part ending with 2. H "Other Information", which should include any quality information not already included in sections 2. A to 2. G. Supportive documents such as specifications, certificates of analysis and SOPs are normally included in an Annex to Part 2.

Part 3 Safety – Reports of all the GLP safety reports go into this part together with reports of the reports on field safety. The headings to be addressed are listed in the legislation (Commission Directive 2009/9/EC) and must be referred to in the dossier, justifying those which are not applicable.

Part 4 Efficacy – All the reports of challenge studies and GCP field trials are included in this part.

Part 5 Bibliographical References – Any supportive literature is included in this section.

The wording for the SPC and packaging materials should be completed using the QRD templates. A guideline (Revised position paper on indications for veterinary vaccines) is available to explain how claims may be worded depending on the outcome of the efficacy studies. Each recommendation on the SPC and labelling must have been supported with data generated with the product itself. This is why it is so important to follow the intended dose, route of administration and vaccination schedule in the safety and efficacy studies intended to be reported in the registration dossier.

Expert reports are still expected in the EU, although they are now called "Detailed and Critical Summaries".

The Application for a Marketing Authorisation

Guidance on how to apply for a MA in the EU can be found on the European Commission's website under "EURALEX". The relevant volume is 6A, Notice to Applicants. Guidance on the submission of the dossier and the application form are provided in this volume.

Manufacturing Standards

All stages of vaccine production, including the production of antigen, must be carried out to good manufacturing practice (GMP) standards. Most parts of the world accept the quality of manufacturing standards of facilities inspected and approved as EU-GMP compliant. In contrast, vaccines and antigens produced in some other parts of the world, including the USA, are not acceptable for importation into the EU unless the facility has been issued with a GMP certificate following a EU-GMP inspection.

The standard of GMP demanded in the EU is extremely high, having increased steadily over the last 35 years. Nevertheless, the rewards for compliance with such standards include the reduction and even elimination of some vaccine testing compared with the requirements of 10–15 years ago.

Routes to Obtaining a Marketing Authorisation in the EU

(a) Centralised Procedure

Since the implementation of Council Directive 92/18/EEC, Title II, harmonised requirements have been publicly available concerning the studies required to obtain an MA for immunological veterinary medicinal products in the EU. Initially marketing authorisations were only issued on a national basis, until Council Directive 90/676/EEC introduced the centralised procedure (CP) with effect from 1 January 1992. However, most veterinary vaccines were not eligible for registration through the centralised procedure, and although some changes in the criteria for eligibility have been introduced, the use of the CP basically remains limited to vaccines derived from biotechnology (mandatory) and vaccines having something about them that is deemed novel (voluntary).

The advantage of using the centralised procedure is that a positive opinion followed by a positive Commission Decision results in MAs being granted in all member state countries plus Norway, Iceland and Lichtenstein.

The great disadvantage for manufacturers of fish vaccines that are eligible on a voluntary basis or even obligated to use the centralised procedure is the fees. Also, the requirements for translation of the SPC and packaging into 23 languages are a burden when the vaccine may only have markets in two or three EU member states.

More information about the centralised procedure is available on the EMA website. http://www.ema.europa.eu/under Veterinary Regulatory/Application Guidance.

For fish vaccines that are not derived from biotechnological methods, three other registration routes are available:

(b) National Procedure

It is still possible to obtain a national MA by submitting the application dossier to just one regulatory authority. This may be desirable for fish vaccines with a specific, limited market.

(c) Mutual Recognition Procedure

If an applicant has obtained one national MA and then subsequently wishes to market the vaccine in another one or more member states, they must use the mutual recognition procedure in which the first MA is mutually recognised by the other selected member states. The process is similar in parts to the decentralised procedure described below.

(d) Decentralised Procedure

The third route is the one that is most appropriate for a new inactivated bacterial vaccine for fish. The decentralised procedure (Best practice guide for veterinary decentralised procedure (DCP) CMDv/BPG/002) is used when more than one EU member state has been identified as a suitable market for a new product.

The first step for the applicant is to select the reference member state (RMS). This is the EU regulatory authority that will assess the dossier and prepare an assessment report.

The next step is to select the Concerned Member States (CMS). The applicant informs both the RMS and the CMSs of their intention to apply for MAs through the decentralised procedure. The entire procedure runs to a strict timeline and normally takes 210 days to complete, after which the RMS and CMS have 30 days to issue identical national marketing authorisations for the vaccine.

Preparing for the Launch

Preparations for the launch of the product will begin during the vaccine development stage. Obviously if the research and development team developed a vaccine that required vaccination of fish every 3 weeks for 6 months to provide protection against the target disease, this would not be a marketable proposition. R&D and marketing need to work together during the development phase to ensure that the SPC and label claims that are eventually authorised are practical and useful for the market.

The initial drafts of the packaging materials that were included in Part 1 of the registration dossier may have been revised by the regulatory authorities during the DCP. Thus the draft packaging will need to be amended accordingly prior to printing.

Although the MAs that have been issued by the individual member states must be identical, there are certain items which have not been completely harmonised in the EU and are left to each country to apply according to their national rules. These include legal category/distribution category – this affects whether the product is to be sold as a prescription-only medicine (POM) or under some other nationally allowed category.

Launch batches will have been prepared in anticipation of the marketing authorisations. The batch tests on these will need to be completed and batch protocols forwarded to the relevant authorities requesting batch release approval. Samples of these batches, in their final packaging, should be provided to the regulatory authorities on request.

Post Launch

The marketing authorisation holder has certain responsibilities after MAs have been granted. These include pharmacovigilance reporting and applying for batch release for subsequent batches of the vaccine. Any changes in the licensed production process or test methods must be subject to variations to the marketing authorisation. Fortunately, by using the decentralised procedure, the approval of variations is a harmonised process in which the RMS and CMSs issue approval to introduce the requested change simultaneously.

Finally, EU legislation and guidelines for veterinary vaccines have undergone a series of changes and improvements over the years, with new guidance being issued and published all the time. It is important that applicants check the EMA website and their national regulatory authorities' websites for relevant updates.

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