EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Personal perspectives from aquaculture specialists on pharmacovigilance challenges

22 November 2023, 10:00-17:00

Aquaculture focus group meeting

What do you consider is the main challenge/difficulty you face relating to reporting of adverse events in aquaculture?

Challenges (1)

- We have electronic prescription and Adverse Drug Reaction online reporting but the system is too much complicate (account, password, mobile application, etc).
- In the specific situation of Mediterranean aquaculture, in which many different species are bred in both freshwater and saltwater in different structures and with different technologies, reporting adverse effects or the ineffectiveness of a drug is difficult as there are many variables at play.

  In the case of fish, the appearance of the pathology is almost always combined with a reduced food intake which leads to underdosing; in other cases it is the qualitative characteristics of the water that can influence the reactivity of fish to VMPs (e.g. pH, salinity, presence of nitrogen catabolites). The inevitable use of the cascade principle, with the use of VMPs not specifically registered for a specific fish species or even for aquatic animals, can lead to the onset of undesirable effects if not supported by clinical and therapeutic experience or a bibliographic basis.

Challenges (2)

- There are very few licensed commercial medicines available for fish. Often use of off-label products. Risk of development of resistance, because of the repeated use . Environmental conditions (oxygen level, density, water temperature) affect the application and effectiveness of the VMPs. Difficult to treat a whole site (all batches) at the same time. Treatments in large number of fish, mass therapy not individual therapy. Sick fish usually receive a suboptimal amount of medicine causing resistance ,under dosing and lack of efficacy to the medicine . Often Aquaculture Companies press vets not to report. Reluctance and fear in withdrawal of the VMPs products
- Fish medicine in fish farming is not based on clinical (individual) follow up, but in population health (large batches), so the assessment of deviations in safety or efficacy is particularly difficult. Moreover, there are really few licensed commercial products for fish, so in many cases, other products are used (cascade system) and used 'off label', so there are few standards (efficacy/safety) to be compared. Aquaculture and fish farming is highly dependent on environmental conditions, introducing higher variability in the response. Potential negative environmental effects of the use of the medicines gain relevance as pharmacovigilance aspect.

Challenges (3)

- Challenge for NCAs:
  - Underreporting – reports only to MAH
  - NVR and reporting in EvVet has made availability to the reports more difficult and is creating more work to NCAs. Result: we have poorer overview of ADRs and phvig for specific products
  - Lack of information in the reports which can substantiate the ADR
  - Number of fish reacting
  - Simultaneous diseases
  - Handling versus treatments

Challenges (4)

- Lack of alternative products and or allowance of combination treatments. At the moment we are not using the products to its full potential and the lack of an coordinated approach is not helping.
- The lack of alternative medications – even if you report adverse events, there are very few other products that you could use instead of the reported medication.
- There are multiple challenges, each contributing to the main issue of higher adverse effect risk in aquaculture. A "perfect storm" in a way. Fully licensed/approved/labelled VMPs for food producing aquatic animals (finfish focused) are only a few compared to terrestrials. Because of this, off-label and cascade use are a norm rather than exception in many MS. Formulations and applications are therefore less standardized and safety/efficacy is less known. Metaphylactic approach is the only one we can use as veterinarians in large population production systems. IN best case scenarios, we can treat separate production units rather than a whole farm,. However due to variable characteristics of production systems, this is highly individualized. It introduces variability in responses to treatments, and diversity of possible/potential adverse effects.
  Similar to the above, water environment variability (ever changing physico-chemical characteristics) introduces increased spectrum of possible interactions between treatments and target population making it increasingly difficult to estimate if an adverse event is or will be occurring.

Challenges (5)

- The added issue is that adverse affects on the environment itself, not just aquatic animals may happen, and this aspect is gaining importance from the pharmacovigilance perspective. Main challenge to reporting is therefore related to higher risk of adverse events and less information about potential for the adverse event to occur in highly diverse farming conditions (species/systems).

What can the Agency do to help improve adverse event reporting in aquaculture?

Improving reporting (1)

- I believe it is important to convey the message that it is important to strengthen the exchange of data regarding the possible onset of undesirable effects at all levels (EU, national, between veterinarians) using a reward system for those who carry out adverse event and non-adverse event pharmacovigilance reports. as often happens in an almost penalizing way. The collection and exchange of reports at all levels should therefore be facilitated by making the data available (obviously in anonymous form) to all operators in the aquaculture supply chain involved.
- Better information to veterinarians and healthcare professionals, combined with an assurance that reporting observed adverse events will not result directly to withdrawal of the VMP product, but to improvement of the efficacy of the VMPs.
  Availability of specific forms to complete the adverse event of VMPs, that are less time consuming. Anonymising the reports.
  Inserting the importance of pharmacovigilance reporting of medicinal products used in aquaculture, in lectures at undergraduate and postgraduate students of Faculties of Veterinary and Biological Sciences. Collaboration with Universities

Improving reporting (2)

- Informative presentations or leaflets to aquaculture producers or organizations (Hellenic Aquaculture Producers Organization-HAPO), emphasize to the potential benefits of reporting adverse events in aquaculture, in order to improve the pharmacovigilance of the VMPs.
- Aquamedicine specific characteristics, particularities and needs are scarcely taken into account in EMA regulations as regulations are mostly developed taking only terrestrial animals as references.
  Metadata analysis on available information on adverse reactions / failures in the administration of aquamedicines.
  Include aquahealth experts as external advisor pannels.
- From NCA:
  - Improvement of IT-systems (EvVet, DWH, UPD and IRIS)
  - Training in the systems
  - Simplified processes in handling ADRs/SD/SM

Improving reporting (3)

- Aquaculture has a disproportional spotlight on its use of medicine. Despite having the lowest use per tonne of production. More objective and comparative publication of results will help with reporting.
- I think the reporting itself is pretty straightforward, but maybe there should be more awareness raised in what should and should not be reported as an adverse effect.
- Regulatory bodies dealing with VMPs have until recently had/have very low/limited expertise and possibly interest in acknowledging specifics of aquaculture production regarding veterinary services. For example, one of large obstacles are complex and complicated (frequently contradictory) regulatory issues related to the production of medicated feed for fish, leading to practices in some members that that medicated feed is imported from other MS or even third countries, further increasing the costs and risks associated with quality control – leading to safety and efficacy issues and increased risk of adverse events.

Improving reporting (4)

- So the root of the problem is lack of streamlined VMP regulatory pathway applicable to the industry specifics.
- We have limited information about adverse effects, and the available information is scattered, disorganized and non-standardized in the format that could be useful in setting up the adverse effect reporting system for aquaculture that is fitting with the role of veterinary services, as well as production stakeholders.
- An effort to produce meta-analysis of the potential for VMPs to cause adverse effects in aquaculture (production populations and environmental populations) is needed.
- Increased involvement of aquatic veterinarians (and possibly other para-veterinary colleagues) in advisory bodies may be of interest both from the regulatory side and industry side and allow for increased awareness of the current/ongoing issues in the field – helping set up better adverse event reporting systems for aquatic animals.

What type of adverse events, related to the type of products, do you observe most frequently in your day-to-day practice?

Adverse events/issues encountered (1)

- Vaccination failure mainly in freshwater species. Therapy failure against Gram positive pathogens.
- The effects I have mainly observed are:
  - general loss of appetite in the case of some classes of antibiotics;
  - photosensitization (especially in the juvenile stages), with consequent darkening of the skin in milder cases (especially in rainbow trout), in some cases with less than optimal water quality, skin ulcers or gill inflammation can develop(also in this case with some classes of antibiotics).
- Pathological conditions caused during the application face of the medicines. Furthermore, unpredictable environmental conditions affect the application and effectiveness of the VMPs.
  Mass therapies, antiparasitic baths and handlings during the anaesthetic phase can cause skin abrasions and lesions.
  Bad use of equipment (needle size) and inadequate injection technique (dose, injection method) during intraperitonael vaccination can lead to adhesions of the abdominal cavity and multifocal post vaccination granulomas. Aquaculture Companies don't hire specialised and qualified personnel (veterinarians)

Adverse events/issues encountered (2)

- Problems associated to incorrect calculations of dose/time and in the correct way to apply the treatments and in the post-treatment follow-up.
  Scarce presence of specialised and well trained personnel (aquavets).
  Veterinarians (day 1 competences) have a very limited knowledge.
- Mortalities (increased)
  Lack of efficacy – antiparasitticidals, vaccine antigens
  Abdominal adhesions/melanisation (vaccines/injectables)
  Skeletal deformities and formation of connective tissues (vaccines/injectables)
  Environmental issues
- Lack of efficacy in sealice products.
- Vaccine-break-throughs.
  Prolonged withdrawal periods due to flesh residues.
  Antibiotic resistance.

Adverse events/issues encountered (3)

- These issues again take root to deeper problems inherent to lack of well-trained aquatic veterinary workforce (both as specialists, and as one-day competencies coming out of the veterinary education programs); interference of non-trained or self-proclaimed aquatic animal health experts; prevalent attitude (sociological aspect) about veterinarians having no knowledge about fish medicine/health and other issues.
  Thinking of the above, a lot of adverse effects can be tied back to incorrect or mis-calculations of concentrations or dose of the VMP, especially related to route of application that frequently does not consider all the variables present in the intended system and target population.
  Such issues (variability of the systems/application routes/populations) are further exacerbated by the frequent lack of post-treatment follow-up due to either inexperience or negligence both on the sides of producers or para-veterinarians involved in the treatment. Veterinarians are also not immune to these errors, but may be more responsible due to possibility of malpractice issues that can be brought up to the court in case of severe and economically relevant adverse events.