Challenges facing the regulation and use of veterinary products in aquaculture in Europe

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• MSc in Aquatic Veterinary Studies in 1978 and worked with fish & exotics ever since. Worked with UK fish farmers since 1978.
  • RCVS Recognised Specialist in ‘Fish Health & Production’
  • also Specialist in ‘Zoo & Wildlife Medicine’ and have FRCVS in Psittacine Medicine & Surgery

• Welfare Interests
  • a member of the of Companion Animal Welfare Council (CAWC) which advises on aspects of health & welfare in companion animals.
  • was a member of the England Implementation Group which worked with DEFRA on implementing its Animal Health & Welfare Strategy.
  • Currently the Senior Vice President of the Fish Veterinary Society
  • A member of the Veterinary Products Committee which offers advice to the Veterinary Medicines Directorate (VMD) on behalf of the Secretary of State, in respect of new and renewal Marketing Authorisations (MAs), Provisional MAs, variations to MAs and Animal Test Certificates (ATCs).

• I am NOT representing the views of any of these groups at this meeting.
I would like to recognise the assistance received for this paper from industry, in particular:

- MSD
- Pharmaq
- Novartis
Outline

- First, a brief review of English fish farming
- Putting drug and vaccine usage in context
- Regulators
- Pharmaceutical areas
Aquaculture in Europe

Development of Fish Farming in the European Union (tons) 2002-2011
### Atlantic salmon production (tons) 2002-2011

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>YEAR</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atlantic salmon</td>
<td>COUNTRY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAROE ISLANDS</td>
<td></td>
<td>45.000</td>
<td>52.526</td>
<td>33.600</td>
<td>18.700</td>
<td>10.724</td>
<td>18.290</td>
<td>31.359</td>
<td>42.132</td>
<td>37.221</td>
<td>49.588</td>
</tr>
<tr>
<td>FRANCE</td>
<td></td>
<td>500</td>
<td>800</td>
<td>700</td>
<td>1.200</td>
<td>1.600</td>
<td>1.800</td>
<td>0</td>
<td>0</td>
<td>802</td>
<td>700</td>
</tr>
<tr>
<td>NORWAY</td>
<td></td>
<td>460.000</td>
<td>520.000</td>
<td>512.000</td>
<td>588.444</td>
<td>617.000</td>
<td>751.000</td>
<td>799.000</td>
<td>870.000</td>
<td>941.001</td>
<td>1,023.000</td>
</tr>
<tr>
<td>UNITED KINGDOM</td>
<td></td>
<td>142.961</td>
<td>161.748</td>
<td>150.000</td>
<td>123.000</td>
<td>118.525</td>
<td>129.930</td>
<td>129.545</td>
<td>142.283</td>
<td>147.412</td>
<td>150.000</td>
</tr>
<tr>
<td>Atlantic salmon Total</td>
<td></td>
<td>671.355</td>
<td>756.694</td>
<td>716.321</td>
<td>748.938</td>
<td>764.716</td>
<td>913.178</td>
<td>970.187</td>
<td>1,067.754</td>
<td>1,139.947</td>
<td>1,238.398</td>
</tr>
</tbody>
</table>

![Graph showing Atlantic salmon production (tons) 2002-2011](image)
English fish farming

- Trout farms
  - Large >100 tonnes /year
  - Medium 20-100
  - Small < 20
  - Hatcheries
    - commercial 2-4M/yr
    - own stock 200,000/yr
- River keepers - less than 10,000 fish often
- Fishery owners - < 2000 fish?

- Carp
  - Farms
  - Fishery owners
Drug usage

- Use antibiotics a number of times a year, say 10-20 x per site, perhaps multiple ponds each time

- mix on each site, two large producers in south have 4 and 5 sites respectively

- Biosecurity is a major concern
  - Lactococcus was introduced from France - wiped out a farm in Kent, at the time the UK’s biggest restocking fish producer - they are now out of business
  - Sleeping Disease (virus) also from France - up to 80% morts in Scottish farm

- One site has a large professional drum blender, others use cement mixers
Routes of administration

- Feeding drugs is the prime means of administration
  - Antibiotics - none are given by injection or immersion
  - Vaccines - as boosters for previously dipped or injected fish
  - Parasiticides (Emamectin)

- Via the water
  - Traditional remedies, formalin, chloramine T
  - Licensed – bronopol

- Via injection
  - Vaccines
  - Hormones
## Injectable vaccines

<table>
<thead>
<tr>
<th>Company</th>
<th>Vaccine Name</th>
<th>Type</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schering-Plough</td>
<td>Aquavac FNM&lt;sup&gt;PLUS&lt;/sup&gt;</td>
<td>non-mineral oil based</td>
<td>licensed for salmon, used on the cascade</td>
</tr>
<tr>
<td></td>
<td>Aquavac Furovac</td>
<td>water based</td>
<td>licensed for salmon, used on the cascade</td>
</tr>
<tr>
<td></td>
<td>Aquavac ERM</td>
<td>water based</td>
<td>licensed for trout</td>
</tr>
</tbody>
</table>
Vaccination machines

- problematic but getting better
- expensive
- anaesthetised fish
- hand fed into machine
Standard practice

- Gun can use a 3mm needle or a 6mm needle
- Generally use 6mm

3mm neoprene glove for grip over turtle skin inners
The point of this is that the scale and type of aquaculture in the EU is very varied,

• with a range of species

• many levels of commercialisation and development

• Strangely similar/related pathogens yet different enough to cause regulatory ‘issues’
Regulators

The Veterinary Medicinal Products Directive 2001/82/EC (as amended) sets out the controls on the manufacture, authorisation, marketing, distribution and post-authorisation surveillance of veterinary medicines applicable in all European Member States.
Pharmaceuticals

- Therapeutic – antibacterials, anthelminthics
- Preventative
  - Vaccines – bacterial and viral
- Husbandry based – hormone treatments
  - Aids to spawning
  - Control of breeding
Other considerations

Atlantic salmon production (tonne) 2002-2011

EMEA/429080/2009
Newer model

- Now being used in human pharma development
Therapeutic

Typical development of a pharmaceutical

Average duration of the phase

<table>
<thead>
<tr>
<th>Phase</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td>15 yr</td>
</tr>
<tr>
<td>Proof of concept</td>
<td>2 yr</td>
</tr>
<tr>
<td>Exploratory development</td>
<td>2/3 yr</td>
</tr>
<tr>
<td>Full development</td>
<td>2/3 yr</td>
</tr>
<tr>
<td>Registration</td>
<td>2 yr</td>
</tr>
</tbody>
</table>

Typical Attrition rates at each phase

<table>
<thead>
<tr>
<th>Phase</th>
<th>Attrition Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td>approx 88%</td>
</tr>
<tr>
<td>Proof of concept</td>
<td>approx 60%</td>
</tr>
<tr>
<td>Exploratory development</td>
<td>approx 20%</td>
</tr>
<tr>
<td>Full development</td>
<td>approx 10%</td>
</tr>
</tbody>
</table>

With fish typically looking at $1,000,000 per year
There is no legislative definition in the EU for major or minor species. However, major species were defined by the CVMP according to animal population data and total consumption figures, using global numbers across the European Union for the purpose of CVMP guidelines in its Position Paper regarding availability of products for Minor Uses and Minor Species (MUMS) (EMEA/CVMP/477/03-Final) [2]. All other animal species, which are not considered major, are as a consequence, by default, classed as minor species.

Major food-producing species:
- Cattle (dairy and meat animals)
- Sheep (meat animals)
- Pigs
- Chickens (including laying hens)
- Salmon

In the CVMP Position Paper EMEA/CVMP/477/03 the CVMP concluded that Salmonidae should be considered as major species. Following subsequent consultation of the CVMP guidelines on data requirements for MUMS products, the CVMP agreed to change this classification as follows: Salmon should be considered a major species, however other species of the Salmonidae family such as rainbow trout should be considered minor species.

The Committee for Medicinal Products for Veterinary Use (CVMP) is the committee at the European Medicines Agency that is responsible for preparing opinions on questions concerning medicines for veterinary use.
New guideline

- May 2012: EMA/CVMP/IWP/314550/2010 ‘Guideline on the design of studies to evaluate the safety and efficacy of fish vaccines’
  - This is a very useful guideline for the development of inactivated vaccine for fish and is regarded in many aspects as being very clear on the requirements.
EMA

- Committed to ensuring/encouraging availability
  - System weighted towards species – major species means maximum return on investment

- Support for SMEs
  - BUT few SMEs are producing product, MANY SME’s need it

See: Quigley K, Minor Use Minor species /Limited Markets Policy. EMA website
Species

- Registration has to be sought for each fish species independently (both safety and efficacy demonstration), there is no such thing as registration with ‘fish’ as target species supported by demonstration of safety/efficacy in key species.
- Some diseases however can affect many different species of fish.
  - There is a considerable list of cultured species even within the EU
• A major challenge is to ensure that veterinarians working in aquaculture have access to the appropriate therapeutic agents for quick responses to disease outbreaks
  • And

• To ensure that where appropriate vaccine development is encouraged by the culture of regulation
Species

- Development then concentrates on the most commercial species – *usually salmon!*
- If the disease then appears in another ‘minor’ species the extension in terms of costs required for demonstration of both efficacy and safety may not be viable
- There is a mechanism for SIC use, but it’s not always easy
- It would assist if:
  - Demonstration of safety in one laboratory or one field trial in the minor use species should be sufficient.
• If a new disease appeared in the Mediterranean for which a vaccine existed outside the EU, perhaps in another species there would be major problems, even though
  • A vaccine will be GMP and has safety and efficacy data in one species

• Such a problem exists with *Streptococcus iniae*, *Lactococcus garvieae*, Infectious salmon anemia virus (ISA), Salmon Rickettsial Syndrome (SRS)
  • The STC system *may* permit emergency import and use
  • Licensing would be costly and take a minimum of 1.5-2 years
Do we have the tools to deal with outbreaks of novel and exotic disease:

- Various aspects:
  - Treatment
  - Biosecurity
  - Prevention

- 3+ years is too long
Temperature...

- Fish are ectothermic
  - Their core temperature and physiological processes are regulated to a degree by ambient temperatures
  - The pharmakokinetics of drugs and immune response developed by vaccines are obviously affected
Temperature...

- Relevant section from the fish guideline:
  - *The different climatic conditions and water temperatures within the Community should be considered, when relevant for the fish species/disease in question. Some studies may need to be performed both at high and low temperature for the relevant fish species/disease distribution.*

- Vaccination at different temperatures for demonstration of safety and efficacy entails a lot of additional work and is also not desirable from an animal welfare point of view.

- Once a vaccine with certain adjuvant in e.g. salmon has registration for use at e.g. minimum temp 6 C and (safety) and efficacy has been demonstrated, it should be possible to advise the same minimum temperature for other vaccines with same adjuvant used in same way (e.g. injected in Salmon of minimum 30 gram).
Field trials

- The scope of the field studies is to ensure that the vaccine is efficacious and safe in the diversified conditions for aquaculture found in Member States for the relevant fish species.

- Because of the scale of salmon culture, it is not possible to cover all the ‘diversified condition for aquaculture found in Member states for the relevant fish species’. Cages often have more than 50,000 fish/cage, making it impossible to have many sites.

- Also because of the large amount of work involved in follow up this is just not possible.
Controls

- If a positive control (e.g. a comparator vaccine) is used, consideration should be given to maintaining a (small) group of non vaccinated fish in a separate test pen to serve as indicators of exposure to disease(s) at farm level.

  *This is not feasible in the field as fish pens contain a large number of fish; not vaccinating these fish is a risk to the farm (high disease pressure in case fish are infected) and also not desirable from an animal welfare point of view.*
There is a new draft guideline: EMA/CVMP/IWP/594618/2010 “Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMPs)”. 
Combined use

- When diseases are emerging, quick availability of vaccines can also reduce spread.
- Diseases can emerge in new areas. Currently fish vaccination is often done using a large ready to use combination, where all antigens are combined in a single vaccine solution.
- As different combinations of fish diseases are present in different member states, an approach of interest is developing a modular vaccination approach;
- this could for example entail a **mix-on-site** procedure, where the desired vaccine components are combined in one bottle to obtain the specific vaccine combination needed. This would also enable fast response when a disease spreads to new area.
- However, the new draft guideline may seriously hamper product development following this strategy.
Mix-on-site

• The current (draft) regulatory guidance makes this unattractive because:
  • When vaccine are mixed:
    • Needs to be tested in each target species
    • Both lab and field trials are required and min/max dose
    • Onset and duration needs to be established
  • Without mixing prior to injection
    • Most sensitive category of target species
    • Both lab and field trials are required
    • Onset and duration needs to be established
In conclusion:

- Both laboratory and field trials are needed.
- Duration of immunity needs to be investigated.
- If more than one fish species is affected, studies need to be done in each.
- When this guideline is implemented, it makes the development of a modular approach of vaccines very unattractive.
- Consequently only vaccines will be developed containing the specific components for the major markets and major fish species.
Live vaccines

- No guidance yet for such vaccines
Potency tests

- For *in vivo* potency tests, tests can have a large variation, especially when using fish, where no ‘SPF’ lineages exist.

- This can result in the need for many additional studies and during registration procedures this can lead to extensive discussion on proper release requirements.

- Vaccines are produced under GMP and there are many controls in place to ensure product quality; it is suggested by industry that the potency test could/should also be regarded as a confirmatory test and as such a more flexible approach could be taken.
The OIE manual of standards

- Both the OIE Manual of Standards and VICH guidelines give important guidance.

- The OIE is actively involved in VICH. So is the vaccine industry.

- However, for new chapters / revision of existing chapters of the OIE Manual of Standards (for OIE listed diseases) and for the generic chapters on vaccine research and production there is no formal mechanism for consultation of the vaccine industry.

- A formal consultation through IFAH would be beneficial.

IFAH-Europe (International Federation for Animal Health Europe)
Emerging diseases

- Emerging diseases occur and may require emergency development of a vaccine.

- Proposal: to enable conditional license for disease, which are threatening but did not yet occur. “a Sleeping/dormant license”.

- Lay down conditions for an emergency license. In case of a vaccination exit scenario, the conditional license should be kept alive but frozen without the need to continue to a full license if vaccination is no longer in place.

- A license to use without a conditional license is attractive for disease control authorities but not for the vaccine industry as the license to use generally has to be withdrawn as soon as there is a licensed vaccine and therefore is unpredictable and risky for the vaccine industry.
Purpose of regulation

- To establish standards:
  - Concern re safety & efficacy with regard to the animal to which products are administered and to society (including the consumer and the environment in which we live)
  - We need to adopt more of a risk-based approach to regulation of drugs and vaccines.
    - The latter in particular are vitally needed in agriculture and aquaculture and the process of licensing simply takes too long and costs too much
“Well, thank God we all made it out in time. ... 'Course, now we're equally screwed.”
- http://www.vichsec.org
- http://www.ifaheurope.org