Current Treatments Used in Aquaculture and Processes to Approve New Substances

ParaFishControl Final Conference
“Innovative Strategies to Control Parasites in Aquaculture Farms”
Brussels, 11th March 2020

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Animalhealth Europe
AnimalhealthEurope: who are we?

14 companies

- Belgium
- Czech Republic
- Denmark
- Finland
- France
- Germany
- Greece
- Hungary
- Ireland
- Italy

18 associations in 20 countries

- Netherlands
- Norway
- Poland
- Portugal
- Slovakia
- Spain
- Sweden
- Switzerland
- Ukraine
- United Kingdom

Representing 90% of the EU market
Working to ensure a ready availability of a wide range of animal health products throughout Europe
Outline of presentation

• FishMedPlus Coalition (2015-2019)
  – Availability of authorised medicines for aquatic species in EU/EEA

• Current legislation in EU (=EU+EEA)
  – Lisensing new medicinal products
  – Approval of Maximum Residue Limits (MRL)
  – Lisensed products in EU
    Veterinary MRIIndex: https://mri.cts-mrp.eu/veterinary

• New Veterinary Medicines Regulation 2019/06
  – Implementation from January 2022
FishMedPlus Coalition
Aim to increase availability of authorised medicines for aquatic species in Europe
3 step approach

- **GAP ANALYSIS**
  Which products are needed on which markets today and in the future, looking at the main aquatic species in the EU and EFTA countries

- **INVESTIGATE BARRIERS**
  Exploration on barriers and solutions to overcome these barriers, with specific attention to environmental risk assessment.

- **STIMULATING MARKETING AUTHORISATION**
  Exploration on ways to explain regulatory requirements, to overcome barriers and to stimulate more authorisations

- Source: https://www.fve.org/publications/fishmedplus/
Parasite infections are main cause of concern for all fish species

<table>
<thead>
<tr>
<th>PRIORITY LIST OF IDENTIFIED DISEASES/INDICATIONS</th>
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<tbody>
<tr>
<td>Ectoparasites - Ich (Ichthyophthirius or Ichthyophthiriosis), costia (Ichthyobodosis), Sea/salmon lice, Monogenea infestation – All species</td>
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<tr>
<td>Bacterial diseases - Aeromonas - All species</td>
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<td>Fungal and Oomycotic infections – All species</td>
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<td>Amoebic gill disease (AGD) – Mostly Salmon</td>
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<tr>
<td>Rainbow Trout Fry syndrome (RTFS) – Flavobacteriosis – Trout and Carp</td>
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<tr>
<td>Sedation and anaesthesia - All species</td>
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<td>Viral diseases – all species (see OIE list)</td>
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<tr>
<td>Hormones for broodstock management/maturation/ovulation induction</td>
</tr>
<tr>
<td>Endoparasites - in all species (mostly secondary effects, lower production parameters and food quality aspect)</td>
</tr>
</tbody>
</table>

Source: https://www.fve.org/publications/fishmedplus/
Examples of products identified in the gap analysis that fish vets need in other countries than authorised:

- **Florfenicol** (Florocol, Aquaflor– MSD)
- **Oxytetracycline hydrochloride** (Aquatet– Pharmaq Ltd)
- **Amoxycillin trihydrate** (Vetremox Fish – Pharmaq)
- **Formaldehyde** (Aquacen formaldehida – Cenavisa SL)
- **H2O2** (Paramove -Solvay” Hydrogenperoksid - Akzo Nobel”)
- **Tricaine methane sulphonate** (Finquel vet - Scan Aqua/Tricaine – Pharmaq Ltd/Nytox – Neptune Pharma Ltd)
- **Benzocaine** (Benzoak vet - ACD Pharmaceuticals AS)
- **Isoeugenol** (Aquic lab – Scan Aqua)
- **Emamectin benzoate** (Slice - MSD Animal Health)
- **Azamethiphos** (Salmosan Vet - Fish Vet Group/Azasure – Neptune Pharma)
- **Teflubenzuron** (Calicide - Trouw Ltd/Ektobann (medicated pellets) – Skretting AS)
- **Deltamethrin** (Alpha Max/AMX – Pharmaq AS)
- **Enrofloxacin** (Baytril – Bayer)
- **Diflubenzuron** (Releeze vet.”EWOS AS” (medicated pellets))
- **Buserelin** (Receptal - Intervet UK Ltd)

Source: work from GAP analysis in FishMedPlus Coalition

https
Parasiticides/Aqua products in EU/EEA

• Most medicinal products for fish are licensed in UK or Norway
  – Largest salmon markets

• In general few licenses across many countries
  – Fish products are often tailor made for species and diseases
  – Environmental risk assessment for local waters needed

• Lack of efficacy / risk of resistance development is a concern

• Parasite treatment important to avoid secondary bacterial diseases
Current European Regulatory Framework

• Directive 2001/82/EC (as amended)
  – Defines:
    – Veterinary medicinal products (VMPs)
    – Need for marketing authorisations (licenses) issued by Competent Authorities
    – Procedures associated with initial authorisation and post-authorisation (renewals, variations, monitoring, etc.)
    – Requirements for description of product characteristics/labelling, release, distribution and Pharmacovigilance

• Complemented by Regulation (EC) No. 726/2004
  – expands upon authorisation options and post-authorisation maintenance.

• Complemented by Regulation (EC) No. 1234/2008
  – describes assessment and approval of post-authorisation changes (variations).

➢ Approvability based on Quality, Safety and Efficacy documentation and a positive benefit/risk evaluation
European Regulatory Framework cont’

• CVMP Guidelines: Committee for Veterinary Medicinal Products
  – Provides additional guidance for specific activities tied to product development and in-line product maintenance
  – Not regulations, but closely followed and “enforced” by Authorities
  – Complemented by concept/reflection papers, position statements, and public statements where warranted

• European Pharmacopeia (Ph.Eur)
  – Monographs and standards

• Reference pages to EU guidelines:

  VICH Guidelines
  http://www.vichsec.org/guidelines/biologicals/bio-quality/impurities.html
Regulatory Procedures for New Marketing Authorisations

- **Centralised Procedure (CP)**
  - Results in a single pan-European licence automatically valid in all Member States and for EEA countries as identical decisions. Mandatory for some technologies.

- **Decentralised and Mutual Recognition Procedures (DCP/MRP)**
  - Result in multiple national licences, which are only valid in the Member States that issue them, but are harmonised across all Member States (including EEA) involved.

- **National Procedure (NP)**
  - Results in a single national licence
  - Some products (e.g. those registered before 1995, feed materials, *in vitro* diagnostics) may have multiple national licences, which are not harmonised across Member States
  - Can now only be used once, in the first country of approval

➢ **Best case 1 year, realistically ~18-24 months**
Maximum residue limits (MRL)

- Commision Regulation (EU) No 37/2010 on pharmacological active substances and their classification regarding maximum residue limits in foodstuffs of animal origin

- Community procedures for the establishment of MRL’s, Regulation (EU) 470/2009
  - Application at least 6 month before a Marketing Authorisation (MA) application

- Extrapolation of MRL’s to other species, Commision Regulation (EU) 2017/889
  - Salmon is major species, other fish species are minor
Licensed products in EU

• **Heads of Medicines Agencies, CMDv**
  – **MRP**, Decentralised or nationally approved:
    Veterinary MRIIndex: [https://mri.cts-mrp.eu/veterinary](https://mri.cts-mrp.eu/veterinary)
    Most relevant source for medicines for aquatic species

• **European Medicines Agency:**
  – Publish all individual product approvals/commission decisions for all products in centralised procedure
  – New product database under development
New Veterinary Medicines Regulation 2019/06
(implementation by January 2022)

- Limited market provisions for all fish species (art 23)
- Exceptional circumstances MA applications (art 25)
- Protection of technical documentation
  - 14 years for fish products (art 39)
- Greater focus on environmental safety (art 37.2 (j))
  - Also for old products with potential harmful properties and without previous complete risk assessment (art 72)
- Greater focus on the use of antimicrobials
- Increased scope of Centralised Procedure
  - Applies to all new active substances (art 42(c))
    ▪ Challenging for fish products which are tailor made for species and region and often not relevant pan European
- The Cascade – new ranking, includes also third country products (art 113)
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