Padros, Francesc, Evgenia Gourzioti, Andrea Fabris, Alexander Figenschou, Amedeo Manfrin, Matthijs Metselaar, Dušan Palić, and Sandra Vesanto. 2024. "Relevance of Pharmacovigilance in Aquatic Animal Medicine. A Perspective from Aquaculture Health Experts Attending a Focus Group Meeting at the EMA." *Bulletin of the European Association of Fish Pathologists* 44 (2). https://doi.org/10.48045/001c.122939.

EXPERT OPINION

Relevance of Pharmacovigilance in Aquatic Animal Medicine. A Perspective from Aquaculture Health Experts Attending a Focus Group Meeting at the EMA

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Keywords: pharmacovigilance, aquatic animal medicine, adverse events, aquaculture, therapeutics, EMA, medicines

https://doi.org/10.48045/001c.122939

Bulletin of the European Association of Fish Pathologists

Vol. 44, Issue 2, 2024

Introduction

Therapeutics and disease treatments are substantial elements in animal medicine, together with diagnostics and prevention. Therapeutics approaches in terrestrial animal medicine, including domestic/companion and farmed animals are supported by an extensive amount of available information derived from pharmacological studies as well as from extensive knowledge about safety and efficacy of treatments. However, compared to terrestrial species, for aquatic animals, the available knowledge is scarce. Possible reasons for limited knowledge about therapeutics in aquatic animals include relatively recent (mid-20th century) inclusion of aquaculture in contemporary food animal production. Focus on health of farmed finfish and shellfish was also disperse due large diversity of aquaculture production systems and farmed species, covering a wide range of biological and physiological characteristics and specificities of the aquatic environment. Consequently, therapeutic elements in aquaculture and fish farming suffer from different limitations also today.

In practice, therapeutics and disease treatments in animals are possible thanks to the availability of veterinary medicinal products (https://fve.org/cms/wp-content/uploads/Gap-Analysis-Outcome-Final2.pdf). In the European Union (EU) and in the European Economic Area (EEA), EMA (the European Medicine Agency or the 'Agency') is the agency responsible for the evaluation and monitoring medicines to protect and promote human, animal and environment health. Concerning medicines for veterinary use, the EMA is responsible for scientific evaluation, supervision and safety monitoring of medicines. One particularly important point, not always well known and understood, is the relevance of the post-authorization activities. These comprise activities to amend marketing authorisations for medicinal products e.g. to authorize their use in new species or for new indications, in addition to

monitoring the safety and efficacy of medicines based on extensive collection and evaluation of potential adverse effects reported throughout the products lifecycle. According to the World Health Organization, pharmacovigilance refers to the surveillance (including prevention, detection and understanding) of undesirable or unexpected effects of any medicinal products, including vaccines (https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance). Pharmacovigilance is therefore paramount in the whole assessment of human and animal medicines, as after authorization, medicines are used in wider and heterogenous populations and under different conditions and for longer periods than those from the rigorous laboratory and clinical trials performed before product authorization. Under these 'real life' conditions, sometimes unexpected effects related to efficacy or safety can be observed. Therefore, it is essential to continuously monitor medicines throughout their use in practice.

For this reason, EMA is particularly aware of the necessity to adopt and develop a strong activity in pharmacovigilance including animal/veterinary medicines, as pharmacovigilance is equally applicable for veterinary medicinal products. In addition to coordinating the EU pharmacovigilance system and operating services and processes to support pharmacovigilance in the EU, the EMA has been particularly interested to have a closer contact with veterinary and other healthcare professionals and stakeholders working in the field. For this reason, the EMA organized[1] specific focus group meetings with veterinarians on promotion of pharmacovigilance for food producing and domestic animals. Concerning aquatic animals, a specific focus group meeting, organized by the Veterinary Medicines Division, was held at the EMA premises in November 2023.

At this meeting, a group of veterinarians and other healthcare professionals representing different organizations such as the European College Aquatic Animal Health (ECAAH), Aquaculture Advisory Committee (AAC) Federation of Veterinarians of Europe (FVE), World Aquatic Veterinary Medical Association (WAVMA), European Association of Fish Pathologists (EAFP), representing independent and organized practitioners, as well as the main veterinary and aquatic animal health organizations in the EU, had the opportunity to meet and extensively discuss with EMA secretariat and representatives from the Committee for Medicinal Products for Veterinary Use (CVMP) and Pharmacovigilance Working Party (PhVWP-V) in order to gain first-hand in-depth knowledge of the challenges and problems faced concerning the use of medicines in aquaculture and particularly concerning pharmacovigilance reporting. In addition, the meeting was also very useful to improve dialogue between practising veterinarians, specialised aquatic

1 Art. 79 (2) of Regulation 2019/6: "The Agency may organise meetings or a network for groups of veterinarians or other healthcare professionals for direct knowledge exchange".

healthcare professionals and the EMA, particularly in the challenges related to pharmacovigilance and finally also to facilitate and encourage adverse event reporting.

Use of veterinary medicines in aquaculture and aquatic animal health management

Compared with terrestrial animals, one of the main characteristics in use of veterinary medicines in aquaculture and mainly in fish farming is the extremely limited number of available veterinary medicinal products authorised for specific use in fish or in fish species (salmon, seabass...etc.) or fish groups (salmonids) and against aquatic animal diseases (Gravningen, Sorum, and Horsberg 2019; Rigos et al. 2021, 2023). Only a limited number of products, mainly antibacterials and antiparasitic commercial medicines are available and in many cases the products are only authorised in a few countries. This situation has mainly arisen because the sector of aquaculture is not always as attractive from the economic point of view for the pharmaceutical companies as other sectors and markets such as swine or poultry and obviously, humans, so the investments required in the process of development, testing and authorisation of products specifically for aquatic animals and diseases do not generate sufficient revenue and profit margins through the commercialisation of these products.

There are also other reasons related to the availability of similar products authorised for other species and available in the national markets that can be used under the prescribing cascade principle. In these scenarios, the interest of the pharmaceutical companies to develop and license new products specifically for aquatic animals can be understandably lower. Connected with these previous considerations, the future list of substances which may be used in aquatic food producing species under the cascade in the EU (EMA/519333/2023) increases its relevance. The substances included in this list will be allowed for use in every Member State, although in practice there might still be difficulties in accessing these products in different EU Member States. This list is particularly important for aquaculture veterinarians, since frequently up 70-80% of prescriptions are for products used according to the cascade. So, the list will affect the availability and accessibility of the products, as only the substances on the list will be allowed to be prescribed under the cascade[2].The reduction of potential for 'off-label' administration may mitigate the 'unfounded misconception' that reporting adverse event may have implications for personal liability, but nonetheless will significantly

2 "Update from EMA on latest developments on substances for use in aquaculture under the cascade. Scientific advice requested by EC mandate in relation to Article 114(1) and (3) of Regulation (EU) 2019/6 regarding the list of substances which may be used in foo-producing aquatic species", presented by Sebastien Girault during the meeting.

increase the therapeutic options available to control aquatic animal diseases. However, since this list does not exist yet, the current cascade rules still apply for the time being.

There is another constraint associated with this problem and linked with the fact that the number of authorised active substances for fish and other aquatic animals, including also active substances with MRL for fish, is also limited compared with the number of authorised terrestrial animals. Human medicinal products are rarely used in aquatic animals. This constraint is unfortunately due to the limited number of scientific studies and technical background and knowledge on pharmacokinetics, pharmacodynamics, clinical efficacy, toxicity and safety and environmental impact of these substances in aquatic animals and in the aquatic environment (Casa-Resino et al. 2021). In this current situation where there is a lack of medicines specifically authorised for fish and aquatic animals, in many cases the only possible solution is to use medicines authorised for other species under the cascade, however prescribed 'off label', in the absence of knowledge of how this product will perform in another species, under different conditions and sometimes with different delivery systems. This uncertainty usually puts additional pressure on the practitioner responsible for the treatment, which also poses an additional complication for pharmacovigilance, as the veterinarian responsible for the 'off label' treatment may have more doubts about the effect on the treated animals (in terms of safety and efficacy) and the environment due to the delivery of the medicine. As there are no clear references on the expected behaviour of the product, even if it is relatively easy to detect an 'unexpected' effect, it is much more difficult to assess if this is due to the medicine itself or to its use in a different species and for a different disease than that indicated. However, it should be emphasised that in either of these cases, the event should be reported as a potential adverse event, since even suspected adverse effects are within the scope of pharmacovigilance.

The delivery route is another important cause of uncertainty in aquatic animal medicine. As said before, due to the high number of animals in the production units, medicinal treatment in aquaculture is based on two main systems: oral and bath. Oral delivery of medicated feeds introduces another element of uncertainty, which is highly dependent on feed intake, which is usually affected when animals are sick, or when palatability of medicated feeds is low, due to the use of certain substances at certain level. Oral medication in aquatic animals may introduce another added problem related to the leaking of medicine during the delivery process, leading to insufficient uptake of the veterinary medicinal product (VMP). In addition, since in many cases the biomass to treat in the affected rearing units can be immense (hundreds of tons), it is necessary to prepare large amounts of medicated feed for the whole treatment period (lasting up to several days). As only feed companies have the specific facilities to produce such large batches of medicated feeds, once the

request is received, the company should immediately introduce these requests within the production programming schedule, which takes some time/days. Finally, once produced, the batch of medicated feed should be transported and delivered from the feed mill to the farm. To sum up, taking into account the time taken between prescription to the receipt of the medicated feed, it could be several days until the affected fish receive their treatment. This undesirable delay strongly decreases the efficacy of the treatment and may increase the likelihood of transmission of the disease within the rearing unit and potentially to other units. The situation can be exacerbated in *ad-hoc* treatments intended for a limited number of fish and when the premedicated feed are rudimentary mixed.

Environment also plays a very important role in treatment in aquatic animals. Temperature is potentially the most important factor to take into consideration as the effects of the different active substances and medicines can dramatically change according to the temperature. This component is much more relevant in ectotherm aquatic animals and not as significant in terrestrial medicine, as the animals (mostly mammals and birds) are homeotherms. In aquatic animals, temperature can significantly affect the metabolism and the pharmacokinetic and pharmacodynamics of active substances. Moreover, temperature and various other parameters (water, pH, salinity, fish density, light, etc) can also affect the dynamics (such as solubility) of medicines when delivered via water. In many cases, the data sheets reflect only certain environmental conditions. Environmental-related suspected adverse events are infrequently reported via the veterinary pharmacovigilance system but despite these uncertainties, should be investigated and reported.

An exception to this general situation is fish vaccines, with an increasing number of newly authorised commercial vaccines available, mainly because prevention in fish medicine is particularly important, the efficacy of vaccines and vaccination programs in fish diseases management has been proven to be very successful. Moreover, also there is already significant and advanced scientific and technological expertise in fish immunology that supports the fish vaccine industry. However, despite the specific characteristics of the vaccines and vaccination procedures being clearly indicated in the technical specifications of the commercial products, sometimes there could be problems associated with vaccine delivery, as the vaccination process in fish requires careful planning and supervision of the procedure, as errors or deviations from the standard recommended procedures can lead to problems of vaccine efficacy and safety. In these cases, the underlying problem may be associated with the vaccination process rather than the vaccine, but nonetheless should be reported as an advert event.

Autogenous vaccines have also been widely used in aquaculture as an emergency vaccination system in the face of situations with new or changing pathogens and in the absence of commercially available vaccines. In contrast

with commercial vaccines, autogenous vaccines are relatively safe when delivered under standard vaccination conditions but are not tested for efficacy. In this way, the uncertainty concerning efficacy is usually very high, so obviously the apparent absence of efficacy in the field can be considered as adverse events.

Another characteristic of the use of medicines in fish farming and aquaculture is that medicines should be applied in a very large number of animals per rearing unit. In fact, aquaculture is the animal farming activity with typically the highest density of organisms in each rearing unit, greater than, for example, poultry. For this reason, the ability to detect unexpected adverse reactions or treatment problems is lower than for some terrestrial species, mainly in companion animals but also in farmed animals such as cattle or horses, where medicines are still administered with a degree of clinical supervision of individual animals. In aquaculture, individuals are rarely important and collective concepts such as the production unit or batch has much more relevance.

The factors described previously are some of the most likely reasons to explain why the number of adverse events reported for aquaculture is markedly lower compared with that for other species, in particular companion animals, but also for food-producing species. However, taking into account the current status of therapeutics in aquaculture and the higher level of complexity and uncertainty associated with their use, compared with that in other animals, reporting any adverse event observed in practice, regardless of whether a potential causal relation to the medicine is suspected, is even more important for improving the knowledge of the use of medicines in aquatic animals.

Pharmacovigilance in aquatic animal health: the need for reporting adverse effects vs reluctancy to report

Despite the particular scenario described before and the higher degree of uncertainty associated with medicine treatment in aquatics compared to terrestrial animal medicine, where veterinarians may expect certain adverse events to occur and might therefore not consider it necessary or useful to report such expected events, it is important to highlight that adverse events should always be reported, even if unsure of whether the VMP is responsible for the event. Despite the potential uncertainties, adverse event reports contain valuable information for improving knowledge on the use of medicinal products in practice. It is worth mentioning that in the last 20 years, only 776 adverse events for aquaculture were reported electronically; these were mainly following vaccine use and the most frequent adverse events reported were lack of efficacy, fish body deformities and increased mortality.

It is important to stress that veterinarians and aquatic animal health professionals are responsible for reporting a suspected adverse event following exposure to a VMP to either the MAH (marketing authorisation holder; the company responsible for the product) or the national competent authority (NCA). MAHs and NCAs have a legal responsibility to report adverse events notified to them and should also follow up with the reporting veterinarian to obtain more information on the adverse event if needed. This includes any adverse event that could be related to environmental conditions and include adverse effects or lack of efficacy following use of commercial vaccines or even autogenous vaccines.

Data related to adverse events reported is a particularly sensitive area in aquaculture, as there can be significant implications, at several levels, if this information is not managed appropriately. On a personal level, the reporting of an adverse event to the MAH by an individual could be misinterpreted as a hostile gesture, or even as a request for financial compensation and the individual reporter may be subjected to potential pressure. Also, the information concerning the adverse effects can also have negatively impact a companies (farm and/or MAH) reputation if confidentiality is not maintained. In addition, some individuals or companies, can be afraid that the anonymity and/or confidentiality of the data may not be respected, so they can be reluctant to report adverse events.

Reporting adverse events to NCAs/regulatory authorities is sometimes also considered risky from the perceived potential backlash from the public towards the whole industry since information may be disclosed following freedom of information requests. At the same time, it should be explored how far certain welfare parameters that are regularly monitored as part of certification obligations, could also become useful indicators for the safety and efficacy of medicinal treatments or vaccinations.

It is important to overcome all these misconceptions and increase awareness of the general benefits of reporting adverse events at a general level, also including aquaculture, despite all the specificities and challenging circumstances of aquaculture medicine.

How to report an adverse event and what happens next

Adverse events can be reported either to the MAH responsible for the VMP or the NCA. Each report contributes to the data monitored continuously by MAHs and the regulatory authorities to improve the information available for VMP users on the safety and effectiveness of the products. This most frequently results in addition of new adverse events or warnings e.g. precautionary measures on the VMP product information (PI; which includes the package leaflet). Other regulatory measures taken on the basis of pharmacovigilance may include, for example, recommendations for post-marketing studies and, less frequently, suspension or withdrawal of the

marketing authorisation for a VMP, which are noted here for completeness particularly to dispel common misconceptions which may discourage reporting of adverse events.

For those interested, adverse event data can be accessed through the EMA website (www.adrreporting.eu) and navigation guidance can also be obtained through EMA. However, it should be highlighted that specific training sessions and webinars organised by the Agency as well any training and educational materials would be particularly welcome for veterinarians in general, including those from the aquaculture sector. Any efforts towards improving timely access to accurate information on VMPs and adverse events accessible via the databases available via the EMA are also welcomed.

Recommendations for the future

Although the current situation in aquatic animal medicine and fish therapeutics is not the best for the accurate collection of adverse events, there is clearly much room for improvement. Reporting adverse events is fundamental to improving the knowledge of the safety and efficacy of VMPs used in practice. Pharmacovigilance reporting becomes even more important given the specificities of aquatic animal medicine and fish therapeutics and the limited number of authorised VMPs available, particularly compared with other species.

Adverse event reporting based on voluntary and mutual collaboration and confidence is always the best option. Reporting should also be envisaged as a good practice, so could potentially in future also be incorporated in the guidelines as a part of certification schemes. Even for some cases with weak natural cooperation, obligatory reporting could be an option.

When displaying pharmacovigilance data (e.g. via the EMA website) providing denominator data along with adverse event reporting frequencies would be useful as an indication of how the adverse events relate to the estimated use of the VMP in the target species.

In conclusion, collaboration and continued dialogue between veterinarians, aquaculture health professionals, farmers, the EMA, NCAs and other EU institutions responsible for food, animal disease and welfare monitoring can provide the foundation for a network for facilitating pharmacovigilance reporting on VMPs used in aquaculture and sets the basis for the future.

Acknowledgements

We would like to thank the CVMP Pharmacovigilance Working Party and all the EMA officers for the excellent organization of the meeting and for all the technical and scientific comments during the session.

Submitted: March 06, 2024 CEST, Accepted: August 23, 2024 CEST

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