CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

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Agenda Item 7

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

UPDATE OF THE PROJECT ON EXTRAPOLATION OF MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS TO ONE OR MORE SPECIES – CAMELIDS

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Discussion paper Submitted by

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(Prepared by the Expert Working Group on Extrapolation Studies Developed as part of the Arab Codex Initiative implemented by Laval University, Quebec, Canada and the Global Food Regulatory Science Society (GFoRSS)).

This discussion paper should be read in conjunction with CX/RVDF 21/25/8 and/or the latest version of the Procedural Manual (Risk Management Policy applied by CCRVDF for the Extrapolation of MRLs to One or More Animal Species)

INTRODUCTION

The Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) has considered the adoption of MRLs by extrapolation since 2010 at its 19th session. The approach was discussed at several meetings, notably the challenges/limits/principles of the methodology based on the aim to establish the modality of its application to different species. The 25th Session of the CCRVDF25 (2021) agreed to forward the Approach for the extrapolation of maximum residue limits for veterinary drugs to one or more species to the Codex Alimentarius Commission for adoption and inclusion as Annex C to the Risk Analysis Principles Applied by CCRVDF. The approach was adopted by CAC44 (2021) as a methodology to develop MRLs for veterinary drugs and was introduced into the procedural manual (risk analysis principles applied by the codex committee on residues of veterinary drugs in foods).

At CCRVDF25 (2021), when discussing the agenda item of extrapolation of MRLs to one or more species (approach including a pilot on extrapolation on MRLs identified in Part D of the Priority List A), a delegation noted the particular need for MRLs for camels and asked that this be considered a priority and that CCRVDF provide for extrapolation of MRLs for this species. The Chairperson noted that information was not currently available on how to best extrapolate MRLs for camels, and that such information would need to be developed. Moreover, delegates requested clarification on how camels would be considered within the ruminant grouping. While camels share characteristics of ruminant animals, they also share some characteristics with non-ruminants. It is unclear whether the metabolism of veterinary drugs in camels would allow extrapolation from other ruminant species such as cattle.

The camel economy, in particular camel meat and milk production, is of considerable importance for arid countries. The sector continues to register great growth given its essential contribution to food security and economic development in Middle East and North Africa Region (MENA). The development of the sector

requires the use of different vet drugs to limit the impact of infectious diseases which impose the establishment of safe standards to ensure food safety and trade facilitation.

This discussion paper aims to explore the application of the guidelines on extrapolation of MRLs developed and adopted by the Codex Committee on Veterinary Drugs in Food (CCRVDF) for the development of MRLs relevant to camels in MENA region. It represents the summary of the work carried out under the auspices of the Arab Codex Initiative in relation with investigating extrapolation-based methods as a means to derive MRLs for substances / tissues of interest in the Arab region. This discussion paper focuses on exploring the opportunity to establish MRLs for Camelid tissues, based on previously set Codex MRLs for other species.

PARTICIPATION AND METHODOLOGY

To investigate the application of the CCRVDF guidelines on extrapolation of MRLs and develop a methodology for the establishment of MRLs relevant for camel farming in the MENA region, the current terms of reference (TOR) were developed:

1. Review Codex (CCRVDF) criteria re. extrapolation of vet drug MRLs for all ruminants (basis, development, application).
2. Review of Codex MRLs approved for use in ruminants with the potential to support guidance for camel farming in the MENA region.
3. Determine Vet Drug requirements for current and possibly future camel farming in the region, currently not covered by Codex.
4. review of the main differences between camels and ruminants notably regarding metabolism, pharmacokinetics and pharmacodynamics of vet drugs and analysis of their potential impact for the availability of drugs and establishment of standards applicable to camels and
5. Analysis of the possible application of the MRL extrapolation approach developed by Codex for camels.

Within the present framework, an expert working group was established under the auspices of the Arab Codex Initiative implemented by Laval University (Quebec, Canada) and the Global Food Regulatory Science Society (GFoRSS)[1] with the charge to prepare a discussion paper related to the study of the possibility to derive MRLs for vet drugs using the CODEX extrapolation approach specific to camel products.

For this purpose, the working group focused on the response to the following questions:

- ✓ Can we consider camels similar to ruminants, notably regarding the metabolism of vet drugs, including associated pharmacokinetic and toxicological aspects?
- ✓ What are the main limitations that would stand in the way of developing such methodology of extrapolation for camels and as a result is the Codex guidance for MRL extrapolation suitable/applicable for camels?

In response to the previous questions on this issue, a comparative assessment of data pertaining to the metabolism of vet drugs between camels and ruminants was considered based on the available scientific literature reviewed.

The time allotted to the study did enable to proceed with a systematic review, rather with the review of the latest accessible scientific information.

SUMMARY OF DISCUSSION

The summary of the discussion will attempt to offer answers to the two questions identified as the charge

[1] GFoRSS is a Disciplinary Group of IUFoST in matters related to food regulatory science

of the study:

Can we consider camels similar to ruminants notably regarding the metabolism of vet drugs, including associated pharmacokinetic and toxicological aspects?

- ✓ For the purpose of MRL extrapolation in the pilot study, CCRVDF adopted the grouping of species namely as ruminants and bony fish. Camels, which are not considered as true ruminants, seemed not be specifically included in the proposed grouping: *Camelids are not ruminants taxonomically, physiologically, or behaviorally. Although camels have a digestion system similar to ruminants (such as cattle, sheep and goats), they are referred to as "pseudo-ruminants" and therefore are classified in a separate family of ruminants.*
- ✓ While camels share certain characteristics of ruminant animals, they also share some characteristics with non-ruminants. The current evidence does not provide a clear understanding whether the metabolism of veterinary drugs in camels is similar to the ruminant category and therefore would allow extrapolation from other ruminant species such as cattle.
- ✓ The anatomy of the fore stomach and the feeding behaviour of the camelids and ruminants may be considered different. Such differences could have consequences on the digestion of feed and the metabolism of vet drugs:
    - The digestive system structure is among the main existing differences between camels and true ruminants. In camels, the stomach has three compartments, C1 or rumen, C2 and C3 with a compartment of the omasum type not well differentiated unlike ruminants having a stomach with four chambers (rumen, reticulum, omasum and abomasum);
    - Even though the gastrointestinal (GI) microbiome is qualitatively the same between camels and cows, the cellulolytic activity of the bacteria is much more important in the camelid forestomach and the retention time of solid particles in the forestomach is much longer.
- ✓ Scientific publications reviewed on the pharmacokinetics of some drugs in camels have shown the existence of notable differences between camelids and other domestic animals, especially regarding the absorption and elimination of drugs. Half-lives for some drugs, used as examples may be longer and the systemic clearance slower in camels compared to other animals suggesting that the activities of metabolizing enzymes and capacity for biotransformation and elimination of drugs are lower in camels than in other ruminants.
- ✓ The pharmacokinetic profiles of several antibacterial, anti-parasitic and anti-inflammatory agents in camels have been reviewed and have shown that notable differences could be observed between camels and ruminant species [2]; the pharmacokinetics of several drugs in hydrated and dehydrated camels are also different from those in other domestic animals (reference)
- ✓ Camels have unique physiological and biochemical characteristics that may be reflected in their responses to active substances, probably impacted by the functions of the liver and the kidneys [4; 5]. The pharmacokinetics of an active ingredient in camels can vary considerably compared to other species. It may be related to the following factors:
    - The activities of certain drug-metabolizing enzymes or isoenzymes are deficient or lacking in camels [1]. This possibility was tested and confirmed for a number of drug metabolizing enzymes in the liver, kidney and duodenal mucosa of camels, sheep, goats and rats [7; 8]. In addition, the protein binding capacities of some drugs in camels may be different from those in other species leading to slower elimination kinetics [6;1; 9].
    - Some drug metabolizing enzymes may be deficient or lacking.
    - The process of dehydration, which occurs in in camels raised naturally, may significantly alter the pharmacokinetic properties of certain drugs, and may therefore necessitate modified dosage schedules in dehydrated camels [5].

What are the main limits linked to application of the Codex principles for MRL extrapolation for camels:

- ✓ Few reports on vet drugs metabolism for camel are available in the literature.
- ✓ The metabolic profile of vet drugs in camels may differ from other species, notably ruminants, and therefore there is a need for specific studies to define the particularity of camels in terms of the metabolic and toxicity profiles of medicine.
- ✓ Camels are not true ruminants taxonomically, physiologically, or behaviourally.
- ✓ The use of pharmacokinetic and toxicological data used for other animal species (particularly cattle) may be unsuitable for application to camels.

CONCLUSIONS

Given some specificities of camels outlined above, the methodology and criteria established by Codex for the extrapolation of MRLs may not be totally or generally adapted for all chemical substances to camels compared to other minor species:

- ✓ Considered as pseudo ruminants, camels cannot be considered as related species to ruminants; the definition given by Codex to the group of food producing animals must be clarified more notably for this species.
- ✓ Metabolism, pharmacokinetic and toxicological profiles of vet drugs in camels may differ from ruminants and more investigations and adaptation of the approach of MRLs extrapolation should be requested to ensure that standards that could be obtained through extrapolation would offer the needed food safety guaranties.
- ✓ The ratio M:T may differ depending on kind of active substance and physiological factors linked to the physiological and particularity of metabolism variable in both for camels and ruminants.
- ✓ Residues of vet drugs may differ in Camel from other species notably ruminants. If no data are available to suggest that the marker residue in the reference species is the parent compound only or is the same as the total residues of toxicological concern, there would be a need for specific studies to define the particularity of the camel in terms of the toxicity profile of the drug and its metabolism.

RECOMMENDATIONS AND PROPOSED NEXT STEPS

Considering the Literature review studied within the present work, it is recommended that considers the following:

The approach of pilot extrapolation on MRLs identified in Part D of the Priority List A conducted by CCRVDF didn't identify or mention camels as a minor species for consideration in MRL extrapolation. Camels, while having similar aspects of ruminant digestion, may not be sufficiently related to the reference category (ruminants) to permit MRL extrapolatio**n. A clarification on how camels would be considered within the ruminant grouping should be considered by the CCRVDF, with the possible advice of JECFA.**

Should CCRVDF, with the advice of JECFA, conclude that the existing similarities between camels and ruminants are such that that camels are related to the reference category (ruminants), it will be important to ensure that there is evidence to demonstrate that the MRL extrapolation criteria re. metabolism have been met.

If considering that camels could be sufficiently related to the reference category of ruminants, for those vet

drugs with very limited to no metabolism in ruminants and other food producing animals (e.g., aminoglycosides) or for which the ADI was established by JECFA based on the on a microbiological endpoint (minimal 50% inhibitory concentration or MIC_{50}), it would be advised for CCRVDF to consider whether these vet drugs be considered for MRL extrapolation to camels.

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