EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Specificities of Products for Veterinary Use

The EU medicines regulatory system and the European Medicines Agency: an introduction for international regulators and non-governmental organisations

Presented by David Mackay, Minna Leppänen, Nicholas Jarrett, Julia Fabrega Climent and Jos Olaerts
18 September 2017
Veterinary Medicines Division

Content of the presentation

- General introduction to EMA activities related to veterinary medicine
  - Innovation in the veterinary sector
  - MUMS
  - Safety of the consumer; MRLs
  - Environmental risk assessment
  - Pharmacovigilance
  - Antimicrobial resistance

General approach to regulation of veterinary medicines at EMA

- Veterinary medicines have their own framework under EU legislation (Directive 2001/82/EC, as amended; specific part of Regulation (EC) No 726/2004)
- Veterinary Division within EMA focusses specifically on veterinary medicines
- Dedicated committee (CVMP) and working parties for veterinary medicines
- Inspections and compliance of manufacturers of veterinary medicines is a shared responsibility with human medicines
- ‘One Health’ approach to medicines regulation (human health, animal health and the environment)

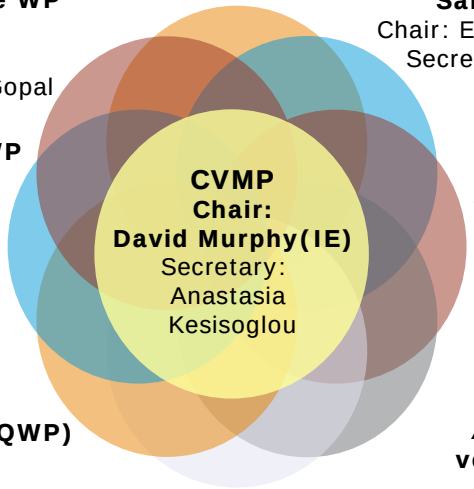
CVMP and its expert groups

Immunologicals WP (IWP)
Chair: Esther Werner (DE)
Secretary: Anastasia Kesisoglou

CMDv
Chair: Laetitia Le Letty (FR)
Secretary: János Kovács

Pharmacovigilance WP (PhVWP-V)
Chair: (vacant)
Secretary: Raquel Gopal

Safety WP (SWP-V)
Chair: Eva Lander Persson (SE)
Secretary: Nicholas Jarrett



Environmental Risk Assessment WP (ERAWP)
Chair: Jason Weeks (UK)
Secretary: Julia Fabrega

***Joint* CVMP/CHMP *ad hoc* expert group on 3Rs (J3R)**
Vice-chair: Ellen-Margrethe Vestergaard (DK)
Secretary: Martin Ilott

Efficacy WP (EWP)
Chair: Gesine Hahn (DE)
Secretary: Barbara Cyrus

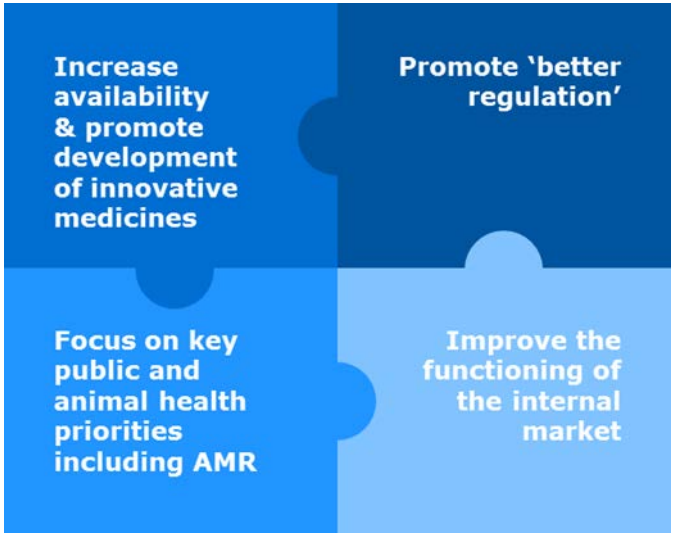
Antimicrobials WP (AWP)
Chair: Helen Jukes (UK)
Secretary: Jordi Torren

***Joint* CHMP/CVMP Quality WP (QWP)**
Vice-chair: Mary O' Grady
Vet Secretary: Teresa Potter

***Ad hoc* expert group on veterinary novel therapies (ADVENT)**
Chair: Jean-Claude Rouby (FR)
Secretary: Minna Leppanen

Scientific Advice WP (SAWP-V)
Chair: Rory Breathnach (IE)
Secretary: Minna Leppanen

EU Medicines Agencies Network Strategy to 2020



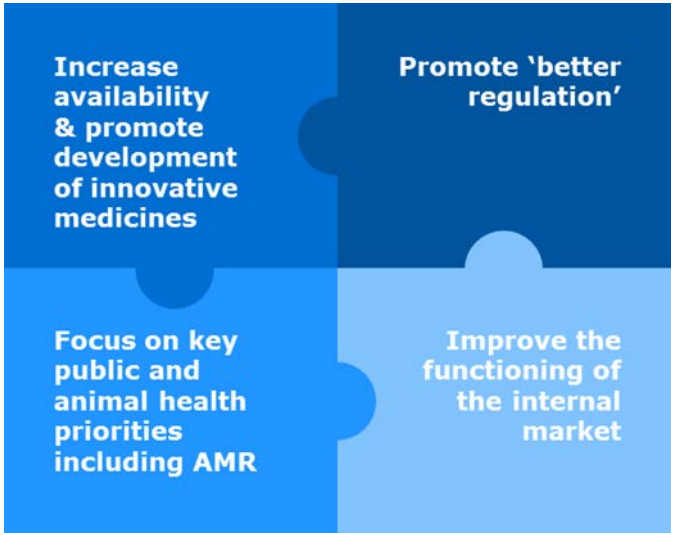
Theme 2: Contributing to animal health and human health in relation to veterinary medicines

Innovation, development and evaluation of veterinary medicines

Minna Leppänen

Veterinary Biologicals and Emerging Therapies

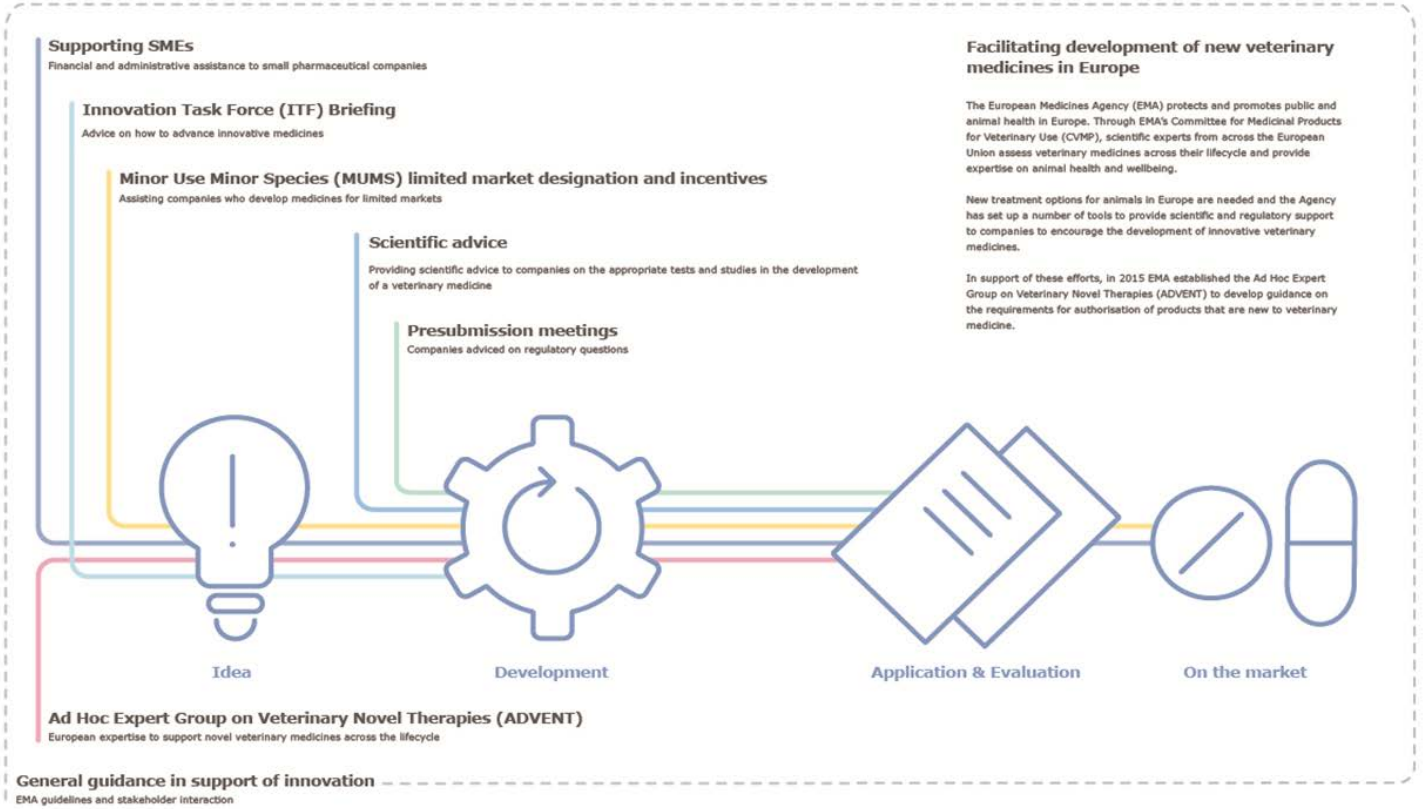
Innovation, development and evaluation of veterinary medicines



EU Medicines Agencies Network Strategy to 2020: Theme 2: Objective 1

- The network will increase the availability of all types of veterinary medicine, giving particular attention to products indicated for minor use in major species and for minor species (MUMS), as well as smaller national markets, and for technologies that are new to the veterinary domain.

Innovation, development and evaluation of veterinary medicines



Fostering development of veterinary medicines, linking to human medicines

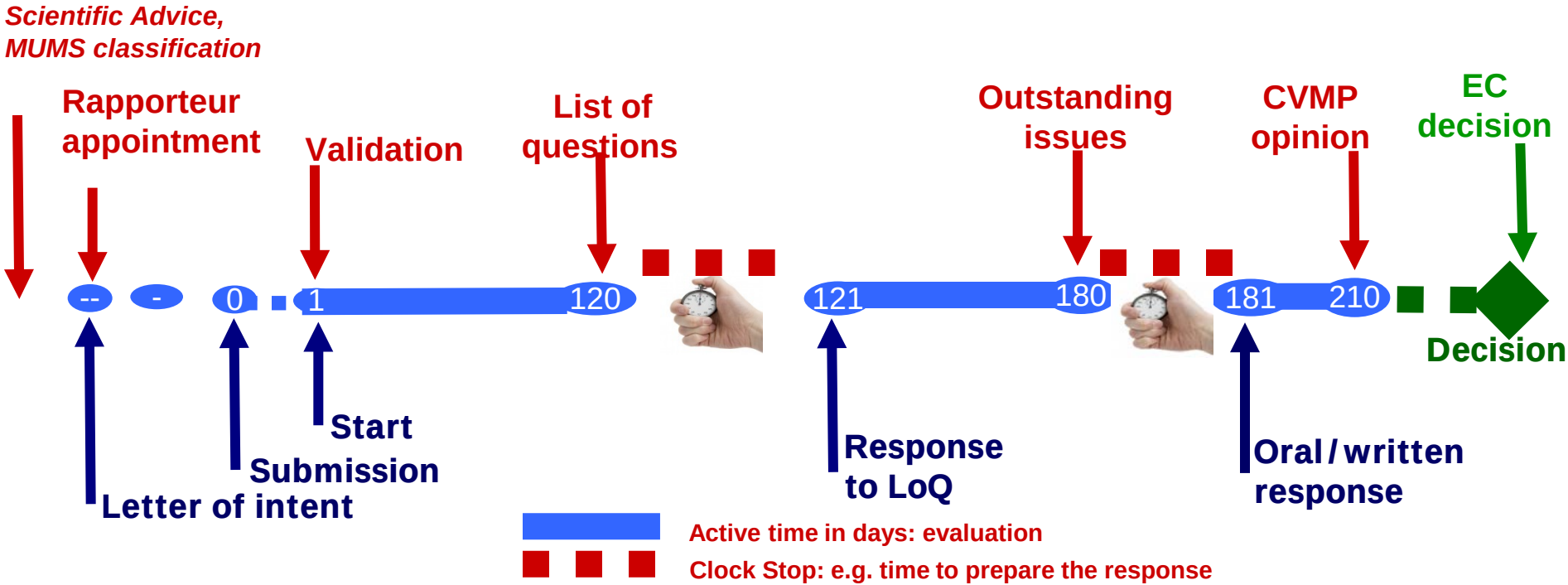
Novel therapies and innovation:

- Guidance in development for stem cells products and monoclonal antibodies
- First procedures for veterinary monoclonal antibody for dogs and stem cell product for horses
- Increase in Innovation Task Force briefings: four requests concerning initiatives for immunomodulation and tissue regeneration
- Scientific advice – some 20 requests per year

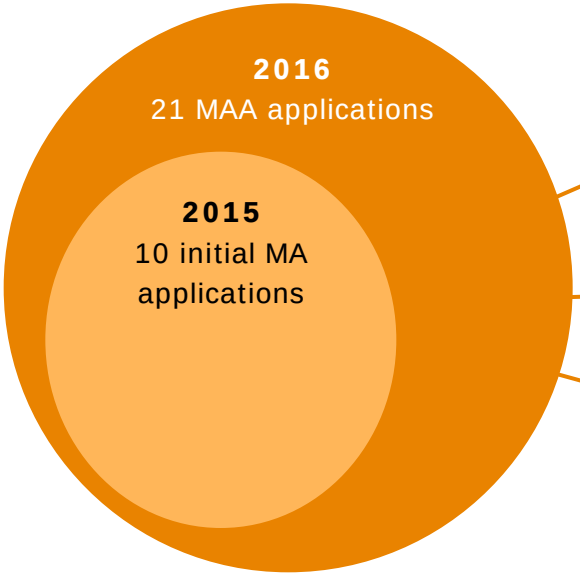
Availability of medicines and emergency preparedness:

- Minor Use Minor Species scheme: some 25 classifications every year
- Some vaccines are against zoonotic infections: action plan for veterinary vaccine availability launched in August 2016

Innovation, development and evaluation of veterinary medicines



Managing evaluation of veterinary medicines, collaborating with other Agencies



Opinion on first DNA vaccine for Atlantic salmon (*Clynav*) - considerations on plasmid integration by EFSA

Vaccine against new type of rabbit haemorrhagic disease (*Eravac*)

Opinion on new fixed combination pharmaceutical product for bees against mites (*Varromed)*

Availability and Minor Use Minor Species (MUMS)/limited market scheme

Minna Leppänen

Veterinary Biologicals and Emerging Therapies

Availability and Minor Use Minor Species (MUMS)/limited market scheme

The network will increase the availability of all types of veterinary medicine, giving particular attention to products indicated for minor use in major species and for minor species (MUMS)

- Minor species: Species that are not defined as major (cattle, sheep, pig, chicken, salmon, cats, dogs)
- Major species: Minor use in a major species: use of veterinary medicinal products for the treatment of diseases that occur infrequently or in limited geographical areas and thus indicated for a smaller market sector.
- Limited market: A market for a veterinary medicinal product that is limited in size due to the product being indicated for a disease or condition therefore including the great majority of products for minor indications including those with a limited geographical distribution

Availability and Minor Use Minor Species (MUMS)/limited market scheme

Case by case approach in classification by CVMP of a proposed product/indication as minor use/limited market

Incentives applicable for products classified by CVMP as MUMS/limited market.

- Reduced data requirements varies depending on the type of the product and the benefit-risk balance that it represents
- Advice and assistance for preparation of MA dossier

Financial incentives for food producing species: fee reduction or waivers for specified EMA procedures

Availability and Minor Use Minor Species (MUMS)/limited market scheme

Additional measures to support availability

- HMA/EMA Vaccine availability initiative
- HMA/EMA Task Force on availability of authorised medicines for human and veterinary use
- Actions to limit attrition of existing products
- Exploration of new ways to improve availability in specific sectors: explore best use of existing or new medicines (e.g. for use in fish medicine as part of aquaculture)

Maximum Residue Limits (MRL)

Nicholas Jarrett

Veterinary Pharmaceuticals

Maximum Residue Limits (MRL)

Regulation (EC) No 470/2009:

"The maximum concentration of a residue of a pharmacologically active substance which may be permitted in food of animal origin"

MRLs are legal values (listed in Regulation (EU) No 37/2010)

- Ensure consumer safety – withdrawal periods must ensure depletion of residues to the MRL or below
- Important for trade – residues in animal produce entering the EU must comply with EU MRLs

Maximum Residue Limits (MRL)

An application for establishment of MRLs is a stand alone, centralised procedure – not part of an application for a MA => all MRL applications are evaluated by the CVMP

CVMP issues a scientific opinion, European Commission in consultation with member states, adopts and publishes the MRLs

The marketing authorisation application must demonstrate that the withdrawal period (product specific) is sufficient to allow depletion of residues to the MRL or below

Responsibility for monitoring residues of VMPs in foodstuffs of animal origin lies with the EU member states

Maximum Residue Limits (MRL)

Safety evaluation (mainly laboratory animal data) – focus on:

Pharmacological effects, toxicological effects, microbiological effects

⇒ Acceptable Daily Intake (ADI) – estimate of the amount of the residues that can be ingested daily over a lifetime without appreciable health risk to exposed individuals

Residues evaluation (mainly target animal data) – focus on:

Pharmacokinetics, residue depletion, analytical methods

⇒ Identify the point on the depletion curve at which residues fall below ADI and so allows derivation of MRLs, demonstrate availability of a method for residue control

Core scientific guidance for both safety and residues is VICH guidance (internationally harmonised

Environmental risk assessment

Julia Fabrega Climent

Veterinary Pharmaceuticals

Environmental risk assessment

Directive 2001/82/EC as amended & Regulation (EC) 726/2004 - ***In a nutshell***

- An ERA is **mandatory for all new applications**, independent of the application procedure (central or national marketing authorisation) and type (“full”, “generic” etc.) and is therefore required for all marketing authorisations submitted in the EU **irrespective of the underlying legal basis.**

- This assessment shall normally be conducted in **two phases**. The **first phase** of the assessment shall **always be performed**
- An **unacceptable risk** to the environment can lead to **non-authorisation.**
- Risk mitigation measures

Environmental risk assessment (ERA)- tiered approach

Phase I – assessment of potential exposure

Decision on Phase II ERA

Phase II Tier A – experimental data for aquatic/terrestrial compartments

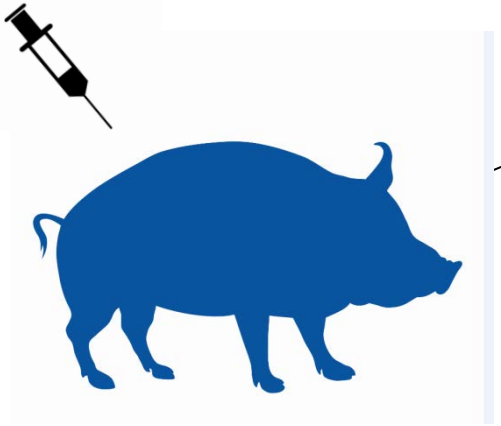
Risk assessment & decision on further assessment (RQ >1 or <1?)

Phase II Tier B – more experimental data for relevant compartments

Risk assessment/risk mitigation

The ERA is conducted for all veterinary medicinal products in accordance with VICH and CVMP guidelines

E.g., How is the ERA done?



Excretion via faces and urine (parent + metabolites)

Predicted Environmental concentration < 100 µg/kg

ERA can stop

Hazard concerns (e.g, endocrine disrupting properties)

Phase I

Predicted Environmental concentration > 100 µg/kg

To **Phase II** (A/B) ERA

Phase II → Additional fate/behaviour, hazard and exposure studies

Risk characterisation

Risk **not** controlled

Consideration of risk mitigation measures (e.g., to prevent/limit environmental exposure)

Risk controlled

ERA can stop

Risk controlled

Veterinary Pharmacovigilance

Jos Olaerts

Veterinary Risk and Surveillance

Veterinary pharmacovigilance – What is monitored?

Post-marketing monitoring of veterinary medicinal products:

- Adverse reactions in animals and in humans
- Lack of expected efficacy (including resistance (antibiotics/antiparasitics))
- Violations of approved residue limits
- Potential environmental problems

- Regulation (EC) No 726/2004 Chapter 3 Pharmacovigilance Article 46 – 54, Article 57 (d)
- Directive 2004/82/EC Title VII Pharmacovigilance Article 72 - 79
- Volume 9B of the Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use. http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-9/vol_9b_2011-10.pdf
- VICH guidelines 24, 29, 30, 35 and 42 http://www.vichsec.org/guidelines/pharmacovigilance.html

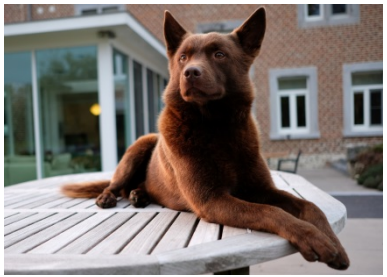
Veterinary pharmacovigilance – Tools

- Mandatory electronic reporting into central EU database for reports having occurred
  - In the EU
  - In “third countries” following the use of the same or similar products (VICH guidelines apply)
- Periodic reporting by MAH (6 monthly or yearly)
- “Signal detection” analysing tools available for monitoring

Veterinary pharmacovigilance – recent examples

- Velactis – for drying-off in cows (Cabergoline – blocks prolactin release)
  - Recumbency

  - Suspension of the marketing authorisation on 22 August 2016
- Targeted review of safety data for certain antiparasitics used in small animals
  - Review of potential “serious reactions”



Antimicrobial resistance

David Mackay

Senior Veterinary Advisor

EMA activities on antimicrobial resistance related to the use of veterinary medicines

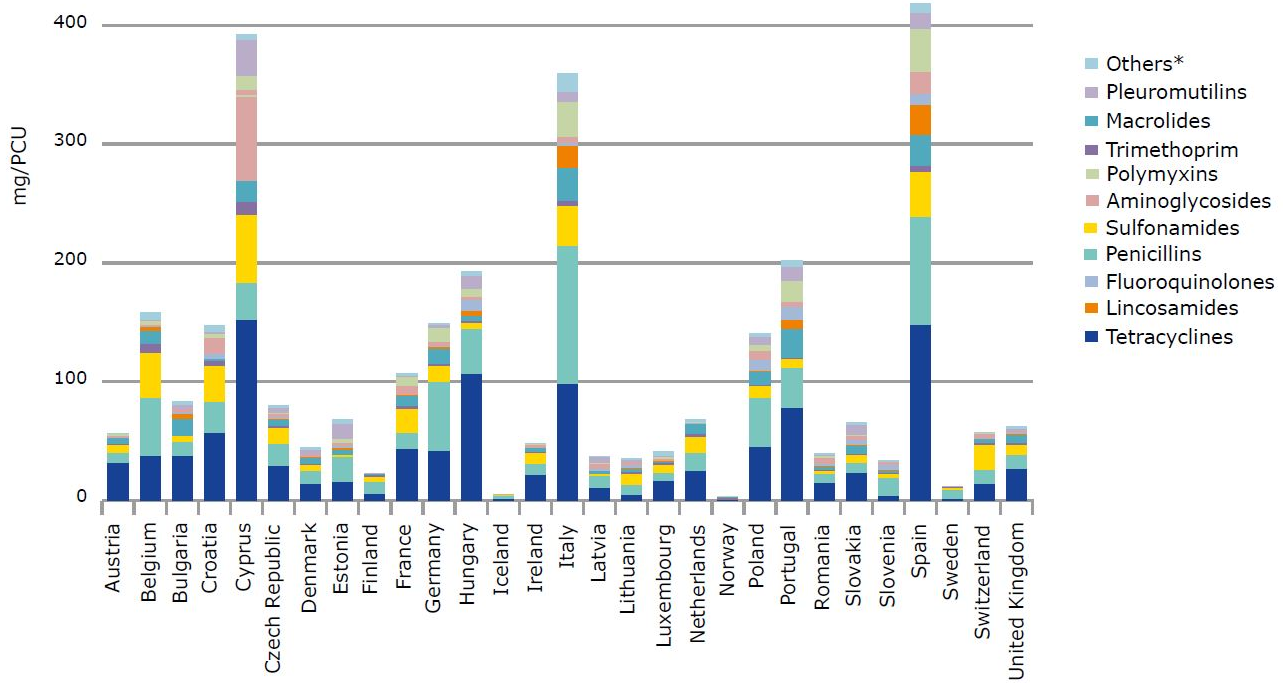
- Implementation of the CVMP Strategy on Antimicrobials 2016-2020

  The CVMP's vision is to ensure the availability of effective antimicrobial medicines for the treatment of infectious diseases of animals while, at the same time, minimising the risks to animals or humans arising from their use.

- Activities include
  - Authorisation and maintenance of veterinary antimicrobials
  - Referrals of classes of antimicrobials to promote prudent and responsible use
  - Scientific opinions and reports, together with other EU Agencies where appropriate
  - Surveillance of use of veterinary antimicrobials through the ESVAC project
  - Development of guidance at EU and international level
  - Contribute to action plans on AMR of the European Commission, OIE and WHO

Spatial distribution of overall sales of all antimicrobials for food-producing animals, in mg/PCU, for 29 countries, for 2014

Sales of the various veterinary antimicrobial classes, for food-producing species, in mg/PCU, for 29 European countries, in 2014



Summary

- Veterinary Medicines Division operates as an integrated part of the European Medicines Agency
- Principles of evaluating quality, safety and efficacy of veterinary medicines are the same as for human medicines
- Practical approach differs where necessary to take account of the specific nature of the veterinary domain
- EMA follow a ‘One Health’ approach

Any questions?

Further information

Dr David K.J. Mackay
Senior Veterinary Advisor, Veterinary Medicines Division

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 8413 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Follow us on **@EMA_News**