Legislation on Veterinary Medicinal Products (VMPs) and legal status of relevant VMPs for anesthesia of finfish

Anesthesia of Big Research Fish

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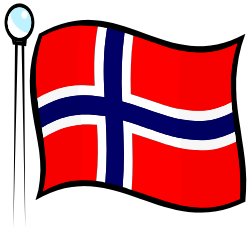
Regulatory framework

- Norway, Iceland and Liechtenstein have the same basic legislation for (Veterinary) Medicinal Products as EU, due to an extended EEA agreement in this area.
  - New EU regulations and directives in this field are continously implemented into Norwegian laws and regulations

- Participate in the EU procedures for Marketing Authorisation (MA) for (V)MPs.
  - Incl. participation in CVMP (Committee for Veterinary Medicinal Products);



Relevant authorities - Norway

- Norwegian Medicines Agency
  - regulating the manufacturing and distribution chain
    - permits
    - inspections
  - marketing authorisation (MA) for medicinal products
  - classification ((V)MP or not)
- Norwegian Food Safety Authority
  - regulating animal health personnell and their use of medicinal products for animals
    - advice/interpretation of the relevant regulations
    - Inspections

Supply and distribution chain strictly regulated

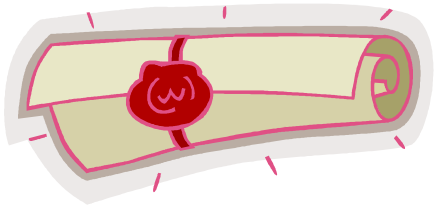
- Manufacture in accordance with Good Manufacturing Practice (GMP)
  - GMP certificate
  - Manufacturing authorisation from national competent authority (in Norway: Norwegian Medicines Agency (NoMA))
  - Inspections

- Distribution in accordance with Good Distribution Practice
  - All import and sale of VMPs requires relevant permit from NoMA
  - No legal sale of VMPs outside pharmacies/wholesalers
  - Norwegian veterinarians and fish health biologists have no dispensing rights (not allowed to sell VMPs)

Possible legal status for VMPs in Norway

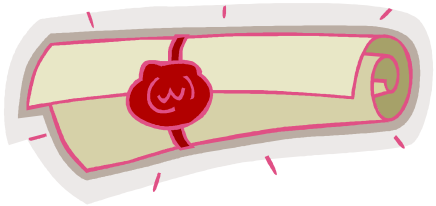
- Marketing authorisation (MA)
- Special exemption (SE) permission to individual prescribers to prescribe VMPs without Norwegian MA
- Exemption under exceptional circumstances: Exemption granted to manufacturer or other. General market access without MA.
- VMP extemporaneously prepared: Manufactured by pharmacies
- Autogenous vaccines: Vaccines made for one animal/holding
- Medicated feed: Prepared by authorised feed mills

Marketing authorisation (MA)



- Required for all (V)MPs «prepared industrially or by a method involving an industrial process»
- Four procedures for applications
  - Centralised procedure (all EU/EEA member states involved)
  - Decentralised procedure (new product, ≥ 2 member states involved)
  - Mutual recognition procedure (existing product, ≥ 2 member states involved)
  - National procedure (new product, 1 member state involved)

Marketing authorisation (MA)



- Timeline for new applications is 210 calendar days + clock stops (when applicant has received questions to which he must respond)
  - First assessment and list of questions after 120 days
  - Second assessment and list of outstanding issues at day 165
  - Decision at day 210
- The final decision to approve or reject an application is based on a benefit:risk assessment. There must be a clear benefit which outweighs the risks.

Requirements for marketing authorisation (MA) of VMPs

Documentation in accordance with directive 2001/82 (as amended by directive 2004/28) and directive 2009/9/EC:

- Administrative information
- Quality documentation
- Safety documentation
- Efficacy documentation

Relevant monographies in the ***European Pharmacopoeia*** should also be followed

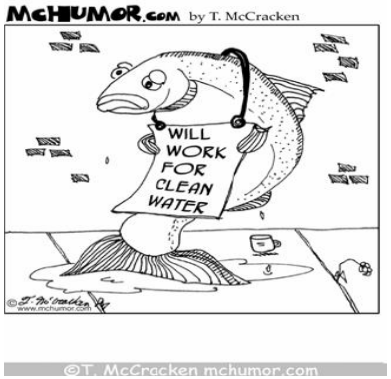
Quality documentation

- Product development information
- Starting materials
- Manufacturing method
- Control tests during manufacture
- Control tests of finished product

The quality documentation is the foundation for acceptable documentation of a medicinal product; batch consistancy is essential.

Safety

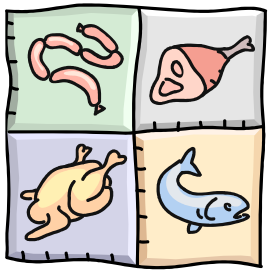
- Basic safety - studies in laboratory animals
  - acute toxicity, chronic toxicity
  - genotoxicity, mutagenicity, carcinogenicity, reproduction toxicity
- Safety for target animal species
  - all relevent species and physiological categories
- Environmental safety
  - Environmental risk assessment (ERA)
  - Different aspects for pharmaceuticals and vaccines
  - Studies usually required for pharmaceuticals for fish



Safety

- Operator safety
  - Exposure scenarios
  - Risk assessment
  - Risk mitigation measures
- Consumer safety, when relevant
  - Requirement for established maximum residue limit for relevant species
  - Residue depletion studies: maximum recommended dose for maximum recommended treatment period
  - Withdrawal period

Withdrawal period (WP)



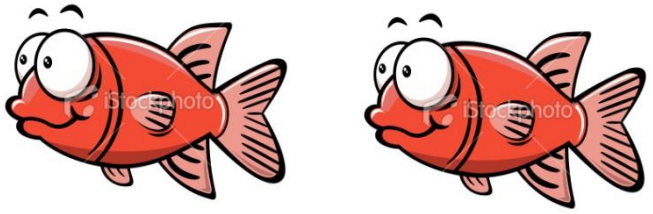
- All VMPs for food producing species require WPs
- Based on:
  - ADI (acceptable daily intake)
  - MRL (maximum residue limit)
- Establishment of ADI and MRL requires a large data package (toxicological data from animal tests)

- Minimum WPs established in EU for *off label* use:
- Fish: minimum 500 degree days

Efficacy

- Pharmacological documentation
  - Pharmacodynamics
  - Pharmacokinetics
- Preclinical documentation
  - Laboratory studies
  - Dose establishment and confirmation
- Clinical documentation
  - All intended species/categories/indications
  - Confirmation of results from laboratory studies

Clinical trials



- Clinical trials in Norway must be approved by the Norwegian Medicines Agency
- No EU harmonisation of veterinary clinical trials
- Different national legislations
- In Norway most clinical trials in animals are VMPs for fish

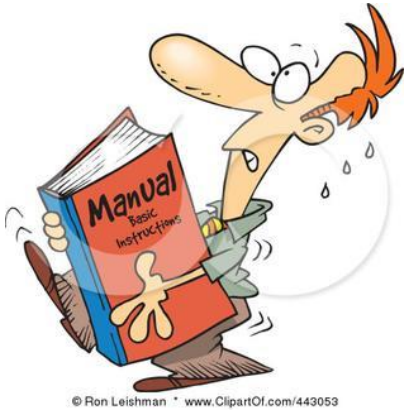
VMPs holding MA have

- Approved product information
  - SPC (Summary of Product Information) – for prescribers
  - Package insert – for operators/animal owners
  - Labelling

- Approved SPCs for all marketed VMPs in Norway are found via NoMA's website and «Legemiddelsøk»:

  https://www.legemiddelsok.no/

Remember



- Read the approved SPC carefully, it:
  - describes what the competent authority consideres acceptably documented.
  - contains relevant warnings and information for safe and prudent use
- Commercial advertisements do not allways contain the complete SPC text
- It is not allowed to advertise for VMPs without MA

Surveillance of marketed VMPs

- Laboratory controls
  - Routine program
  - Possible/suspected quality issues
- Pharmacovigilance
  - Spontaneous reports from prescribers
  - Periodical reports from MA holder
  - Signal detection by competent authorities

European collaboration

Please report suspected adverse reactions!

Use of VMPs is regulated (the «cascade»)

1. Use a VMP authorised for the relevant species and indication
2. If not possible, use a VMP authorised for another species/same indication or same species/another indication
3. If not possible, use a VMP from another EU/EEA member state, or a national HMP
4. If not possible, use an extemporaneously prepared product

Use of VMPs

- All EU/EEA member states have arrangements for permitting use of VMPs from other member states when justified (required by EU directive)
- The type of arrangement differs between member states
- The Norwegian arrangement is called «special exemptions»

Special exemptions

- Prescriber fills in an application form https://legemiddelverket.no/veterinermedisin/legemidler-du-ma-soke-om/spesielt-godkjenningsfritak-for-legemidler-til-dyr#søknadsskjema-og-gode-råd-for-utfylling
  - Justification important
- Application submitted via pharmacy or directly to NoMA
- Applications normally assessed within 1-2 working days
- Response sent either to pharmacy or to applicant, as requested
- The VMP must be imported via a licenced importer (usually the prescribers regular pharmacy/wholesaler chain)

Other special products relevant for fish

Autogenous vaccines

- Used when no MA-holding vaccine exist or is suitable
- One or more components
- Based on islolate(s) from the relevant fish farm/site
- Requires an approval from the NoMA in each case

Other special products relevant for fish

Medicated feed

- Made by feed mills approved by NoMA for such manufacture
- Based on MA-holding premix: No application required
- Based on premix holding MA in other EU/EEA member states: special exemption for the premix required
- Based on simplicia (active substance): special permit required from NoMA to use active substance

Anaestethics used for fish in Norway

Aqui-S vet (isoeugenol)

Legal status: MA, marketed

MA holder: Scan Aqua AS

Approved for Atlantic salmon and rainbow trout.

Indication: Sedation and anaestesia in connection with handling (sorting, moving, transport, sea lice counting, stripping of breed stock and vaccination)

Anaestethics used for fish in Norway

Benzoak vet (benzocaine)

Legal status: MA, marketed

MA holder: ACD Pharmaceuticals

Approved for salmon and trout.

Indication: Anaestesia and sedation

Anaestethics used for fish in Norway

Finquel vet (tricaine mesilate)

Legal status: MA, marketed

MA holder: Scan Aqua AS

Approved for Atlantic salmon, rainbow trout and cod.

Indication: Sedation and anaestesia in connection with vaccination and handling (sorting weighing, stripping of breed stock etc.)

Anaestethics used for fish in Norway

Nytox vet (tricaine mesilate)

Legal status: MA, marketed

MA holder: Neptune Pharma Ltd

Approved for fish, incl. ornamental fish

Indication: Sedation, immobilisation and anaesthesia of fish for: vaccination, transportation, weighing, tagging, clipping, stripping of breed stock, blood-sampling and surgical procedures.

Anaestethics used for fish in Norway

Tricaine Pharmaq (tricaine mesilate)

Legal status: MA, marketed

MA holder: Pharmaq Ltd.

Approved for fish, incl. ornamental fish

Indication: Sedation, immobilisation and anaesthesia of fish for: vaccination, transportation, weighing, tagging, clipping, stripping of breed stock, blood-sampling and surgical procedures.

Anaestethics used for fish in Norway

Aquacalm (methomidate HCl)

Legal status: Special exemption (SE) required

MA holder: n.a.

The active substance does not have MRL

SE requires justification, and may only be granted for use in fish not intended for human consumption (e.g. research fish)

Anaestethics used for fish in Norway

Product name	Active substance	Regulatory status in Norway	Approved for	Comments
Aqui-S vet	isoeugenol	MA (marketed)	Atlantic salmon and rainbow trout	
Benzoak vet	benzocaine	MA (marketed)	Salmon and trout	
Finquel vet	tricaine mesilate	MA (marketed)	Atlantic salmon, rainbow trout and cod	
Nytox vet	tricaine mesilate	MA (marketed)	Fish	Contraindicated for certain tropical species (see product information)
Tricaine Pharmaq	tricaine mesilate	MA (marketed)	Fish	Contraindicated for certain tropical species (see product information)
Aquacalm	Metomidate hydrocloride	Special exemption	n.a.	Special exemption required. Must be justified. Granted only when products with MA are not suitable. Not for fish intended for human consumption.

More information on VMPs for fish in Norway

- On NoMA web page
  - General information
  - MA-holding vaccines
  - MA-holding poharmaceuticals

https://legemiddelverket.no/english/veterinary-medicine/fish-medicine-information-in-english

Relevant information and guidelines

European Medicines Agency (EMA), regulatory information:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/landing/veterinary_medicines_regulatory.jsp&mid=

European Medicines Agency (EMA), scientific guidelines for veterinary medicinal products:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000173.jsp&mid=WC0b01ac058002d89a

Relevant EU legislation – human and veterinary medicinal products

European Commission

https://ec.europa.eu/health/documents/eudralex_en

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