CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 3 **CRD9**

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

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COMMENTS OF HEALTHFORANIMALS

Comments from HealthforAnimals on JECFA Decision on Sisapronil

1. BACKGROUND

HealthforAnimals wishes to thank the 81st JECFA for its scientific review of sisapronil and completely supports the conclusion of a No Observed Effect Level of 0.3 mg/kg BW/day. This is the exact same conclusion as recommended by the Sponsor and as determined by the Committee for Veterinary Medicinal Products (CVMP) in the European Union.

Nevertheless, HealthforAnimals is disappointed in the final outcome of the assessment whereby the 81st JECFA was of the opinion that there was insufficient information submitted in the Sponsor dossier to set an appropriate Uncertainty Factor and thus establish an Acceptable Daily Intake (ADI). The consequence of this, of course, is that Maximum Residue Limits could not be established.

HealthforAnimals is of the opinion that JECFA reached agreement on the most difficult part of the evaluation, that is, the establishment of the NOEL. A determination of an Uncertainty Factor should have been straightforward as the Sponsor provided more than sufficient information for this task. The appropriate Uncertainty Factor is 100. In support of this value, HealthforAnimals offers the following comments:

- The Sponsor recommended an Uncertainty Factor = 100 in its submission.
- The CVMP concluded in its assessment of sisapronil that an Uncertainty Factor = 100 was appropriate and was able to progress and elaborate MRLs.
- The regulatory authority (MAPA) in Brazil was able to establish a 120-day withdrawal period (WDP) for the commercial product. The 81st JECFA had full knowledge of this decision. This WDP is consistent with an Uncertainty Factor = 100.
- JECFA concluded that the safety endpoint was a true NOEL, not an NOAEL or a LOEL. Thus, there was no additional uncertainty in the assessment that needed to be taken into account. [JECFA has commonly included an additional 2X or 3X uncertainty factor in its calculations when an NOEL was not achieved. However, this is not the situation for sisapronil].
- The Sponsor provided multiple Benchmark Dose Analyses within its dossier to refine and support the elaborated NOEL of 0.3 mg/kg BW/day. The use of BMD analysis removes uncertainty from the calculation. Therefore, the proposed factor of 100 may actually be conservative.

The 81st JECFA indicated that additional information on pharmacokinetics in multiple species as well as a long-term toxicity study relevant to humans (e.g. 1-year dog study) would be of value. HealthforAnimals disagrees that any additional work is necessary and offers the following for consideration:

- All key pivotal toxicological studies were supported by full histopathology to clearly define the endpoints for establishment of the agreed NOEL of 0.3 mg/kg BW/day. Additional plasma data would not supersede or improve on this assessment nor provide enhanced understanding of overall uncertainty.
- The Sponsor provided a long-term study (one-year) in rats and a 90-day study in a second species (dogs).
- In the WHO Technical Report Series No. 997 (section 2.10), JECFA makes the statement that “the nature and potency of effects observed after oral administration for 90 days rarely showed any change after a further 9 months of administration; in other words, the effects and the NOAELs at 12 months were the same as at 90 days.”

- Due to the long half-life of sisapronil in dogs (and in comparison to the half-life in all other species tested, including monkeys), exposure following 90-days of administration (in dogs) was very high, exceeding what is considered relevant for human safety assessment. Extending a study to 1-year may indeed show additional effects but the relevance would be highly questionable due to excessive exposure.

2. HEALTHFORANIMALS PROPOSAL

- The Sponsor, JECFA, the CVMP and the regulatory authority (MAPA) in Brazil are all in agreement that the appropriate NOEL for sisapronil is 0.3 mg/kg BW/day.
- The Sponsor, the CVMP and the regulatory authority (MAPA) in Brazil are all in agreement that the appropriate sisapronil Uncertainty Factor = 100.
- The Sponsor, the CVMP and the regulatory authority (MAPA) in Brazil are all in agreement that the appropriate ADI for sisapronil (0.3 / 100 x 60 kg BW) is 0 – 180 µg/day.
- JECFA should have been able to easily reach all of these same conclusions.
- The CCRVDF has the authority to accept, reject or modify the recommendations of JECFA.

HealthforAnimals is committed to the two primary missions of the Committee, namely, establishing international food safety standards and facilitating international trade. With this in mind, HealthforAnimals proposes that the 23rd CCRVDF take the position adopted by the Sponsor, the CVMP in the EU and MAPA in Brazil, modify the (non)-decision taken by JECFA and agree on an uncertainty factor of 100 for sisapronil. By default, the CCRVDF would then conclude that an ADI of 0 – 3 µg/kg BW (or 180 µg/day) would be appropriate as a CCRVDF (Codex) standard.

HealthforAnimals then proposes that sisapronil remain on the priority list to allow JECFA to establish Maximum Residue Limits consistent with this ADI using its current policies at its next meeting for Veterinary Drugs. There are substantial residue depletion and analytical method data within the Sponsor dossier to allow for elaboration of MRLs.

To be clear, the instructions to JECFA would be to only establish MRLs for tissues of cattle. Any reassessment of the ADI is unnecessary and would be excluded. Furthermore, HealthforAnimals also wishes the Committee to understand that there will be no further (toxicology) data forthcoming on sisapronil. Generation of such data would not be relevant to a human food safety assessment nor would it be consistent with the principles of the 3R's. An adequate dossier was provided to the 81st JECFA for consideration. Sponsors must always critically evaluate their allocation of research and development funds to projects. In this particular case, investment in a one-year dog study, which would cost approximately $800K, is improbable, when the conclusions from such a study would be irrelevant to human food safety.

Should the 23rd CCRVDF disagree with what HealthforAnimals considers to be a very reasonable proposal, the Committee will have lost an opportunity to fulfil its two primary missions. The decision to submit a dossier to JECFA for evaluation must always be carefully evaluated by Sponsors as it always entails a certain degree of risk. To help encourage future applications, Sponsors look to CCRVDF and JECFA to provide some degree of certainty in the evaluation outcome with the absence of extraordinary conditions and further requests that prevent progression towards adoption of the needed international standards.

HealthforAnimals reiterates that this proposal is simply to ask for agreement on the Acceptable Daily Intake of 0 – 180 µg/day. Sisapronil would still need to be assessed by the next JECFA for veterinary drugs for elaboration of Maximum Residue Limits.

HealthforAnimals thanks the 23rd CCRVDF for its consideration of this proposal.

Agenda Item 3: Matters of Interest arising from FAO/WHO and from the 81st Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA); Document Reference CX/RVDF 16/23/3 – Sisapronil

Introduction

HealthforAnimals represents the interests of its Brazilian association SINDAN (the Brazilian National Association for Animal Health Product Industry). They wish to thank the 81st JECFA for its scientific review of sisapronil and notes JECFA's full agreement with the NOEL derived by the Sponsor, the CVMP in the EU and as accepted by the Ministry of Agriculture, Livestock and Supply – MAPA in Brazil. However, having a NOEL set by 81st JECFA, it does not agree with the final outcome of the assessment whereby the 81st JECFA was of the opinion that there was insufficient information submitted in the Sponsor dossier to set an appropriate Uncertainty Factor and thus establish an Acceptable Daily Intake (ADI).

The monographs of the 81st JECFA were reviewed and detailed discussions with the Sponsor with respect to the scientific quality of the sisapronil dossier were conducted. As such, the proposal that the 23rd CCRVDF move forward to establish and ADI for sisapronil based on elaboration of a 100-fold uncertainty factor is fully supported.

We are committed to the two primary missions of the Committee, namely, establishing international food safety standards and facilitating international trade.

Sisapronil is approved in Brazil, license n°10.114/2015, since 03 Aug 2015, for the treatment and control of cattle tick – *Rhipicephalus (Boophilus) microplus* and bot fly larva – *Dermatobia hominis* larva; and as an aid in the control of screwworm of – *Cochliomyia hominivorax* larvae, and horn fly – *Haematobia irritans*, with a withdrawal period of 120 days. Thus sisapronil will become an important tool for cattle producers in parasite control. The withdrawal period, which demonstrates a clearly defined approved use according to the principles of Good Veterinary Practice in Brazil, was elaborated consistent with MAPA's agreement with the NOEL and the 100-fold uncertainty factor.

Considering Brazil has just been approved to export beef meat to US, and taking into consideration the recent trade issues between BR and US related to ivermectin MRLs, we are very concerned about not advancing sisapronil as the lack of an MRL will likely have a negative impact to the meat trade between countries, especially in light of the new trade agreement with between BR to US.

We are also sensitive to the concerns of its Member Companies whereby the scientific relevance of additional safety studies (e.g. a one-year dog study) must be carefully evaluated versus the potential relevance of the study outcome, moreover in this specific opportunity of adopting an uncertainty factor of 100 (a 10 X 10 factor) to guarantee safety and setting the ADI. In the particular case with sisapronil, SINDAN/HealthforAnimals point out that little relevant additional safety information will be obtained and, living in a world that cares about animals, additional animal studies seems unjustified.

Again, on the other hand, using the proposed uncertainty factor of 100 would assure safety for establishing the ADI.

To facilitate international trade between BR, the US and future countries as sisapronil use expands, we would like the 23rd CCRVDF to accept the position:

- as proposed by the Sponsor,
- as adopted by the CVMP in the EU,
- and as accepted by MAPA in Brazil.

to recommend an uncertainty factor of 100 for sisapronil to elaborate an ADI of 0 – 180 µg/day.

Sisapronil will then remain on the priority list.

We reinforce that Sisapronil would need to be assessed, again, by JECFA, so JECFA can progress Maximum Residue Limits consistent with this ADI using its current policies at its next meeting for Veterinary Drugs.