Therapeutic gaps in the Fish sector

Meeting of 13/12/21

Participants: Mathieu Jamin (Veterinary practitioner at Morlaix (29), representative of SNGTV aquaculture); Christelle Roy (Veterinarian, Director of GDS Corrèze and Nouvelle Aquitaine); Marine Levadoux (CIPA Director); Yves Rolland (CIPA lawyer); Valérie Chesneau (Prunier Manufacture, CIPA "veterinary medicinal products" working group); Xavier Sauzéa (Veterinarian, SELAS Gouessant, CSMV representative); Sophie Lebouquin-Leneveu (Deputy Head of Unit for Epidemiology, Health and Animal Welfare - Anses Ploufragan); Ségolène Calvez (Maître de conférence in Animal Husbandry, Nutrition and Health, Oniris vet school); Antoine Rostang (Maître de conférence in Pharmacology/toxicology, Oniris vet school); Thierry Morin (Head of the Fish Virology, Immunology and Ecotoxicology Unit (VIMEP) – Anses Ploufragan)
for ANMV: Jean-Pierre Orand; Laure Baduel; Sophie Barreteau; Benoît Courty; Caroline Guittré; Jacques Bietrix; Laurent Fabry

Pathology	**Issue encountered*:** **PhV:** Pharmacovigilance (unsatisfactory efficacy or safety) **Disp:** Availability, shortage **Reg:** Regulatory ("cascade" application, withdrawal time, restricted access) **0 VMP:** No veterinary medicinal products **0 ThS:** No therapeutic solution	**Problem type * (PhV / Disp / Reg / 0 VMP / 0 ThS)**	**Alternatives identified**	**PRIORITIES** **Major: M** **minor: m**
<u>External parasitism</u> Treatment by balneation of skin-branchial parasitism mainly due to protozoa and monogenic worms	• **Therapeutic use of various products with a biocide activity, without marketing approval (MA) of veterinary medicinal products** (VMPs) but some of the substances used are approved as biocides (TP3). Use of peracetic acid or formaldehyde that acts on the parasites of the water mass. Use of endoparasiticides, such as SLICE, as systemic parasiticides on salmon in Norway, while they act directly on the parasite. The others have more of a fungicidal or bactericidal biocide action. Use of peroxide H2, formaldehyde, CuSO4 and Bronopol. Use of product marketed under the TP3 biocide status: HALAMID (chloramine T). No current challenge to biocide *vs* VMPs regulatory status.	**Reg**	**ANMV info about formaldehyde:** The WG report was finalized in March 2020. The ANSES opinion was signed in July 2021. The latter specifies "that the alternatives identified may not be sufficient or suitable in certain situations (physiological stage, category of fish or parasites)". As the WG did not wish to work on the use of formaldehyde in certain situations, the ANMV has undertaken a work on the risks associated with such use and the conditions that could allow the authorisation of the import of the Spanish VMP containing formaldehyde. This analysis shows that: - such import would be limited to certain indications, only in the case of therapeutic failures; - the risk to applicator could be limited by strict compliance with a certain number of PPE (respiratory mask in particular); - the consumer risk following ingestion of treated fish is considered low. - the environmental risk can neither be excluded nor a priori limited by management measures.	**M** **No. 1**

Therapeutic gaps in the Fish sector

Meeting of 13/12/21

			Discussions are underway with DG Anses / DGAL / sector on possible measures that would make it possible to specify and reduce the impact on the environment. ➢ **The import authorisation for the Spanish VMP** will only be considered on the basis of concrete proposals deemed satisfactory. In Spain, the context is different: use in enclosed environments => easier treatment of effluents. For classified facilities, there is a declaration obligation to be specified above a certain release threshold for formaldehyde. Context for setting up an antibiotic resistance study (ABR) in water => links to be created between the two groups involved within ANSES. .	
	• **Regulatory problem according to interpretation of the action, prescription problem, diversity of types of breeding**…	**Reg**	➢ Maintain the current level of understanding of the authorities, pragmatism and agility. Risks associated with increasing environmental requirements => define an acceptable framework for the future(1)	
	• **A single "aquaculture" VMP with MA:** PYCEZE, single indication (saprolegnose) and only two target species. **Marketing withdrawal initially planned in France** by Elanco, but following the actions initiated after the 2019 meeting, implementation of works for a return to the market.	**Disp**	➢ Import of the Chilean VMP CRESS authorised by the ANMV since the 2019 meeting☺: only one application in 2021, 4 in 2020. CRESS used in hatcheries to prevent saprolegosis on eggs and fry. Transport time to be taken into account (ship), hence the need to establish safety stocks. ➢ ANMV info: Waiting for a timetable for PYCEZE to return to the market (in 2022?).	
<u>Treatment of most common bacterial diseases</u>: yersiniosis, furunculosis, vibriosis, lactococcosis etc. Metaphylactic oral treatment of septicaemic bacteriosis after coating the premix on the food.	**Almost no antibiotics VMPs for fish:** - TRIBRISSEN POISSON abandoned in 22/10/20 (after 4 years of zero sales) - Flumequine: stop the medicated premix for salmon & trout. Only remaining 3% powder for oral solution: very diluted but better than nothing => to be preserved. Significant clearance which enables short withdrawal times to be maintained. Questions regarding the dosage schedule, especially with such a diluted formulation. There seems to be a rapid development of resistance when used in the field.	**Disp**	Reduction of the use of antibiotics thanks to vaccines and the increase in **the auto-vaccines use**. The 3-year Médic'Eau project has been initiated with Oniris (FEAMP funding) to work on ATB dosages in fish farming, taking into account the influence on the commensal flora and the risks associated with the selection and diffusion of antibiotic resistance genes. The ecotox assessment is not currently foreseen in the project(1). The objective is to identify antibiotics of interest with	**M No. 2**

-	- Oxolinic acid: unusable in triploid trout (allergic) - Oxytetracycline (medicated premix): inappropriate recommended dosage (55 mg/kg instead of 90-100 mg/kg) ⇨ Antibiotics are used mainly through the "cascade" for a medicated feed on-site manufacturing (mainly) or in feed mills, either from: - registered medicated premixes (but not available before 4-5 days at best so not usually applicable) or - VMPs registered for other species. E.g. Sulfadiazine-TMP (oral or injectable solution used by on-site coating on feeds), in more than 50% of cases (for aeromonas, furonculosis, vibriosis), enrofloxacin, florfenicol (for flavobacteria or aeromonas)		appropriate and "agile" use and to find practical solutions or recommendations with a better "scientific framework" for the cascade use while taking into account the breeding conditions. The **antibiotic cascade** (see opposite) is well suited as it is reactive; the following day, the breeding can be treated. Now antibiotic prescriptions are emergency treatment prescriptions. Antibiotic use focuses on young fish (80% of fish have never received antibiotic treatment). Need to facilitate **the import of medicated premixes if necessary**…	
	• **Yersiniosis:** vaccines and autovaccines work very well and this disease has significantly decreased. MSD vaccine often out of stock, which poses a major problem for the sector. AQUAVAC ERM oral (oral emulsion) is no longer available, remain AQUAVAC RELERA suspension (for bath or injection) and AQUAVAC ERM (dipping for young fish). Vaccines satisfactory for trout, but specificity problem in other species.	**Disp**	**Switch to autovaccines when possible to get a waiver. Bivalent autovaccines work very well** (4 applications registered by the ANMV in 2021). Interest ++ because 2 or 3 bacteria are generally associated. Autovaccines account for approximately 50% of commercial vaccine prescriptions. **Wish for a bivalent injectable vaccine** with yersiniosis and furunculosis valences for large trout and a furunculosis vaccine for Arctic char and brown trout.	
	• **Furunculosis: no vaccine with MA in FR** therefore, for high added value species, import from NO of Alphaject 3000 for furunculosis–vibriosis even if "vibriosis" is not useful in FR. Otherwise, **more or less effective autovaccine.**	**0 VMP**		
	• **Vibriosis:** occasionally auto-vaccine use		Vibriosis autovaccines: 2 applications registered by the ANMV in 2021.	
Control of uncommon bacteria or "minor" aquaculture species: • Turbot (edwardsiellosis) • Sturgeon (Siberian streptococcosis)	• **Efficacy gap in turbot and edwardsiellosis, attenuated or recombinant vaccine from Asia (Japan)** could be interesting, to be explored further, **otherwise ATB (marbofloxacin…).** Turbot remains a marginal sector.	**Disp**	=> See import of vaccine from Japan? (no import request recorded by ANMV)	
	• **Sturgeon:** search for a vaccination route on streptococcosis, but **problem of research on immunity in sturgeons** (ploidy).	**0 VMP**	=> Antibiotic therapy in other species	

Therapeutic gaps in the Fish sector

Meeting of 13/12/21

• Fight against flavobacteriosis: juveniles of rainbow trout	• **Lack of a robust protocol in trout to control this disease. Antibiotic therapy in case of acute crisis.** Mainly florfenicol used. No resistance to date, slight increase in MIC.		**Wish for a flavobacteriosis rainbow trout vaccine: research ongoing?**	
<u>Virosis prevention:</u> • IPN (Infectious Pancreatic Necrosis - Togavirus) • Emerging virosis (reovirosis).	• NPI affects all salmonids: salmon when transferred to sea and trout from 1st feeding (very small fry) at a time when vaccination is not feasible. => Salmon vaccines cannot be used on rainbow trout. • Some reovirosis in salmonids. The 2 main virosis are not subject to vaccination under the FR regulation for eradication (NPI and SHV, category 1 health hazards). **No vaccine solution.** Reovirus culture difficulties. Work on identification and diagnostic test ***Note:*** 2 MAs for injectable vaccines granted in 2019 & 2020 against the sea bass viral nerve necrosis virus (ICHTIOVAC VNN and ALPHAJECT MICRO 1 NODA) – Mediterranean market.	**Reg** **0 VMP**	In FR, little use of vaccines for viruses due to environmental problems because of circulation of virus-carrying and asymptomatic fish. **Management by biosecurity, transport and sites hygiene.** Consider developing **imports if vaccines exist** (from NO but they remain very expensive and often heptavalent). Only one vaccine import request for NPI registered by ANMV. **Vaccination of breeders** to be considered. Customised viral vaccines (improperly called "viral autovaccines") could be authorised by ANMV **on a case-by-case basis**. DGAL PNES policy to eradicate virosis in the fish sector, so no recourse to vaccines. Genetic selection programs also exist for IPN in trout.	**M** **No. 3**
Anaesthesia for: -vaccination by injection; - eggs collection for consumption; - eggs collection for fertilisation; - weighing and sorting (in particular in marine or freshwater perciform farms)	In the FR aquaculture sector (marine or fresh water farms, various species, etc.) **phenoxyethanol was discontinued** because of lack of legal status. Current use of: 1. Tricaine imported from PharmaQ, rather on trout 2. Benzocaine imported from AQUACEN (ES), rather for sea bass in temperate water. 5L bottle not very practical (use of extemporaneous preparation for smaller volumes). 3. Eugenol and isogenol (extemporaneous preparations) Imports are an answer to the problem, but they are cumbersome. => why not a MA in France (e.g through mutual recognition of the Spanish VMP) ? Problem of withdrawal period (WP). The WP for tricaine is 70°days ≈ 1 week: OK for vaccination but not applicable for eggs harvesting.	**Disp** **Reg**	Fish are completely rinsed before the eggs are harvested. Determinations showed no residues or values below the MRL. An anaesthetic with a zero day egg WP would be required. ⇨ Risk of residues to be further evaluated ? Harvesting eggs from live fish is mainly a french practice.	**m**

Meeting of 13/12/21

	Anaesthesia for egg harvesting (trout caviar) is done for animal welfare considerations but the WP is not applicable and substances are not metabolised. A complete rinsing of the fish is therefore carried out before the eggs are harvested.			

(1)***Post-meeting info:*** a concept paper for the development of guidelines on environmental risk assessment for veterinary aquaculture medicinal products was proposed for public consultation in 2021: https://www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-development-guideline-environmental-risk-assessment-veterinary-medicinal-products_en.pdf. The European ERAWP sub-group of the CVMP is currently working on the comments received. The objective is to propose guidelines for Oct. 2024.

Three priorities have been identified:

1. **Control of external parasitism**
   Including the unblocking of the situation regarding the use of formaldehyde
2. **Use of cascade**
   Maintain the current understanding of authorities by keeping a pragmatic and "agile" approach
3. **Transparency and pragmatism**
   Maintain the current transparency with ANMV (in particular through these meetings on therapeutic gaps) regarding practices in the sector

Actions	Who	Deadline
➢ **Formaldehyde use:** define possible measures to specify and reduce the impact on the environment	ANSES / DGAL / sector	2022
➢ Monitoring return to the market of PYCEZE	ANMV	2022
➢ **Availability of antibiotics:** recommendations on antibiotics of interest and adapted dosages	Oniris Médic'Eau project	2024
➢ **Wish for a French MA for:** **-an injectable vaccine** bivalent : yersinosis + furunculosis valence for large trout and a furunculosis vaccine for arctic char and brown trout -**a flavobacteriosis vaccine for rainbow trout** **- tricaine or benzocaine (MR of the Spanish VMP)**	RFSA (info to MAH via minutes of this therapeutic gaps meeting)	02/2022

Therapeutic gaps in the Fish sector

Meeting of 13/12/21

➢ Pharmacovigilance reports: criteria and thresholds to be established for serious cases (see below)	SNGTV - ANMV	2022

Answers to other questions/queries from 2019 meeting:

- Pharmacovigilance topic, increase declarations, declaration on vaccines. It would be interesting to determine a threshold (number of dead fish) for pharmacovigilance declarations.
  The subject has not progressed since the last meeting. The sector had been asked to establish criteria to characterise a lack of efficacy (in particular for vaccines) on the model for characterising serious adverse effects in other sectors but the ANMV's reminders were unsuccessful.
  => This point should be taken up with the SNGTV. The aim is to facilitate the reporting of declarations and to define, in particular, mortality thresholds above which it is necessary to report. The "serious cases" must be defined using a pragmatic approach (case-by-case approach, therefore difficulty of implementation).

- New veterinary medicinal product regulation 2019/6 - Art 115 on application of the cascade and withdrawal period (WP) (see below):

  (d) for aquatic species producing meat for human consumption the withdrawal period shall not be less than:
  (i) the longest withdrawal period for any of the aquatic species indicated in the summary of the product characteristics multiplied by factor of 1,5 and expressed as degree-days;
  (ii) if the medicinal product is authorised for food-producing terrestrial animal species, the longest withdrawal period for any of the food-producing animal species indicated in the summary of product characteristics multiplied by a factor of 50 and expressed as degree-days, but not exceeding 500 degree-days;
  (iii) 500 degree-days, if the medicinal product is not authorised for food-producing animal species;
  (iv) 25 degree-days if the highest withdrawal period for any animal species is zero.

- Opening of a pharmaceutical establishment specialised in vaccines and autovaccine, in FR
  ANMV: For the manufacture of fish autovaccines, it is currently Biovac which has become CEVA-Biovac.
  Requests for auto-vaccines: 17 in 2021 for trout (*Yersinia ruckeri* serotype 1 and *Aeromonas salmonicida*) and 2 in 2021 for sea brass (*Listonella anguillarum*, *Vibrio anguillarum*).