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Industry View on the draft GL on the assessment of the risk to public health from AMR due to the use of an antimicrobial VMP in livestock

(EMA/CVMP/AWP/706442/2013)

Focus Group Meeting, EMA 19th September 2018

Outline

1. Risk assessment methodology
2. Data requirements
3. Risk Management
4. Direct exposure
5. Generics
6. General thoughts
7. Concluding remarks

1. Risk Assessment - Methodology

- **Risk assessment approach is welcomed and supported:**
  - Stated DRAFT GL aim: 'to provide a systematic approach .... and to improve transparency and consistency of the regulatory decision-making process"
- **Qualitative risk categorisation (VL, L, M, H) is not always well defined.**
- **More guidance needed:**
  - to categorise risk outputs *i.e.* Release (Table 2), Exposure (Table 3) and Consequence assessment (Table 4)
  - to produce overall qualitative risk estimation (*i.e.* risk integration)
- **As a result, the assessment is:**
  - Open-ended
  - Is not predictable
  - Lacks transparency
  - Does not enable a preliminary assessment of potential to obtain marketing authorisation

1. Risk Assessment – Methodology (ctd.)

Animalhealth Europe would welcome:

- **Harmonisation in regulatory approaches**
- **A possibility to leave the risk assessment at an early stage should be incorporated (similar to FDA Guidance 152 and as published by *Alban et al.* 2017)**
  - *e.g.*, a discussion (with the Agency) of the hazard characterization and data needed, before sponsor decision to submit a full assessment
  - *i.e.* "lack of information in any important step excludes the potential hazard from further analysis" (similar to FDA Guidance 152 and cited from Alban et al. 2017)
- **Clear and transparent guidance on the risk categorisation and the overall risk estimation (examples on next slides)**

FDA Guidance 152 excerpt – risk ranking example

Table 3. Prevalence of *Salmonella* contamination of various animal-derived food commodities and qualitative contamination rankings.

Commodity	Baseline prevalence (%)[1]	Calendar Year 2001 Prevalence (%)[1,2]	Qualitative ranking[3]
Ground Turkey	49.9	26.2	High
Ground Chicken	44.6	19.5	Medium
Broilers	20.0	11.9	Medium
Market hog	8.7	3.8	Low
Ground Beef	7.5	2.8	Low
Cows/bulls	2.7	2.4	Low
Steer/Heifer	1.0	0.6	Low

[1]As reported in the USDA/FSIS "Progress Report on *Salmonella* Testing of Raw Meat and Poultry Products, 1998-2001"[6]

[2]Prevalence data for CY 2001 for all size slaughter establishments and establishments that produce raw ground product

[3]Relative qualitative ranking of the level of contamination among various food commodities: Low (< 5%), Medium (5 – 25%), High (> 25%) is a general ranking, proposed here for illustrative purposes only, and may be subject to modification to more appropriately reflect the most current data.

FDA Guidance 152 & CODEX GL77 excerpts - Integration:

FDA Guidance 152

Table 6. Possible risk estimation outcomes based on the integration of the release, exposure, and consequence assessment rankings

Release	Exposure	Consequence	Risk Estimation
low	low	important	low
low	medium	important	low
medium	low	important	low
low	low	highly important	low
low	high	important	medium
high	low	important	medium
medium	medium	important	medium
medium	high	important	medium
high	medium	important	medium
high	high	important	medium
low	medium	highly important	medium
low	high	highly important	medium
medium	medium	highly important	medium
medium	low	highly important	medium
medium	high	highly important	medium
high	low	highly important	medium
high	medium	highly important	medium
low	low	critically important	high
high	high	highly important	high
low	medium	critically important	high

CODEX GL77

Table 2. Integration of the Outputs of Hazard Characterization and Exposure Assessment into the Qualitative Risk Characterization

Exposure Assessment Probability of Exposure	Hazard Characterization Severity of Adverse Health Effect	Qualitative Risk Characterization
Negligible	Negligible	Negligible
Low (Unlikely)	Negligible	Negligible
Medium (Possible)	Negligible	Low
High (Almost Certain)	Negligible	Low
Negligible	Low (Mild)	Low
Low (Unlikely)	Low (Mild)	Low
Medium (Possible)	Low (Mild)	Medium
High (Almost Certain)	Low (Mild)	Medium
Negligible	Medium (Moderate)	Low
Low (Unlikely)	Medium (Moderate)	Low
Medium (Possible)	Medium (Moderate)	High/Medium
High (Almost Certain)	Medium (Moderate)	High
Negligible	High (Severe)	Low
Low (Unlikely)	High (Severe)	Medium
Medium (Possible)	High (Severe)	High
High (Almost Certain)	High (Severe)	Very High
Negligible	Very High (Fatal)	Medium/Low

1. Risk Assessment – Minor Comment

It should be specified in Annex 1 of the guideline that *Pasteurella multocida* strains causing pneumonia in food-producing animals are not zoonotic in nature, this only applies to strains causing primary pasteurellosis / haemorhagic fever (capsule antigens B+E).

2. Data requirements

- Data requirements are very clear and well outlined.
- The same level of guidance detail would be required for the risk categorisations (Tables 2,3 and 4).
- Guidance detail is needed on how to integrate Release, Exposure and Consequence assessments to produce the overall risk estimation.
- At risk of generating a "*plethora of details on the expense of the overview*" as experienced by Alban et al. 2017.

3. Risk Management

The draft GL is lacking risk management considerations which could range from denying authorisation, restricted use conditions, post-approval monitoring *etc*.

Table 8. Examples of potential risk management steps associated with the approval of antimicrobial new animal drugs in food-producing animals based on the level of risk (high, medium, or low).

Approval conditions	Category 1 (High)	Category 2(Medium)	Category 3 (Low)
Marketing Status[1]	Rx	Rx/VFD	Rx/VFD/OTC
Extra-label use (ELU)	ELU Restrictions	Restricted in some cases[3]	ELU permitted
Extent of use[2]	Low	Low, medium	Low, medium, high
Post-approval monitoring (e.g., NARMS)	Yes	Yes	In certain cases
Advisory committee review considered	Yes	In certain cases[3]	No

[1]Prescription (Rx), Veterinary Feed Directive (VFD), Over-the-counter (OTC)
[2]See Table 7 for characterization of extent of use
[3]These risk management steps may be appropriate for certain Category 2 drugs that were ranked critically important for consequence assessment **and** ranked "high" for release **or** exposure assessment

Excerpt from the FDA #152 on mitigation measures dependent on the level of risk identified

4. Direct Contact Route of Exposure

Should be removed from the Guideline as:

- **Hazard has been adequately addressed by ECDC/EFSA/EMA, SAGAM (AMEG) and many others.**
- **For food-producing animals, the contact population of humans is very small, i.e. low level of occupational exposure.**
- **Unprecedented requirement unlike any requested worldwide transfer via direct contact specifically excluded in FDA Guidance152:**

"The FDA believes that human exposure through the ingestion of antimicrobial resistant bacteria from animal-derived foods represents the most significant pathway for human exposure to bacteria that have emerged or been selected as a consequence of antimicrobial drug use in animals."

5. Generics – Clarification Needed

- **Line 129:** ***The guidance does not apply for generic applications made under Article 13.1 of the Directive.***
  - What about a generic application that could lead to an increase in volume of use? (*e.g.* geographic expansion)?
  - What about line extensions or other "in scope" changes of generics?

- **From CVMP's response to comments on Draft 1 of the guideline:**
  "If an AMR risk is identified, then all related products could be addressed under a referral procedure for the class"
  - Who is responsible for the risk identification?
  - Who is responsible for performing the risk assessment?
  - A class referral is not a good approach to address AMR risk for a generic entering the market.

6. General thoughts

It is key for industry that the process will be:

- **Pragmatic :** the guideline takes a pragmatic approach following established risk assessment principles.
- **Proportionate:** the guideline should exclude direct exposure.
- **Predictable in outcome:** the guideline should have more details on risk assessment characterisation/estimation, overall risk integration of the three assessments and risk management options.
- **Harmonised where possible:** the guideline should take into account other developed regulatory systems: alignment with FDA Guidance 152, CODEX GL 77, and OIE Chapter 6.11 is strongly recommended.

7. Concluding Remarks

- The guideline is supported in principle .
- There is a lack of predictability and guidance missing in some aspects of the risk categorisation and overall risk integration and mitigation.
- Lack of predictability and transparency could have unintended consequence of further discouraging future medicine availability to animals.
- Such guidance is already available (FDA, OIE, CODEX) should be considered to facilitate international harmonisation.
- Guideline should be in the spirit of the EC's stated aims for the new Veterinary Medicines Regulations and other EMA documents: to stimulate innovation and recognise that new veterinary-only antimicrobials might decrease animal and public health risk.

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