EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Draft principles for assignment of technical units of measurement

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Disclaimer

DDDA and DCDA are technical units of measurement solely intended for the purpose of drug consumption studies. They should not necessarily be assumed to reflect the daily doses recommended or prescribed. The assigned DDDA and DCDA values will nearly always be a compromise.

Outline

1. Aim of principles
2. Aim of assignment of DDDA and DCDA
3. Approach
4. Principles for establishment of DDDA and its justification
5. Principles for establishment of DCDA and its justification

Aim of the principles

- Serve as a «manual» for EMA/ESVAC for the assignment of DDDAs and DCDAs for antimicrobials
- To ensure
  - Consistency
  - Transparency

«Headlines»

- Harmonize principles with human medicine when appropriate
- Lists of DDDAs and DCDAs to be manageable in terms of
  - Analysing and reporting consumption data by species
  - Maintenance

Aim of collecting data on consumption animals[1]

- to aid interpretation of patterns and trends regarding AMR;
- as a basis for risk profiling and risk assessment regarding AMR;
- as a basis for setting risk management priorities;
- as a basis for evaluation of the effectiveness of control measures being implemented;
- to identify emerging consumption of antibacterial drugs, e.g. of specific drug classes such as critical important antibiotics;
- to aid comparison of consumption of antibacterial drugs between and within countries and between time periods etc.;
- as a basis for focused and targeted research and development.

[1] Appendix of the request from EC (2008 ((SANCO/E2/KDS/rz D(2008) 520915)) to the Agency on collecting data on consumption of antimicrobials for animals

Aim of assignment of DDDA and DCDA to reflect aim of collecting data by species

✓Human medicine: DDDs – aim

–In human medicine defined daily dose (DDD) was established in the mid-1970'ties for the purpose of drug consumption studies and mainly in order to follow therapeutic trends.

✓Veterinary medicine: DDDA and DCDA antimicrobials

– Main aim AMR (slide 6)
– To follow therapeutic trends

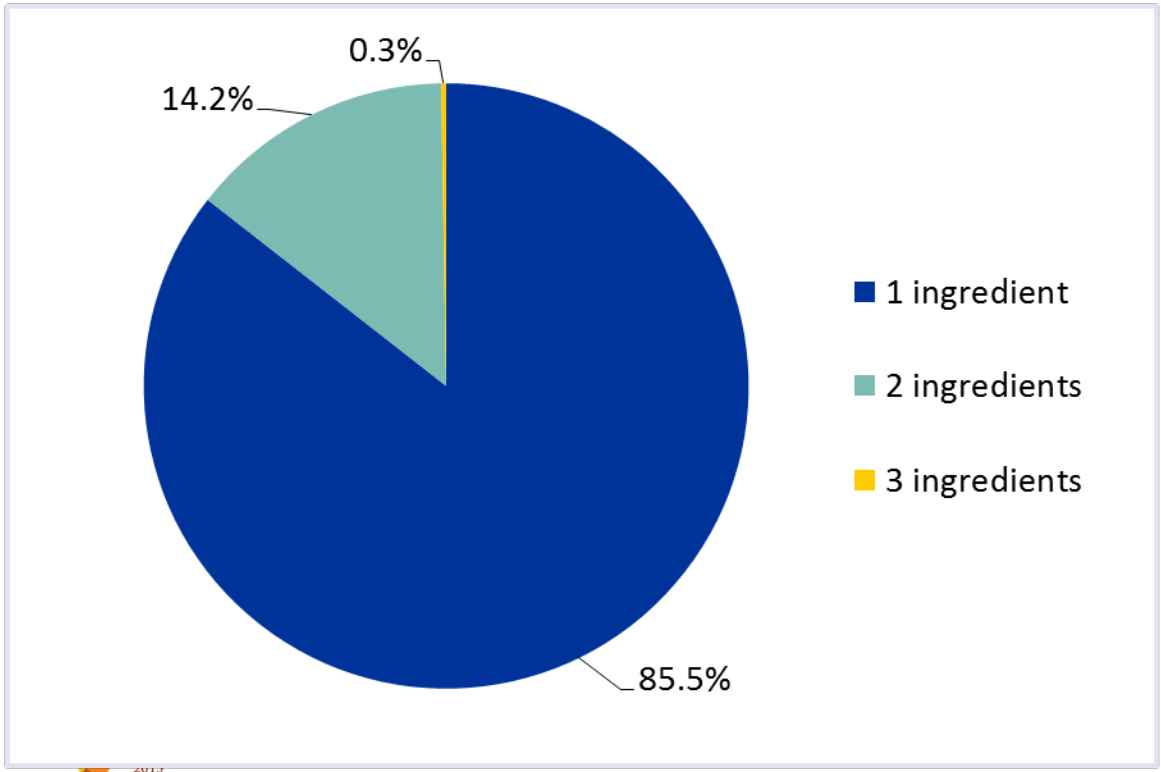
DDD – combinations human medicine

- In human medicine the DDDs assigned for combination products are based on the main principle of counting the combination as one daily dose (main indication), regardless of the number of active ingredients included in the combination: *"If a treatment schedule for a patient includes e.g. two single ingredient products, then the consumption will be measured by counting the DDDs of each single ingredient product separately"*

- Combination antimicrobial products in human medicines consist mainly of sulfonamide-trimethoprim combinations (synergism) and antibiotics combined with an enzyme inhibitor.

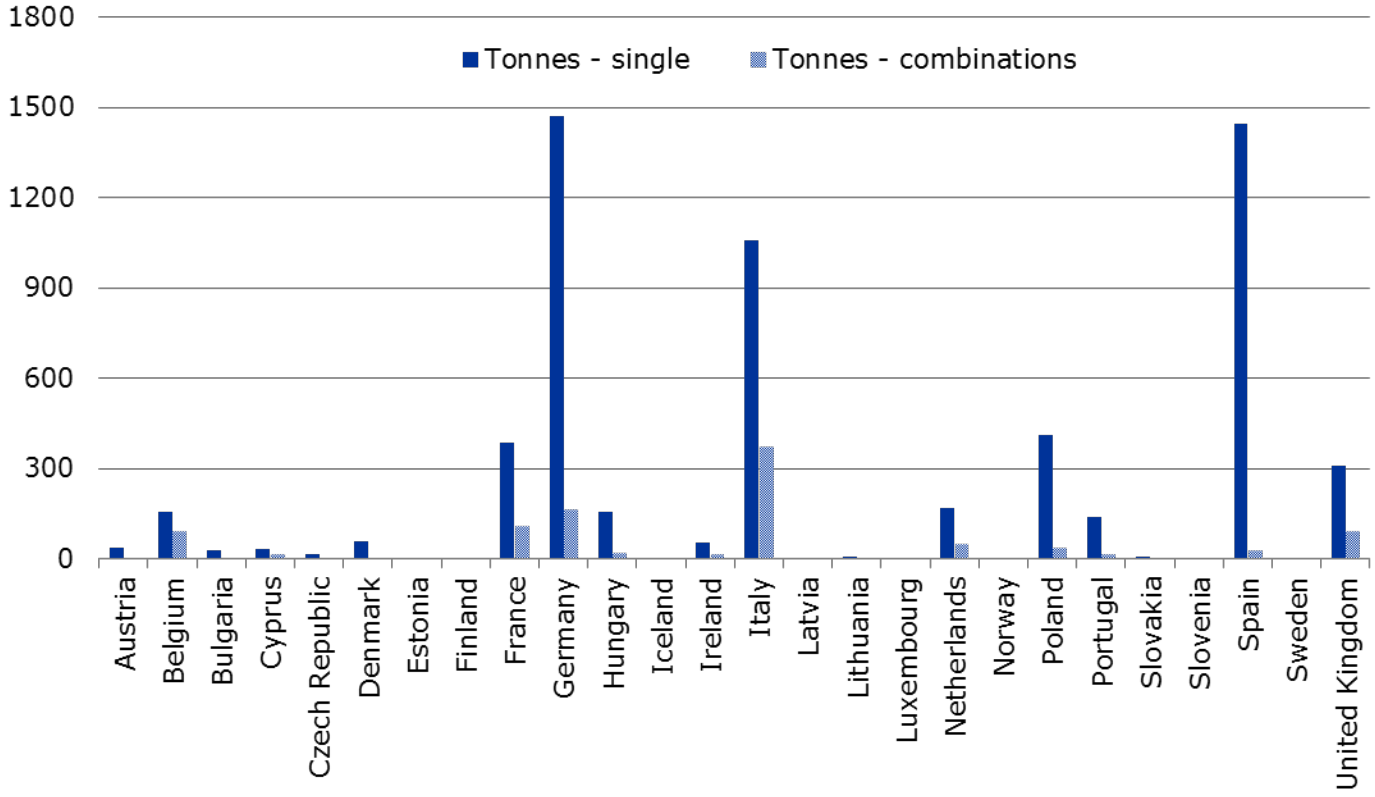
Harmonization with human medicine - differences to be addressed

Percentage of sales, in tonnes of active ingredient, of premixes, oral powders and oral solutions containing 1, 2, and 3 antimicrobial agents in 26 EU/EEA countries in 2012



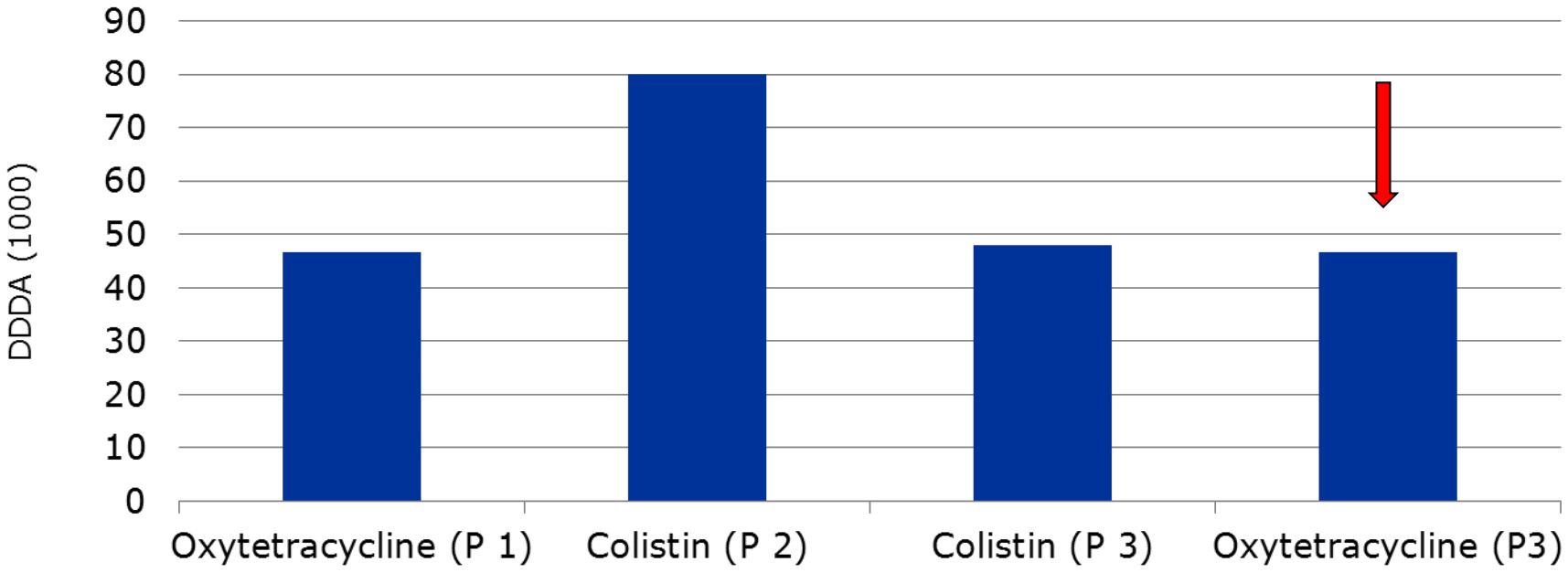
In particular for the analyses of data on prevalence of AMR by species together with data on consumption in the same species, it is important to assess the consumption of each substance in a combination VMP.

Aim of assignment of DDDA and DCDA to reflect aim of collecting data by species cont.



In contrast to human medicine sale of combinations is high and thus impact the exposure/AMR

To measure the exposure….



It is suggested to assign and report DDDA and DCDA also for the 2nd (and 3rd) ingredient for combination VMPs.

Data used as basis for the principles

- Template developed to collect SPC information on dosing (SPC template) - assisted by the ad hoc WG. Prior to the call for data SPC template tested by four countries
- Instructions on how to fill in the template in a harmonised/standardized manner developed assisted by the ad hoc WG
- Data management of data provided by the 9 MSs:
  - Quality
  - Harmonization
  - Outliers (extreme values) were defined as values greater/smaller than the average dose (or duration) ±2 Standard Deviation (SD).

Calculation of **daily dose and course dose** for each observation

- **Daily dose**
- If range given – calculated as mean of range
- Each long-acting injectable calculated as e.g.:
    - 20 mg/kg oxytetracycline injection - duration of effect of 2 days = daily dose 10 mg/kg
- **Course dose**
- Daily dose*number of treatment days
    - If range given for # treatment days first calculated as mean of range

Data on dosing (daily/treatment days) collected from 9 EU MSs – covers 65% of food animal production in EU

Number of observations per species per administration route/form for **single** substance products in the preliminary data sets (9 EU MSs)

	Bolus / tablet	Injection	Injection long–acting	Oral paste	Oral powder	Oral solution	Premix	Total
Broilers					102	257	49	408
Cattle	18	329	83	1	54	95	15	595
Pigs	3	419	82	3	189	292	208	1,197
Total	**21**	**748**	**165**	**4**	**345**	**644**	**272**	**2,199**

Number of observations per species per administration route/form for **combination** products in the preliminary data sets (9 EU MSs)

Species	Bolus / tablet	Injection	Oral paste	Oral powder	Oral solution	Premix	Total
Broilers				14	43	19	76
Cattle	12	125		23	17	14	191
Pigs		195	2	61	85	78	421
Total	**12**	**320**	**2**	**98**	**145**	**111**	**688**

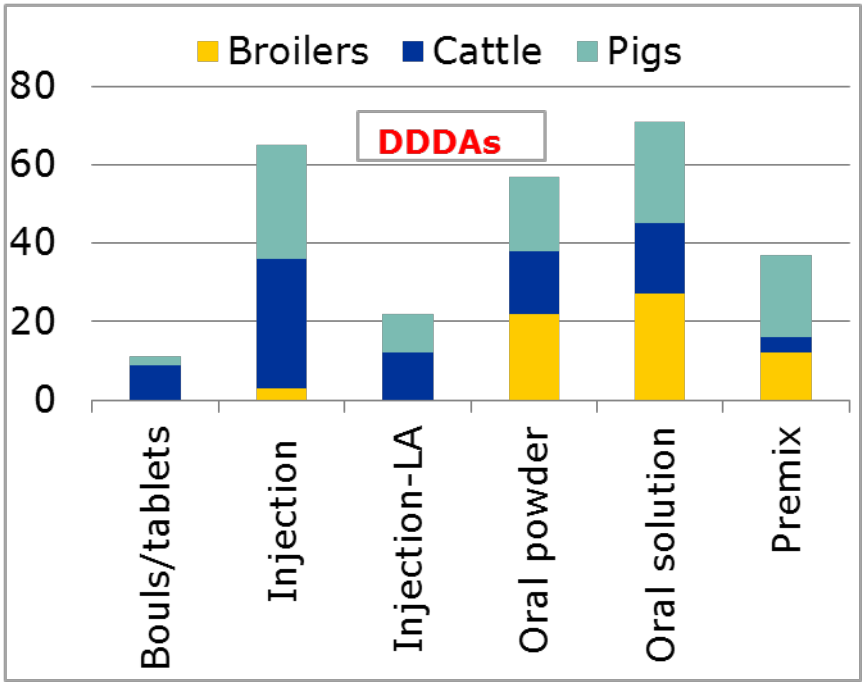
Calculation of preliminary DDDAs and DCDAs

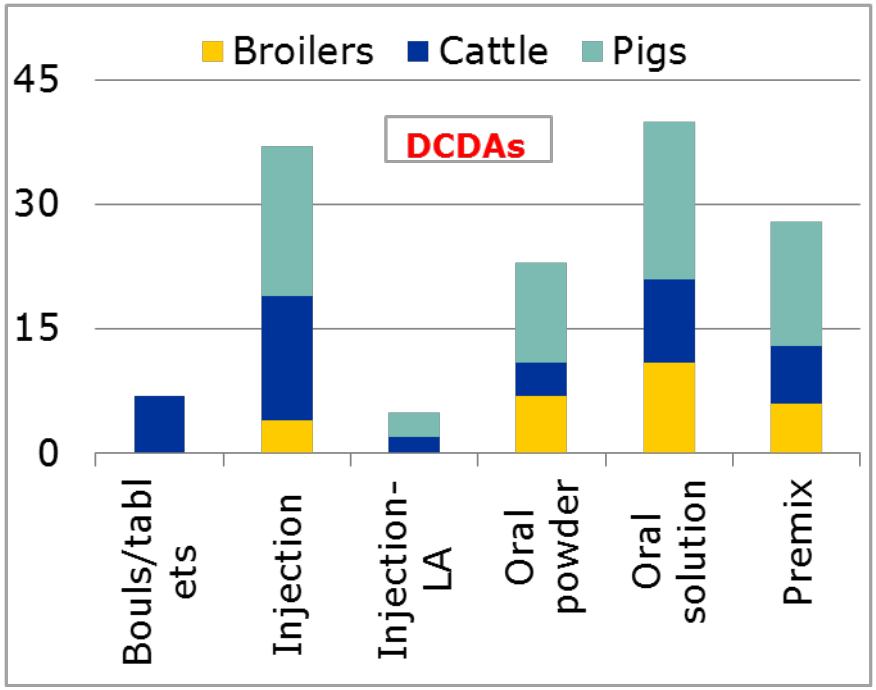
- DDDA calculated as the average (arithmetic mean) of all observations on **daily dose** for each unique combination of species, antimicrobial substance and administration route/form included in the data sets – e.g. pig/oxytetracycline/premix

$$\text{Average} = (a_1 + a_2 + a_3 \ldots + a_n)/n$$

- Same approach for calculation of DCDAs – i.e. average of all observations on **course dose**.

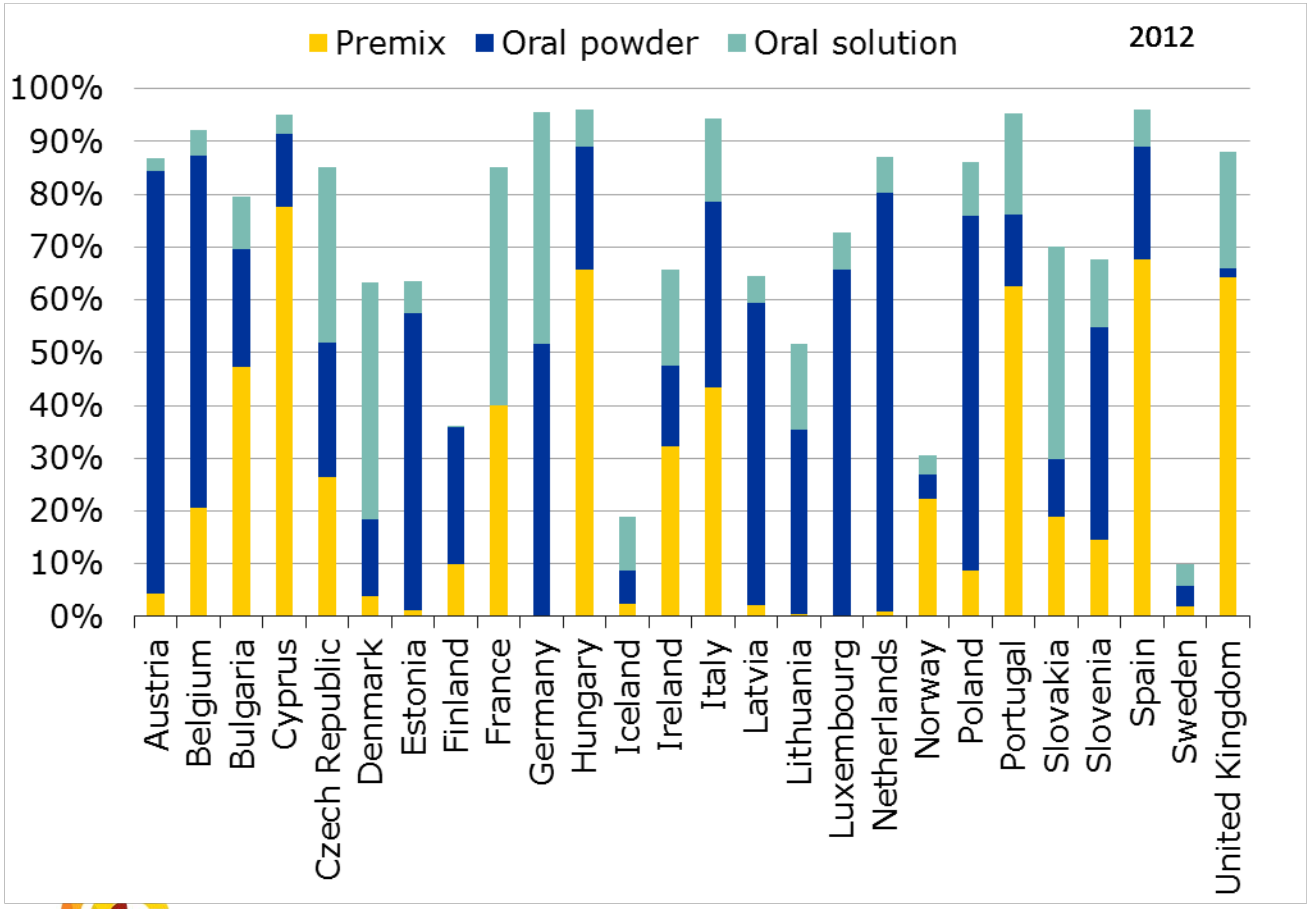
Preliminary numbers (≈ 800) of DDDAs and DCDAs - all administration routes included in the data sets





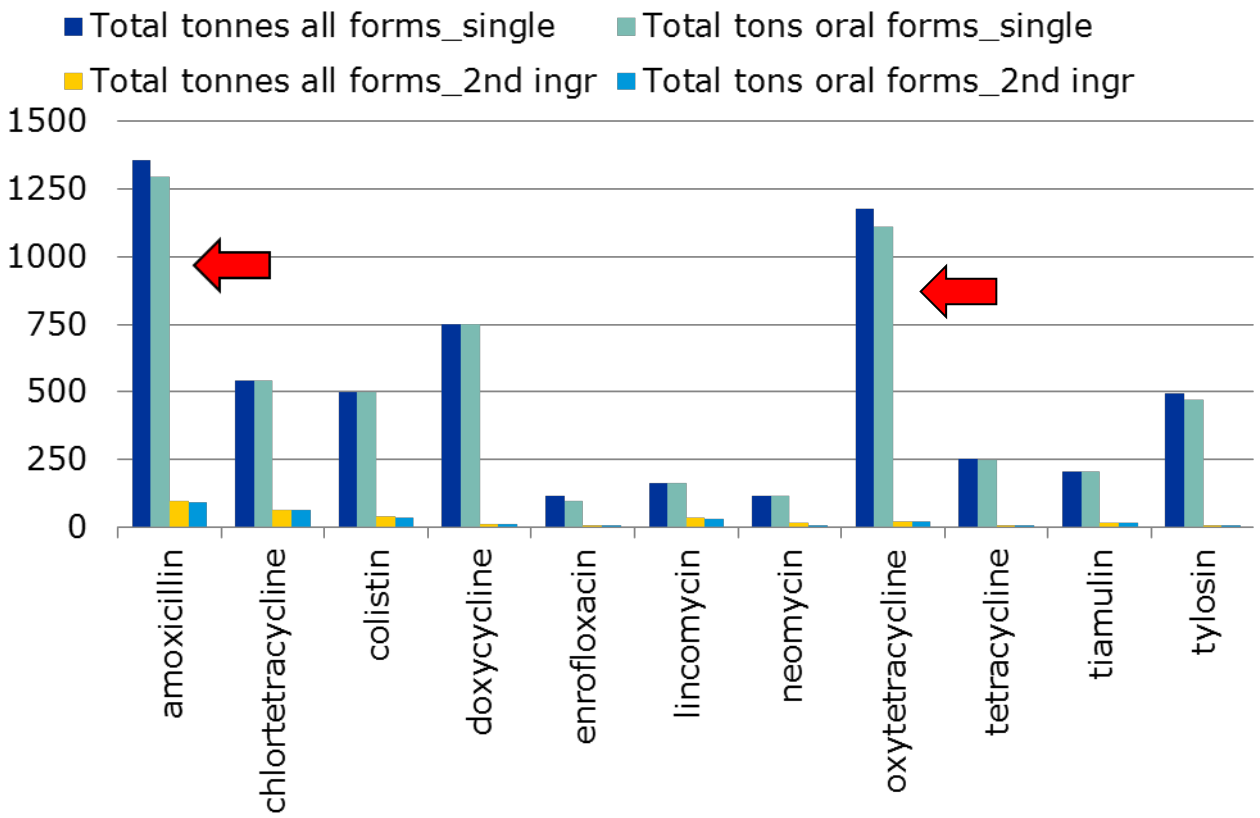
In addition: intramammary DC and LC; intrauterine devices

Percentage of sales of antimicrobial VMPs for group/herd treatment by country



- The proportion used of these oral forms varies substantial between countries
- If substantial differences in DDDAs exist between these oral forms this will impact the calculated numbers of DDDAs used

Justification selection of substances for impact analyses oral products



Filter steps:

1) Sales single substance VMPs > 100 tons in 26 countries 2012 (11 substances represented 90% of single substance VMPs)
2) Sales same substances in combination VMPs

Assignment of DDDAs oral administration routes and injectables

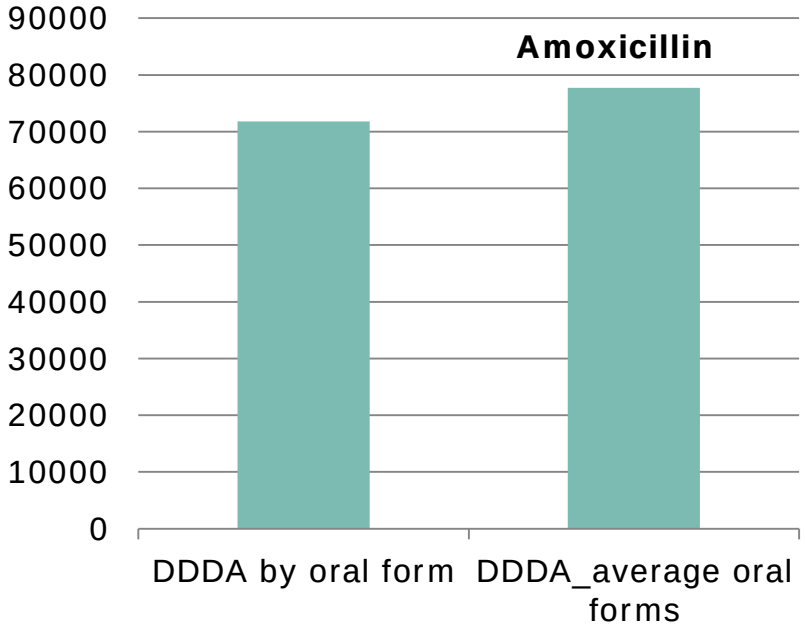
Oral administration routes

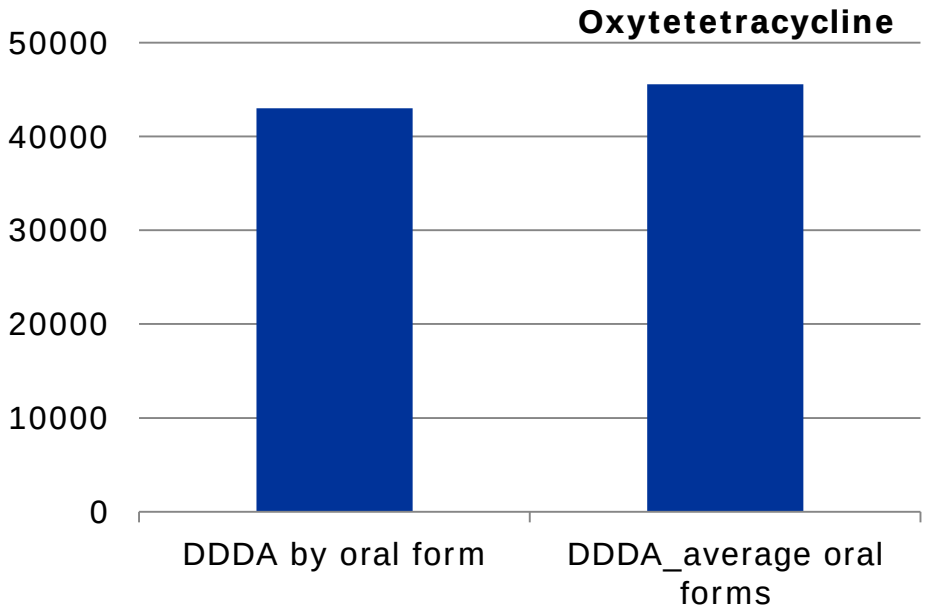
- Assign same DDDAs for all orals or separately – by antimicrobial and species?
- Assign single DDDAs for same substance/species in a combination oral VMP?

Injectables

- Assign DDDAs as average of injectables and long-acting injectables by substance and species?
- Assign same DDDAs for a substance (species) in combination VMP?

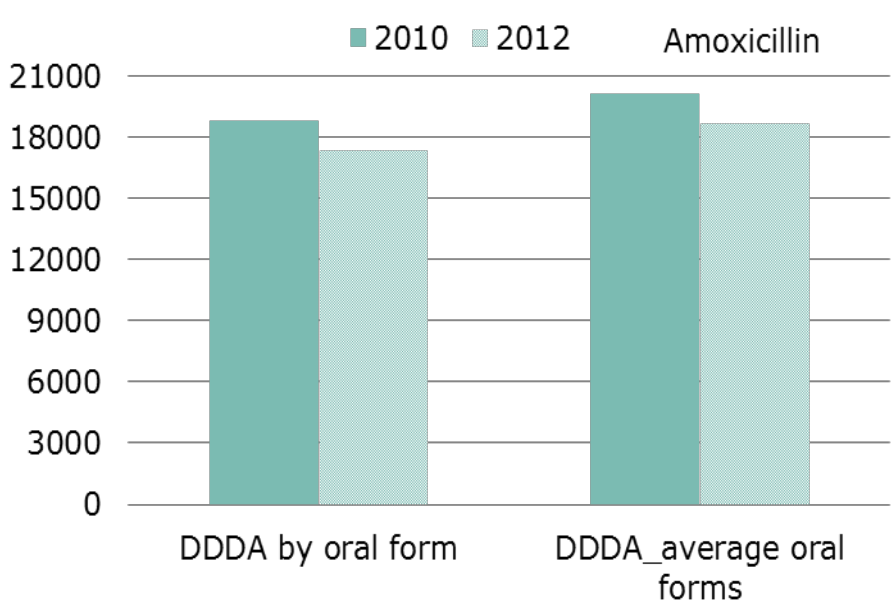
Calculated numbers of DDDAs (10^6) sold of single amoxicillin and oxytetracycline VMPs as oral powder, oral solution and premix. Sales data represent data from 26 EU/EEA countries assuming that the total amounts sold were used in pigs

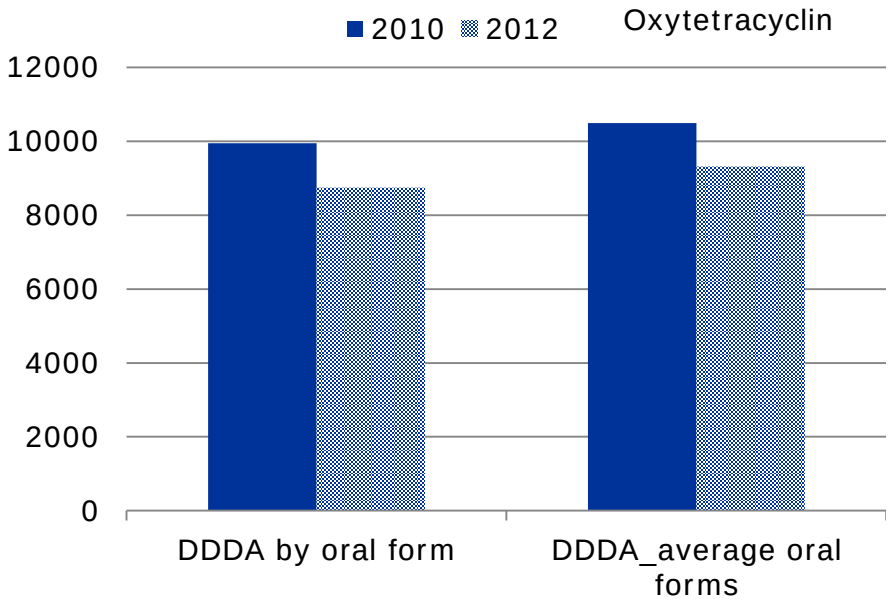




Conclusion: Applying **average** DDDA for oral forms minor impact on annual output

Calculated numbers of DDDAs (10^6) sold of single amoxicillin and oxytetracycline VMPs as oral powder, oral solution and premix. Sales data represent data from **one** EU MS in 2010 and 2012 assuming that the total amounts sold were used in pigs

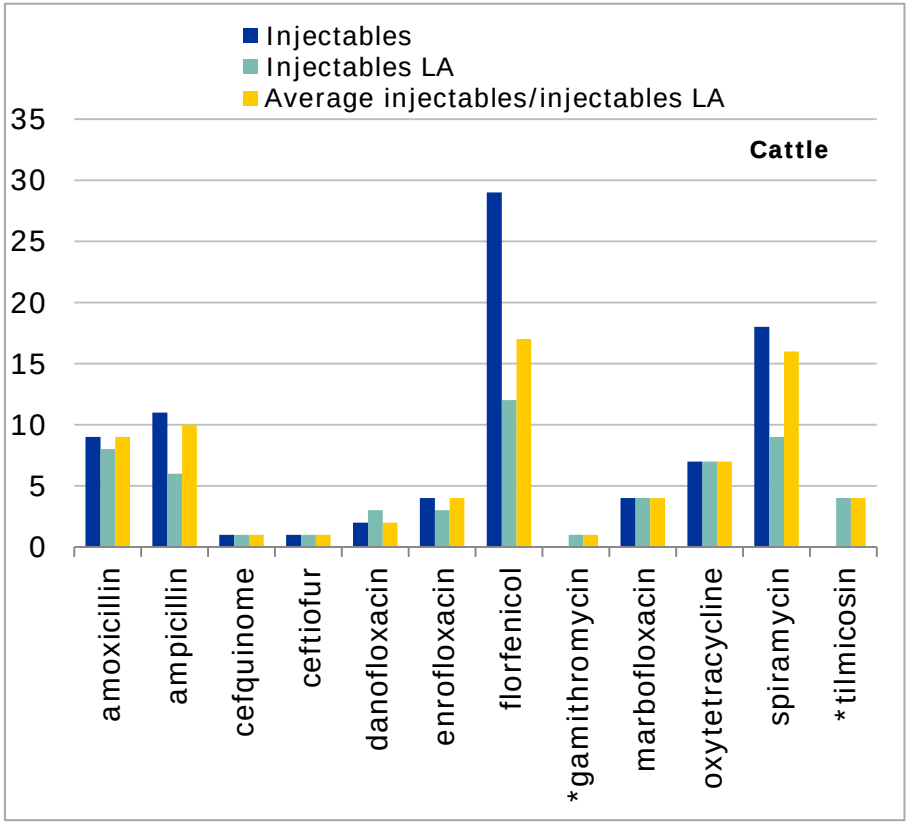


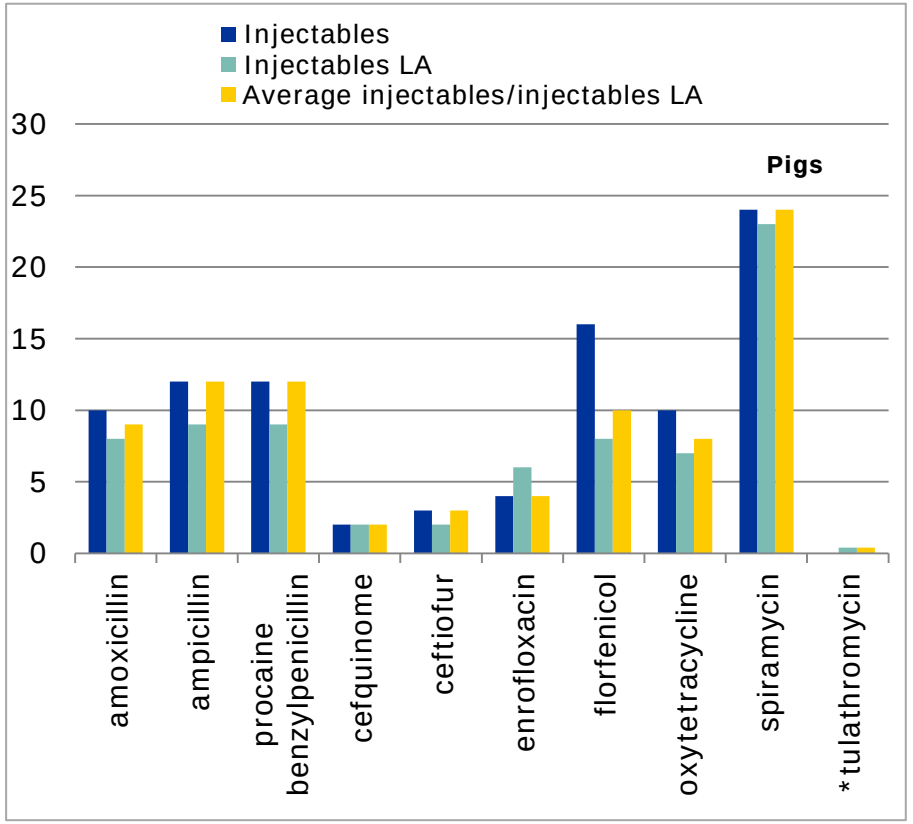


Conclusion: applying average DDDA almost no impact on assessment of changes across time

Can assigning the same (average) DDDA for all injectables for each combination of antimicrobial and species be justified?

Preliminary DDDAs (mg/kg)



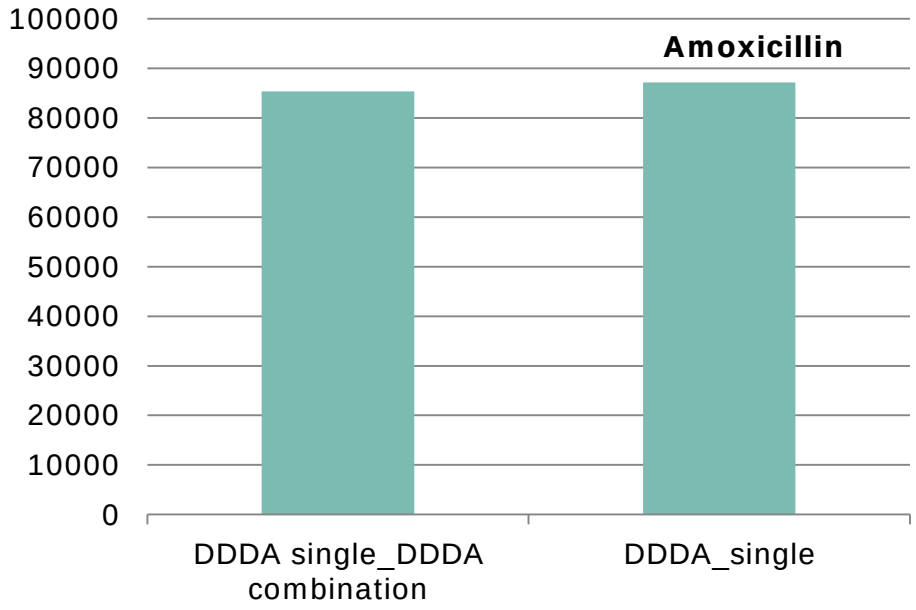


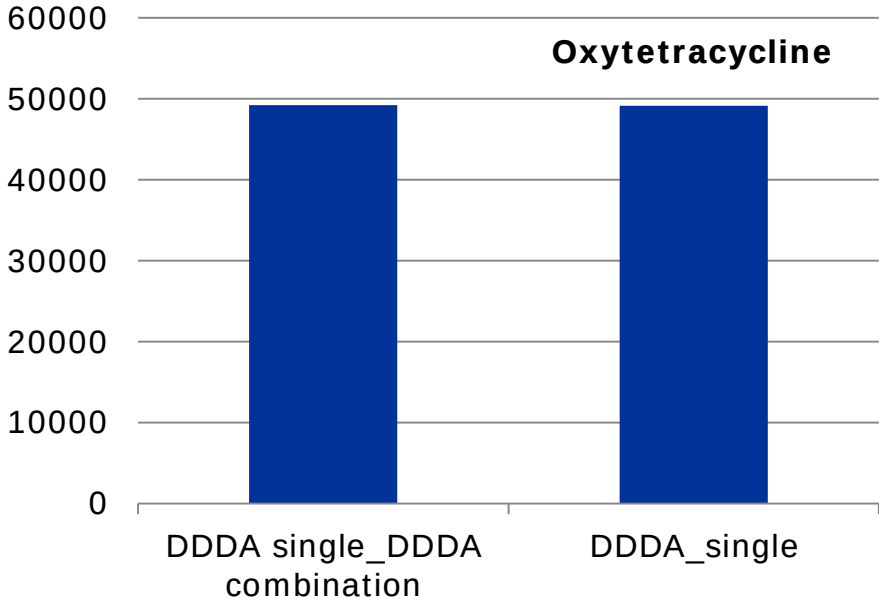
* Only long-acting

Injections/long-acting injections cont

- For the most-selling injectable substances – amoxicillin and oxytetracycline - minor differences are observed between the preliminary DDDAs (mg/kg) for injections and long-acting injections. This is also the case for CIAs with highest priority for human medicine. The most predominate outliers are seen for **florfenicol** (both species), spiramycin (cattle) and ampicillin (cattle). For these substances the proportional sales of injectable VMPs of total sales of all forms in the 26 EU/EEA countries in 2012 were very low.
- **Conclusions:** It is suggested to assign the same (average) DDDA for injections and long-acting injections. Exceptions will be described in the list of DDDAs

Estimated numbers of DDDA sold (10^6) of oxytetracycline and amoxicillin oral powder, oral solution and premix as single and combination VMP calculated by application of DDDA single and DDDA combination and by application of DDDA single for all sales assuming that all was administered to pigs





The results indicate that use of the same DDDA for amoxicillin and oxytetracycline for analysing sales of these in combination VMPs and single substance VMP has almost no impact on the output in calculated numbers of DDDAs.

Summary principles for assignment of DDDAs

Oral single	Oral combinations	Injectables single	Injectables combinations
• Assign the same DDDA for all oral forms	• Assign the same DDDA as for single oral forms*	• Assign the same DDDA for injectables and long-acting injectables** • Prodrugs will be assigned separate DDDA	• Assign the same DDDA as for single injectables, long-acting injectables and prodrugs

Exceptions will be explained in the list of DDDAs

* E.g. synergistic combinations

** E.g. florfenicol

DCDA single

- The number of treatment days is typically higher for premix compared to oral powder and oral solution and in particular for **pigs**; this is reflected in the preliminary DCDAs single (and combinations)
- One approach could be to assign separate DCDAs for premix and for all other oral forms.

Assignment of DCDAs oral administration routes and injectables

Same assessments and considerations as for DDDAs

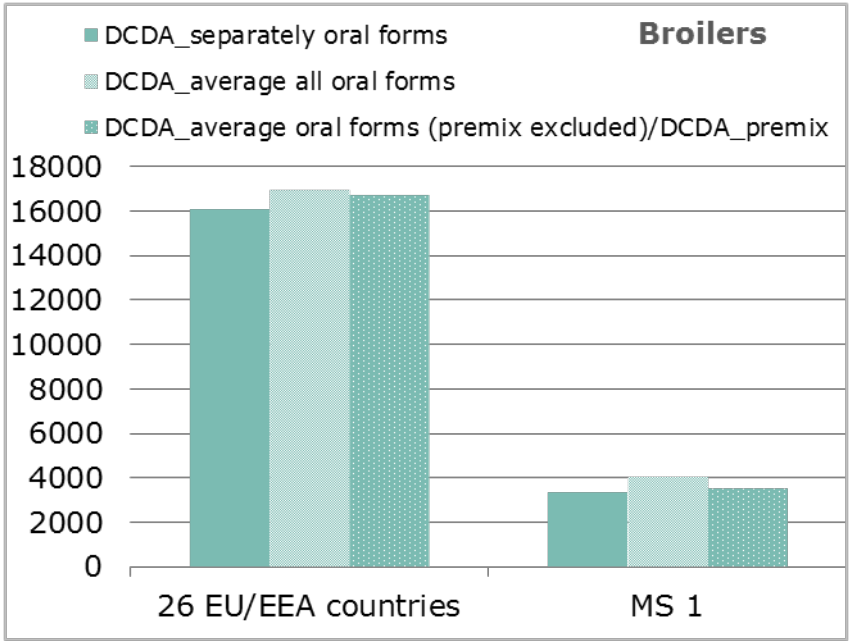
Oral administration routes

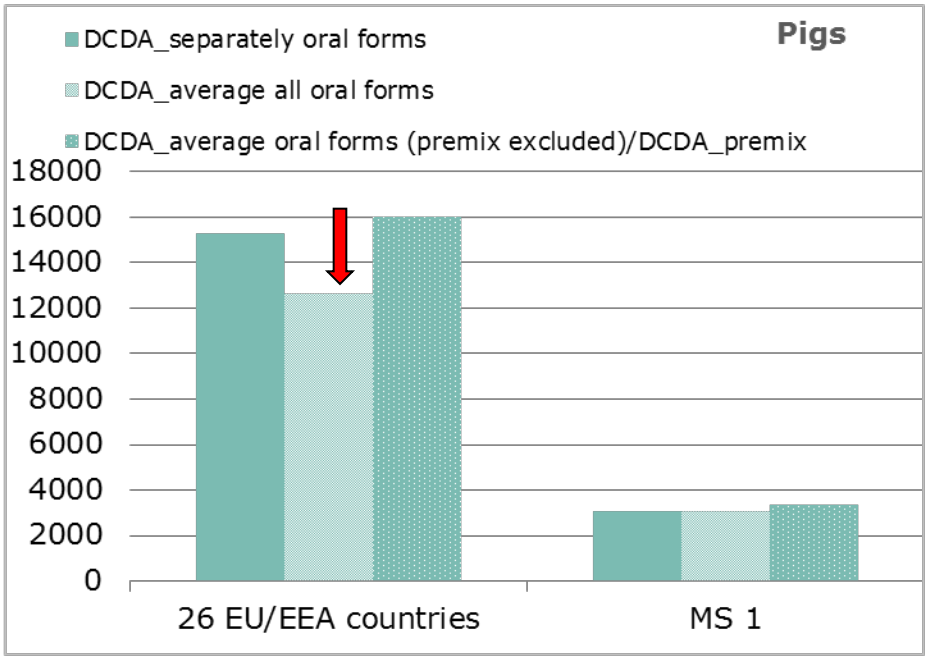
- Assign same DCDAs for all orals or separately – by antimicrobial and species?
- Assign single DCDAs for same substance/species in a combination oral VMP?

Injectables

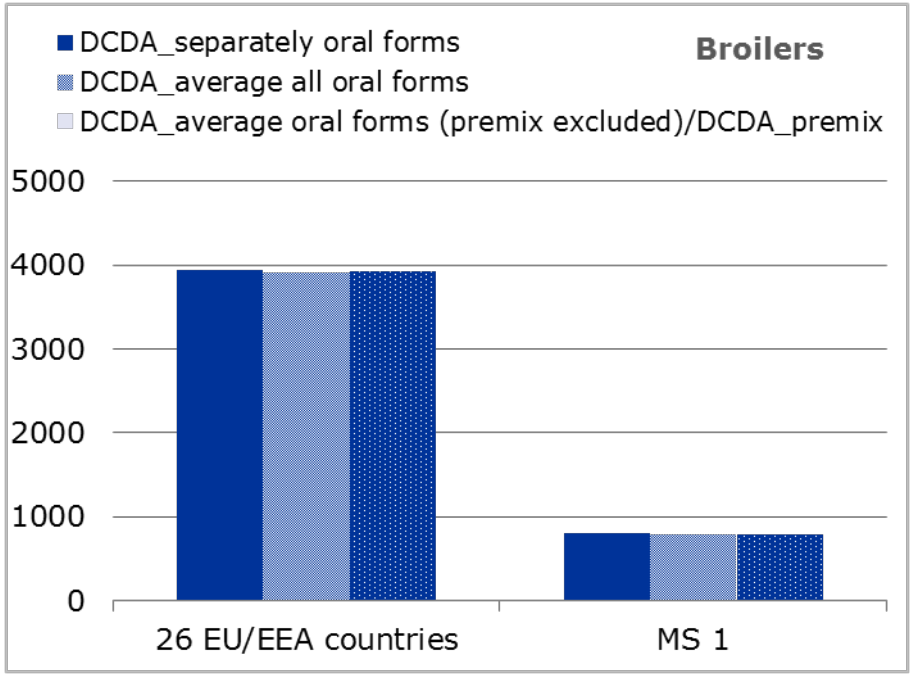
- Assign DCDAs as average of injectables and long-acting injectables by substance and species?
- Assign same DCDAs for a substance (species) in combination VMP?

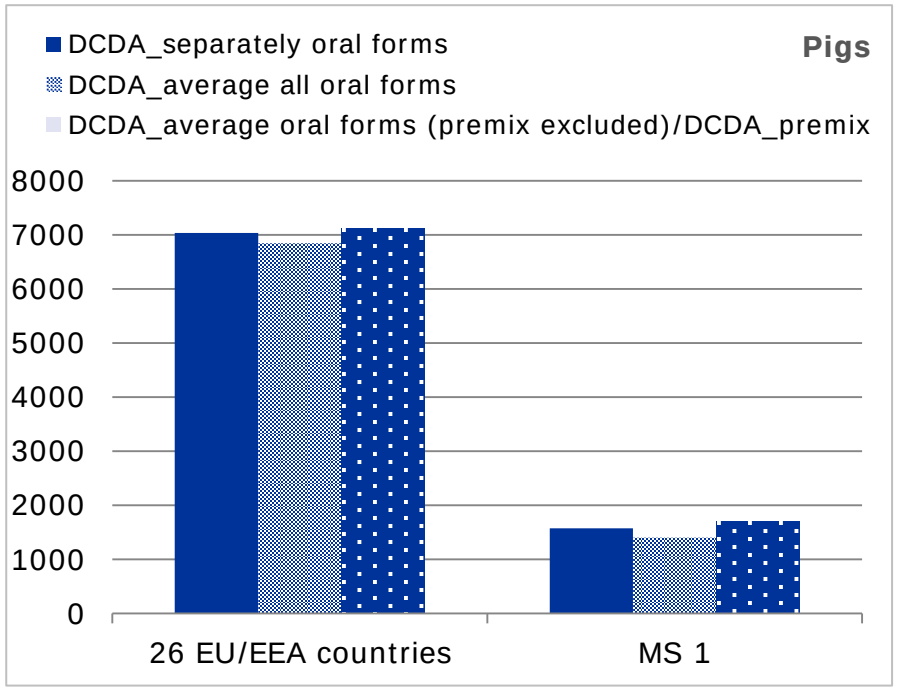
Numbers of DCDAs (millions) of single oxytetracycline VMPs calculated for oral powder, oral solution and premix. Sales data for 26 EU/EEA countries and 1 MS in 2012 applied for calculation assuming that the total amounts sold were used for either broilers or pigs





Numbers of DCDAs (millions) of single oxytetracycline VMPs calculated for oral powder, oral solution and premix. Sales data for 26 EU/EEA countries and 1 MS in 2012 applied for calculation assuming that the total amounts sold were used for either broilers or pigs





Summary

The results of the analyses show that the impact on the output when using separate DCDA for premix and DCDA for all other oral VMPs versus the DCDA average of all observations of oral forms is influenced

- by premix being an outlier for pig
- by the distribution of sales as oral powder, oral solution and premix - overall and by MS.

It is suggested to assign the same DCDA for all oral forms for each combination of antimicrobial and species. Exceptions will be identified in the lists of DDDA and DCDA (e.g. for pigs)

Summary principles for assignment of DCDAs

Oral single	Oral combinations	Injectables single	Injectables combinations
• Assign the same DCDA for all oral forms*	• Assign the same DCDA as for oral single**	• Assign the same DCDA for injectables and long-acting injectables. • Prodrugs will be assigned separate DCDA	• Assign the same DCDA as for single injectables, long-acting injectables and prodrugs

Exceptions will be explained in the list of DDDAs – e.g.

* Premix pigs – to be decided case by case?

** Synergistic combinations