

Translation

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**Comments on Risk Assessment Guideline (proposal) for Livestock Use Antimicrobials on Food Safety**

ACCJ Animal Health Sub-Committee  
EBC Animal Health Committee

Antimicrobials have been used in the livestock industry in Japan for more than a half-century, contributing to the development of the livestock industry, and improving feed utilization and the development of a steady food supply. , At the same time, it is imperative, concerning the problem of bacterial resistance, that risk assessment be based on scientific data to ensure safe livestock-food production and further advancement of Japanese livestock industry.

The goal of the proposed guideline announced recently is to have a science -based assessment of antimicrobials use in Japanese livestock industry. We believe that it is critically important and useful to enhance Japanese risk assessment and to seek consistency of governmental regulations with other countries.

After reviewing the proposed guideline, we have listed our questions and requests as shown in the attachment. We would like the Food Safety Commission to reconsider these points.

1. Process of Risk Assessment

The process of risk assessment described in Section 1-4 says that the “risk assessment will be done with qualitative procedure in principle. ...semi-quantitative and quantitative procedure can be used if necessary judged by food safety commission...”. Risk assessment guidelines in the USA and Australia, however, state “accept semi-quantitative and/or quantitative risk assessment if they are justifiable” or “assessment should be done quantitatively as much as possible”. Therefore, we would like to request that an option be included in the draft proposals accepting semi-quantitative and/or quantitative risk assessment instead of the qualitative risk assessment from the beginning if the document sponsor submits documentation confirming the quality and reliability of the semi-quantitative and/or quantitative assessment.

2. Document quality

Section 1-5 “evaluation documents” regarding document quality states that “in order to secure reliability it is necessary, as a rule, to conduct tests at GLP qualified facilities”. However, the current regulations in Japan accept non-GLP studies for MIC or pharmacokinetics data, which is also the major part of the data required to prepare the risk assessment document in accordance with this guideline. Thus it is not easy for document sponsors to show an official endorsement for objective quality and reliability. Especially for old data, it is rather difficult to prove data quality directly or indirectly. However old data is important for qualitative risk assessment to see resistance trends from the past to the present. Thus, we would like to propose that old data be accepted in a flexible manner with reasonable evidence such as “used for the evaluation by the relevant authority”, “conducted at the research facility in university majoring in microbiology”, “conducted at an independent laboratory reputed for microbiological research”, “laboratory belonging to the drug sponsor but evaluated to have qualified facility/equipment and researchers ”.

3. Hazard identification and their risk assessment

In the draft guideline it is written that the hazard identification step evaluates whether or not the subjective antimicrobial substance is hazardous, such as resistant bacterium or resistant determinant. Thus, if the substance belongs to a totally different class from human drugs and is judged to have little possibility of producing a hazard, then it should not have to proceed to the next steps of risk assessment. A statement expressing this exemption is written into FDA guidance #152, and we recommend that a similar sentence be included into this draft guideline.

4. Mandatory data and optional data

Regarding the documents to be assessed, the draft guideline states that this “can be evaluated with the information written below”. This sentence can be interpreted that “some data would not be mandatory or can be substituted or extrapolated with other data” but the expression of this sentence is rather vague and weak.

Also the draft guideline targets two totally different types of antimicrobials vis-à-vis usage methods and applications, i.e. animal drugs and feed additives, and the data which can be submitted and can't be submitted for each category of these products differs substantially. In other countries, the guidelines in US and Australia have sentences that allow some flexibility for the data sets. Thus, we would like to ask that the text be amended to express

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that these data lists are not necessarily to be requested for all of the risk assessments, and allow the document sponsor to adjust the data sets in consideration of the characteristics or indications of the substance.

### 5. Indicator Micro-organisms for Hazard Identification

Section 2-1 lists *Vibrio parahaemolyticus* and *Listeria* as food-born zoonotic bacteria as target micro-organisms for hazard identification. However, it is difficult to consider these substances as hazards, as *Vibrio parahaemolyticus* does not exist in aqua-cultured fish and *Listeria* exists everywhere. Due to the epidemiological characteristics of these microorganisms, the guidelines in the USA, EU and VICH do not list these two microorganisms as examples of hazards in their risk assessment guideline.

Because of this situation, no relevant information is available for hazard identification, and thus, we would like to request that the FSC and MHLW or another public organization conduct the epidemiological surveys and risk assessment for the importance in public health for these two organisms and then based on this data judge whether or not it is necessary to conduct a resistance bacterium risk assessment, and if that is the case determine what the relationship with food animals is. It would not be too late to put these two organisms as examples of hazards until after this has been confirmed.

Since the proposed guideline assesses antimicrobial resistance risk selected with the direct antimicrobial use in livestock, we would like to request to eliminate these two microorganisms from the example of the hazard organisms.

### 6. Risk of antimicrobials “non-use” and/or benefit of antimicrobial use

Section 3 (Other Considerations) in the guideline states “required risk management will be considered as necessary.”

However, any risks of “non-use” of antimicrobials (or benefits of their use) are not mentioned. In case of “non-use of antimicrobials”, livestock animals may produce less safer food products caused by unhealthy and poor animal-welfare conditions. Additionally, negative impact to environment may result from poor feed utilization. In fact, Australian guidelines include a benefits review with respect to the environment. A benefits review is part of the general risk review in Australia (JETACAR Report in 1998), New Zealand (Antibiotic Operation Committee in 1999), Canada (Health Canada in 2002) and the USA (National Research Council in 1998).

Therefore, we request that the Japanese risk assessment guidelines include a more appropriate risk management approach that considers both the risks and benefits; i.e. the risk and benefits of both use *and* non-use of antimicrobials.

### 7. Preparation of public data

Various human data will be needed to conduct the risk assessment in accordance with this guideline. Data for human antibiotics and drug sensitivity and importance in human medicine are requested for “hazard identification”, “release assessment”, and “consequence assessment”. However, it is difficult for animal drug sponsors to directly access to this data, and it would perhaps be better if this data was collected and kept by the Ministry of Health Labor and Welfare (MHLW), the ministry directly supervising the medical institutes. We would like to ask MHLW and Food Safety Commission (FSC) to compile this data, arrange it by product class, analyze it statistically, and make an effort to accumulate effective data and information.

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### 8. Acceptance of oversea data

This draft guideline does not touch on the acceptance of oversea data. But in many of the cases, it would be difficult to conduct risk assessment only with domestic data. For example, active surveillance data for each food-borne infection's epidemiology can be obtained in other countries, but not in Japan.

We would like to request that a sentence be added in the guideline to allow the use of overseas data.