ERA of VMPs
The journey and the way forward

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Workshop: *How to achieve an appropriate Environmental Risk Assessment of Veterinary Medicinal Products*

Brussels, 7 June 2017

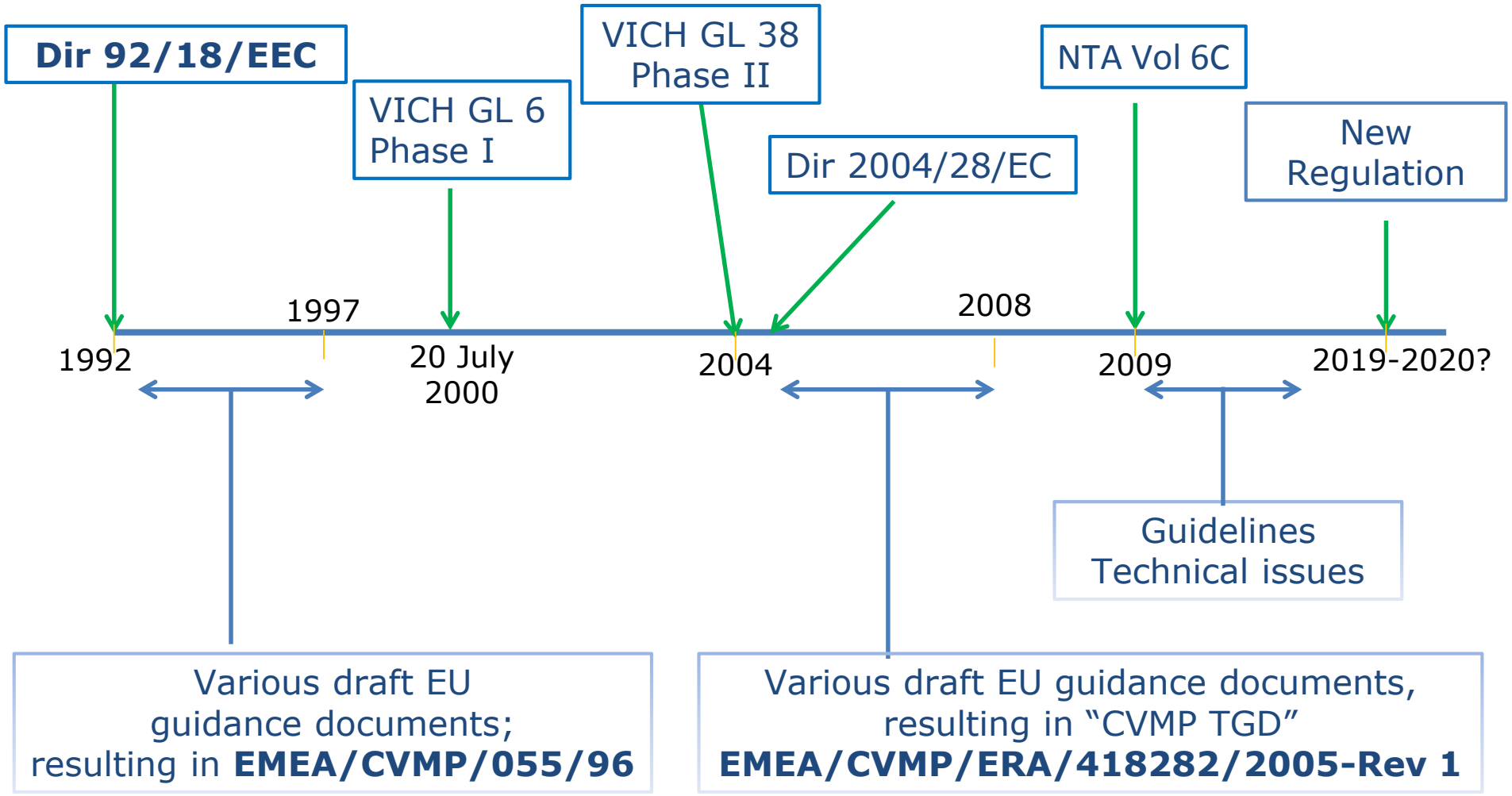
How it started, Dir 92/18/EEC

- **An environmental risk assessment shall be performed to assess the potential harmful effects, which the use of the veterinary medicinal product may cause to the environment and to identify the risk of such effects. The assessment shall also identify any precautionary measures which may be necessary to reduce such risk**
    - This assessment shall normally be conducted in two phases. The first phase of the assessment shall always be performed. The details of the assessment shall be provided in accordance with accepted guidance. It shall indicate the potential exposure of the environment to the product and the level of risk associated with any such exposure
    - In the second phase, further specific investigation of the fate and effects of the product on particular ecosystems shall be conducted, in accordance with established guidance.

A journey indeed…

- **Dir 92/18/EEC amending Dir 81/852/EEC (1992)**
- **Various draft guidance documents, resulting in EMEA/CVMP/055/96 (early 1997)**
- **VICH GL 6: Phase I assessment (July 2000)**
- **VICH GL 38: Phase II Assessment (Oct 2004)**
- **Various draft guidance documents, resulting in "CVMP TGD"**
  - EMEA/CVMP/ERA/418282/2005 (April 2007)
  - EMEA/CVMP/ERA/418282/2005 - Corr. (Sept 2007)
  - EMEA/CVMP/ERA/418282/2005 – Rev 1 (Nov 2008)
  - EMEA/CVMP/ERA/418282/2005 – Rev 1 Corr. (June 2016)
- **FOCUS group meeting on implementation "CVMP TGD" (Jan 2008)**
- **CVMP Reflection Paper NTA Vol 6C (June 2009)**
- **Various new guidance documents**

In a nutshell:



Actually…

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1992 - 2017

Photo credit: Co.uk

Implementation

- **Moving target! From 1992 until...as we speak**
- **ERA scope (further) clarified in 2009 (Notice to Applicants Vol 6C):**
  - New applications (including generic applications)
  - Variations/Extensions
  - Renewals (case-by-case)
- **VICH/TGD: predictability and harmonisation on the technical side (2000, 2004, 2008)**
- **BUT: legislation under revision**
- **AND: additional guidance documents**

Guidance documents/ Reflection papers

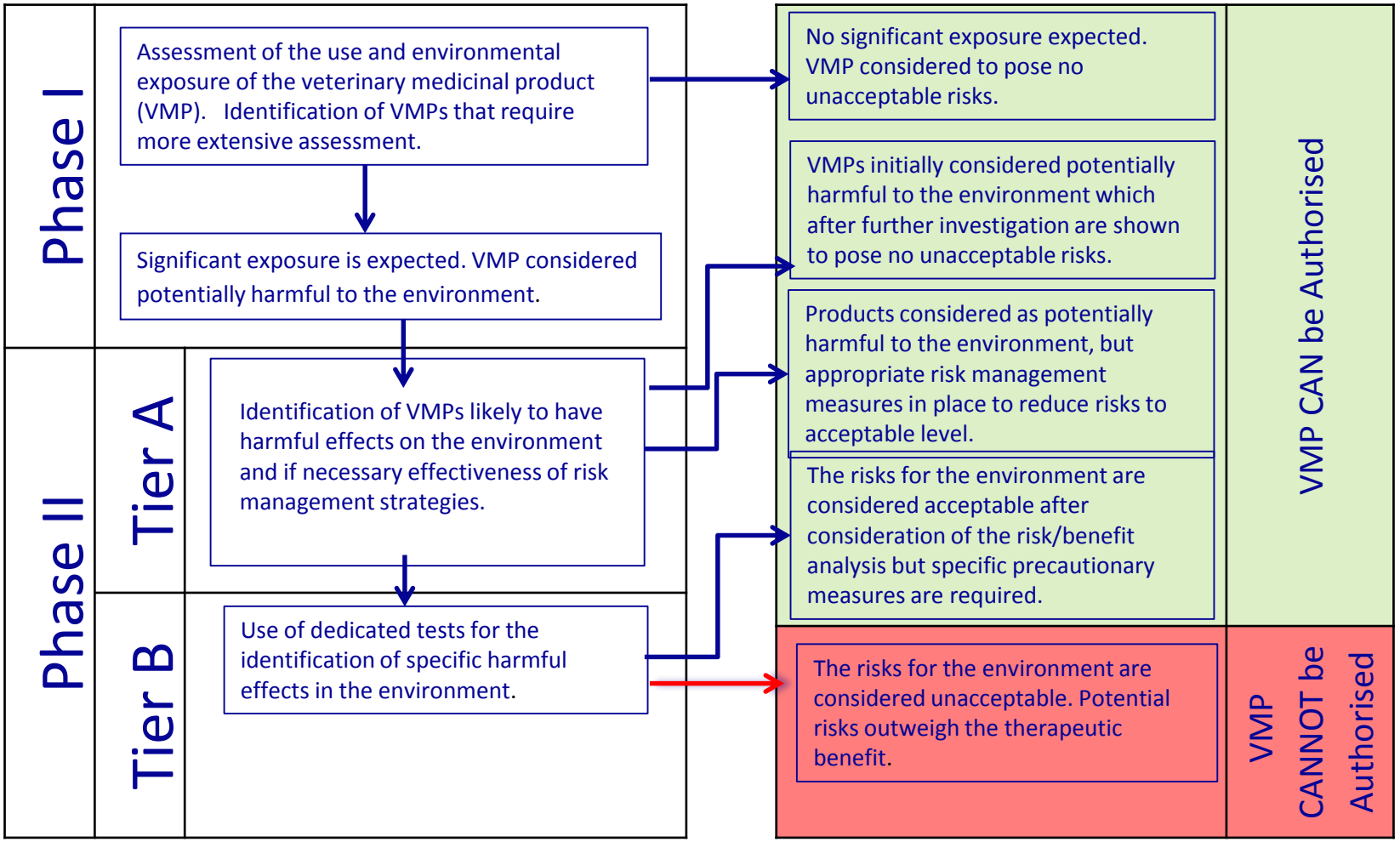
- **Implemented:**
  - Environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (CVMP TGD) +Questions and answers on implementation (Rev. 5, 14 July 2016)
  - Determining the fate of veterinary medicinal products in manure
  - Plant testing strategy in the risk assessment for veterinary medicinal products
  - Poorly extractable and/or non- radiolabelled substances
  - Risk-mitigation measures related to the environmental risk assessment of veterinary medicinal products
  - Assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicinal products
  - Reflection paper on authorisation of veterinary medicinal products containing (potential) persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances

Guidance documents/ Reflection papers

- **Draft:**
  - Assessing the toxicological risk to human health and groundwater communities from veterinary pharmaceuticals in groundwater
  - Higher-tier testing of veterinary medicinal products to dung fauna

- **2017 work plan:**
  - Reflection paper on environmental risk assessment of veterinary medicinal products used in aquaculture
  - Reflection paper on antimicrobial resistance due to presence of veterinary antimicrobials in the environment
  - Reflection paper on exposure models of heavy metals within the environmental risk assessment of veterinary medicinal products

Risk-based assessments



Question:

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How to achieve an appropriate environmental risk assessment of veterinary medicinal products

Considering the comprehensive existing frameworks, can you please clarify what is inappropriate in the risk assessment at present?

(and please be specific regarding veterinary medicines)

Our understanding of the issues

- **Desire for transparency to environmental agencies, academia, water companies, the wider public**
- **Avoiding multiple data sets and divergent assessment**
- **Desire to have data sets for all substances including those in older products: substance- and hazard-based**

Our proposed way forward

Desire for transparency

- **Proposed solution: in case of Phase II - endpoints plus assessment in the EPAR, in a standardised format**
- **Would serve a number of stakeholders**

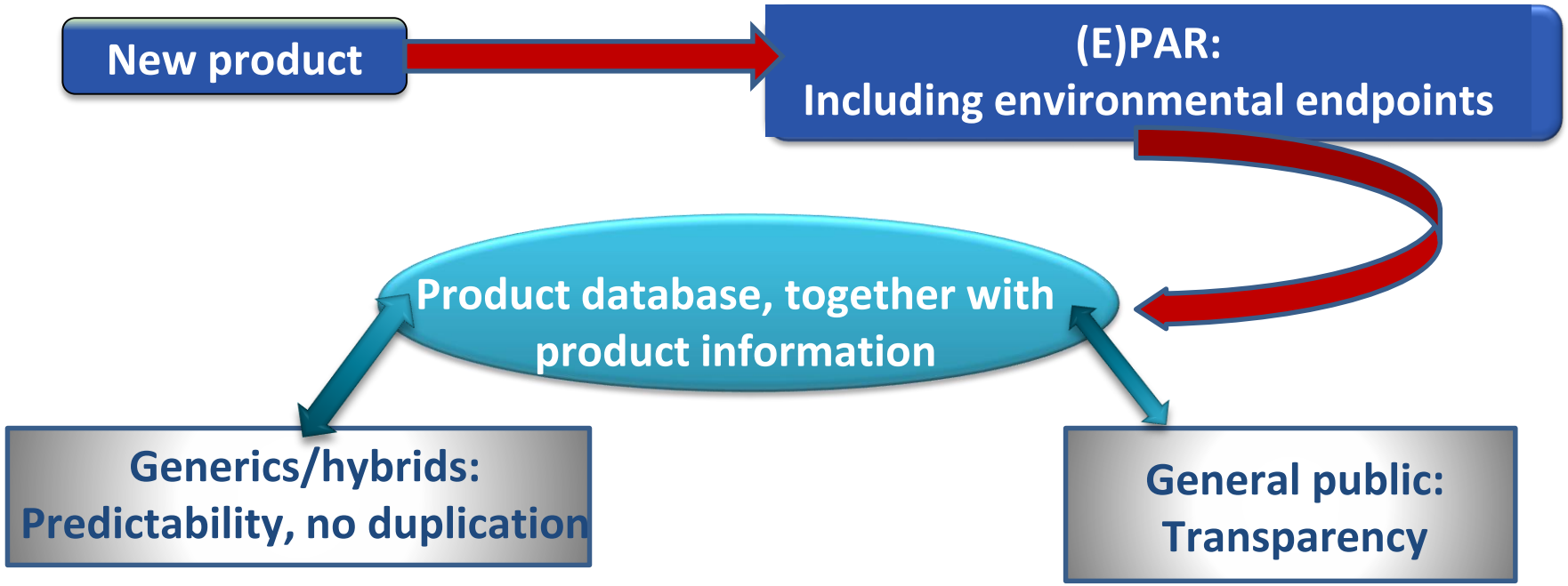
[a] Please mention guidance used for each of the studies (OECD, ISO, ASTM,…)
[b] Please fill in appropriate endpoints, not all endpoints may be required due to the phased approach.
[c] Please delete or add additional studies as appropriate.
[d] Please mention the exposure period

ENVIRONMENTAL INFORMATION	
Chemical characteristics	
International Non-proprietary Name (INN) Chemical Name CAS Number Molecular Formula Molecular Weight Structural Formula	
Physico-chemical properties – Study results[a, b]	
Melting point/Melting range Solubility in water Dissociation constants pKa UV-Visible absorption spectrum Vapour pressure Octanol/water partition coefficient (log K_{ow})	
Environmental fate studies – Study results[a, b, c]	
Adsorption coefficient Soil biodegradation Degradation in aquatic systems Photolysis Hydrolysis Bioconcentration in fish	
Environmental effect studies – Study results[a, b, c, d]	
Algal growth inhibition *Daphnia magna* immobilisation Fish acute toxicity Nitrogen transformation (28 days) Terrestrial plants Earthworm subacute/reproduction *Daphnia magna* reproduction Fish, early-life stage Sediment invertebrate species toxicity Nitrogen transformation (100 days) *Last update*	

Avoiding multiple data sets

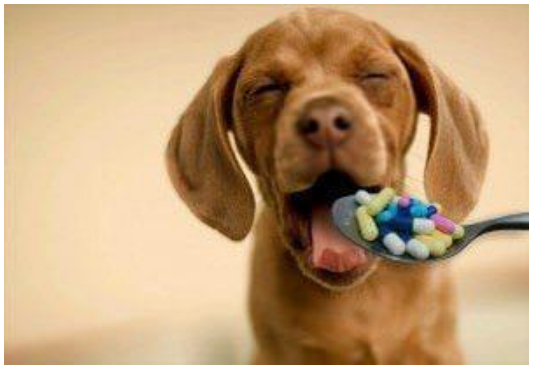
- **What is the reason for multiple data sets?**
  - Dir 2004/28/EC amending Dir 2001/82/EC
  - Generics/hybrid applications no longer able to refer to ERA part of safety file, forced to generate multiple data sets

- **Solution:** no ERA for generics/hybrids unless well founded reasons to assume increased risk



Desire to have data, substance- and hazard-based

- Current approach: **risk-based assessments**
- **Hazard** is linked with **substance**
- **Risk** is tied to **product:** its use, and if and how it would **expose** the environment to its active substance
  - E.g. aquatic toxicity but no aquatic exposure?
- True risk assessment for VMPs can only be **product based**



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Hazard versus use, exposure and risk

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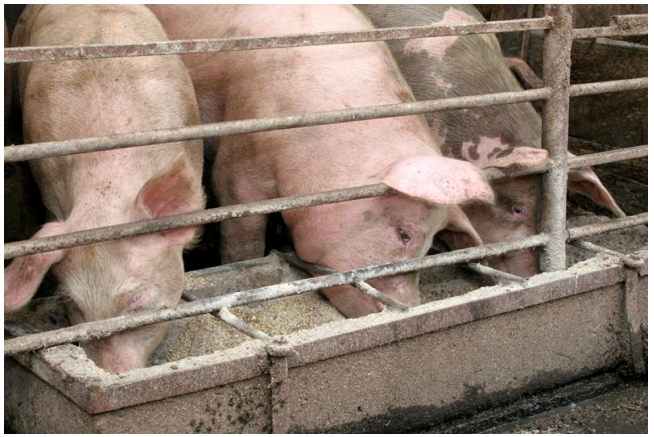
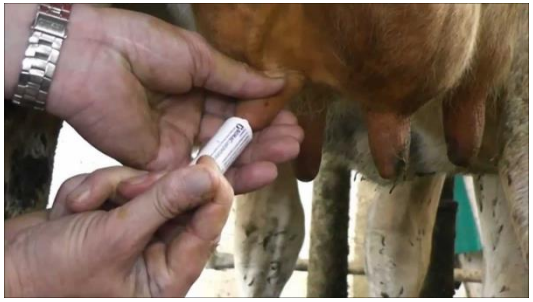


All of these animals may be receiving medication with the same active ingredient, yet exposure and risks are vastly different …



Justification for adding to existing legal frameworks ?

- There is a desire to establish a collection of data (monograph, master file, …)

- The purpose of having such a collection of data, and how this would better protect the environment compared to the current risk-based approach, is not clear *(other than data transparency and data duplication, which can be addressed more easily in other ways)*

- In addition, its benefits compared to the current risk-based approach must be clearly and scientifically justified

- A collection of data is just that; it is definitely not a risk assessment – just merely a book of potential hazards. Identification and management of risk requires consideration of use and exposure

Data for older products

- ERA submitted to NCA/EMA since mid-nineties
  - Renewals – depending on MS
  - New applications, extensions
- All MRPs (1997- present), CPs (1997- present) and DCPs (2004 - present) have an ERA

A wealth of information from all various companies is already residing within NCA and EMA

- Prioritisation and focussing on real risks is key

- Any collection of data could only be justified in case a serious concern has been identified; handled through a referral procedure, the complete set of data would end up in an EPAR anyway
  - what is the added value of a separate master file system?

- For medicinal products, benefit-risk assessment is an ethical obligation

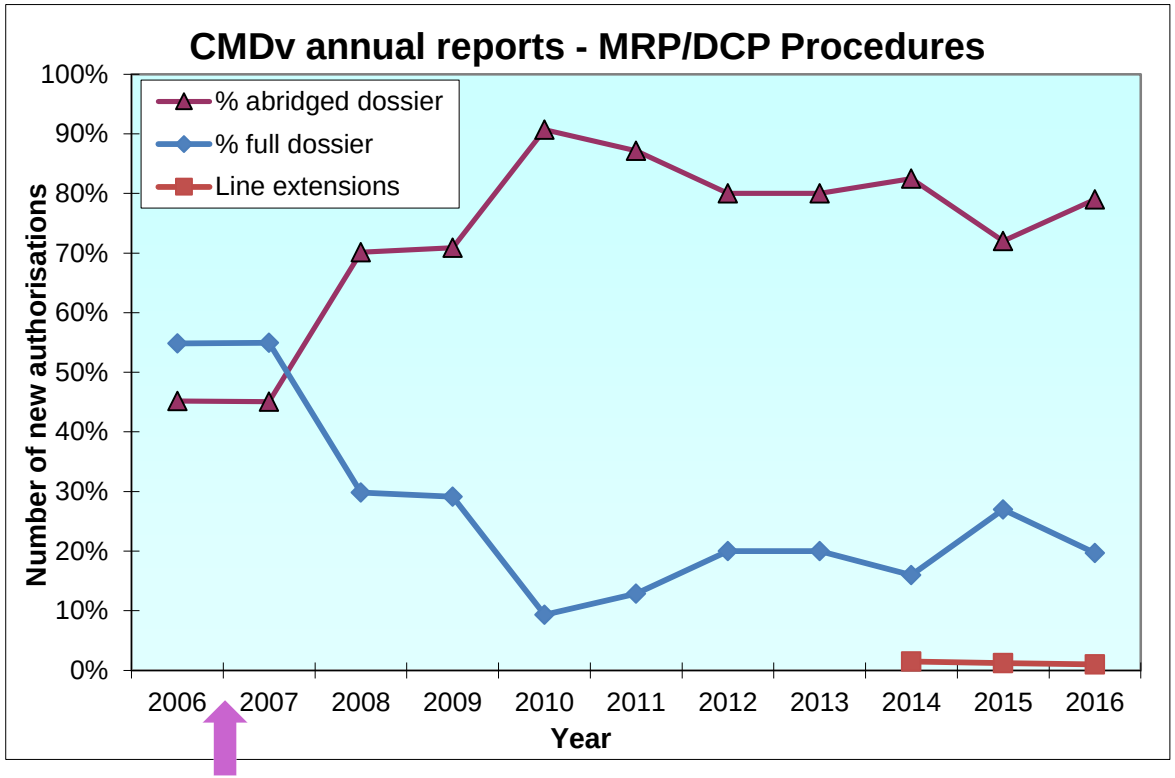
More questions requiring answers

- Who would draft each monograph? Who would approve it? Who takes ownership, and responsibility for its maintenance? Which information would it contain, and who will provide that?
- How will the endpoints be selected for inclusion in the monographs? How will divergent data for the same active be handled when writing a monograph?
- What would be its (legal) status?
- How would it be used? Will use of the selected endpoints be enforced?
- How would this relate back to products? Will the companies requesting marketing authorisations be able to provide and discuss their own data in their application dossiers (with divergent assessments!)?
- Would the marketing authorisation holders have the possibility to comment on the monograph during its elaboration phase?
- How would the system be funded? Would there be penalties for not contributing to the monograph? Many existing active ingredients are in use by multiple companies and several are also used in the human medicines sector, or even some as biocides. How would this multi-sectorial aspect be dealt with in a monograph system?

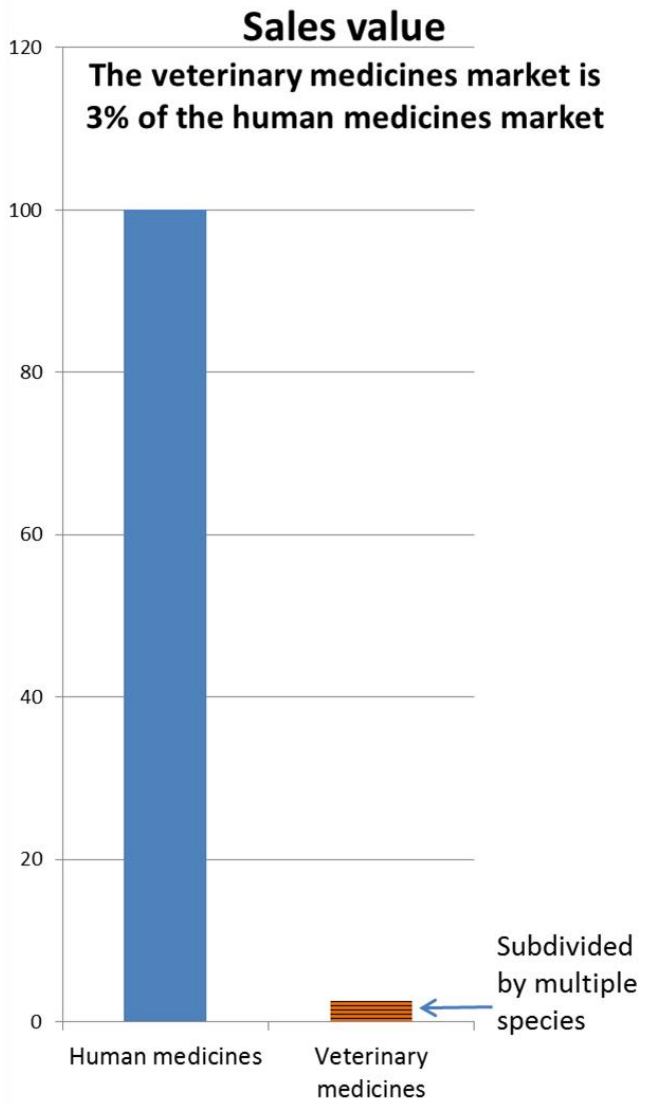
Concerns regarding medicines availability

- **Previous workshop (2014): representatives from EMA and CVMP referred to the experience when MRLs were introduced:**
  - Massive administrative burden (agencies, industry)
  - Loss of active substances or their use in food-producing species
  - Disincentive for development of new products (the hidden trap)
- **The existing framework already leads to a decrease in product development for the EU** – accelerated by every new guideline requirement (the hidden trap)
- **Full ERA for stand-alone MUMS:** a major hurdle
- **Through the lack of incentives for development of products for food-producing animals, the EU is slowly evolving to a stagnating generic market**
  - Volunteers to update existing data might be scarce
  - Companies will just abandon products
- **Sector too small to continue to carry all burdens**

Some figures



Impact of 2004 legislation



Conclusions

- ✓ **Transparency and avoiding multiple data sets can be easily resolved within the VMR – no separate framework required**
- ✓ **Older products: need to prioritise and address potential issues with targeted solutions, but without introducing additional steps or hurdles**
- ✓ **Substantial data sets are already available within the Regulatory Network – this may offer opportunities**
- ✓ **We welcome discussion and cooperation.**

Thank you