CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

Viale delle Terme di Caracalla, 00153 Rome, Italy - Tel: (+39) 06 57051 - E-mail: codex@fao.org - www.codexalimentarius.org

Agenda Item 10 **CX/RVDF 18/24/10**

January 2018

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Twenty-fourth Session

DISCUSSION PAPER ON THE EVALUATION OF THE RATIONALE FOR THE DECLINE IN NEW COMPOUNDS TO BE INCLUDED IN THE CCRVDF PRIORITY LIST FOR EVALUATION BY JECFA

(prepared by HealthforAnimals)

Introduction

1. Concern was expressed by HealthforAnimals at CCRVDF23 and prior, that newer veterinary drugs are not being put forward for Codex Alimentarius Maximum Residue Limits (MRLs) and subsequently a scientific risk assessment by JECFA, and that JECFA agendas are becoming populated by re-assessments of drugs previously evaluated by the Committee. At CCRVDF23, observer HealthforAnimals offered to prepare a discussion paper to consider the reasons for the decline in candidate substances for Codex Alimentarius MRLs and to identify causes and propose solutions. To prepare this paper, an independent expert was commissioned to interview 12 Codex member representatives, JECFA experts, the JECFA Secretariat, and sponsors. Eleven recommendations are made in this paper.

Benefits of JECFA evaluation

2. There is strong support for the work of JECFA from its own expert panel, from the secretariat, and from sponsors. Although JECFA and Codex are well-respected as standards setting international organizations, the same level of confidence for the Codex Alimentarius MRL adoption process is not shared by all.

3. The benefits of a JECFA evaluation, resulting in a positive outcome, including the subsequent development of a Codex Alimentarius standard, are recognized extensively. They include:

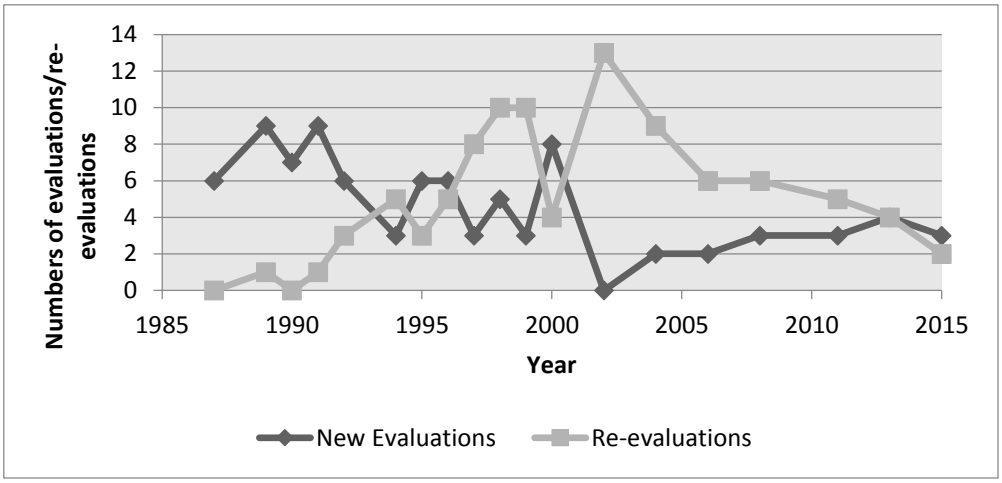
- a transparent risk assessment of a veterinary drug by a globally well-regarded and scientifically competent body that is transparent and free from political interference;
- an agreed international food standard; and
- a comprehensive risk assessment that can be used by other countries, including those without developed regulatory processes that will facilitate entry to the market or domestic use in those countries.

4. The assessments are essential for animal and public health in emerging and developing countries. They help to address food safety and public health challenges, and bring direct benefit to farmers, ranchers and consumers in developed, but especially in less-developed countries with more limited public resources.

Challenges

5. Figure 1 shows that the number of new drugs submitted for evaluation declined dramatically after 2000. In some years, the numbers of re-evaluations (evaluation of a compound previously evaluated) considered by the Committee predominated. The reasons for this are a complex mix of reasons that have a demotivating impact to submitters. They are set out in this paper and relate to: challenges in the process, lengthy timelines, risk that JECFA/Codex outcomes may negatively affect existing markets, costs, limited resources at FAO/WHO/Codex, changing food-animal market dynamics and uncertainty regarding national application of Codex standards.

Figure 1. New and Re-evaluations by JECFA for the Period 1987 to 2015



Process challenges

6. There is wide recognition that JECFA processes have improved over recent years to make the JECFA meeting itself more efficient, but further improvements are possible. Beyond the timing and cost challenges, set out further, there are process challenges built into the JECFA/Codex system.

7. JECFA sometimes applies different risk assessment approaches / principles to those taken by regulatory agencies. Some recent positive examples include the use of the Estimated Daily Intake (from median residues), and the further promotion of the Acute Reference Dose Concept including clarification on its use with respect to the microbiological ADI. While recognizing that JECFA must maintain its independence, better recognition and adoption of similar (national) scientific practices should facilitate the JECFA process and result in MRL values which would be more acceptable at CCRVDF (and more practical for sponsors). In addition, prior to implementing proposed changes related to ADI and MRL processes, it is worth publishing them and inviting public comment. This process could provide useful insights.

8. For example, the novel approach to consumer exposure, which may be justifiable on the grounds of regional consumption factors, might lead to the use of a greater portion of the ADI value (and lower MRLs and longer WDPs) thus leading to less scope for MRLs for other uses/commodities. Moreover, if the subsequent MRL values are markedly different from those established by regulatory agencies using the market basket approach, there is scope for disagreement.

9. It is worth noting that in VICH - a program aimed at harmonizing technical requirements for veterinary product registrations - many countries' regulatory agencies have devoted substantial effort to set, agree and apply common standards. It may be appropriate to consider the 50+ VICH guidelines and especially elements related to risk assessment to seek even more convergence.

10. While direct dialogue with assessors is possible in most major markets (CVM, CVMP, APVMA), JECFA no longer has assessor/sponsor hearings. The current JECFA approach of engaging in more preparatory work prior to the meeting, and e-mailing very specific questions to sponsors before the meeting is an efficient process. The decision was taken in the past to stop these hearings as they were not considered efficient and best use of time. Nonetheless, the lack of direct interaction has diminished opportunities to address panels questions directly and immediately in a discursive style.

11. One requirement for JECFA evaluation is that the active substance is contained in a veterinary medicinal product which is authorized/licensed/approved in at least one country. The reason for this is that without an authorization, there will be no agreed formulation, method of administration, dose regime, approved target species and withdrawal period, and therefore no approved label available. Removing this restriction, at least in part, might encourage sponsors to put forward more compounds for evaluation. For example, JECFA might consider conducting an evaluation based on a draft label. It could run a pilot based on this concept. The earlier a submission can be made to Codex, the faster a product can be available across multiple markets.

12. The policies for drugs that have "*a long history of safe use*" and the setting of provisional MRLs is no longer as freely applied as it was. This has led sponsors to be less inclined to submit products.

Recommendations for consideration

1) Because the novel approach to consumer exposure and specifically, its decision not to use the market basket in its evaluation is overly conservative, resulting in the use of a higher proportion of the ADI value, and leads to discrepancies to values determined by regulatory agencies, JECFA could reconsider the impact of using this approach. In general, such novel approaches should be more thoroughly assessed and implemented only after a transition time in which the new principle is proven to work.

2) Reintroduce hearings between sponsors and the Committee. For efficiency, these hearings should be focused and restricted to specific issues which have arisen during the evaluation process. They could be telecalls during committee meetings.

3) Reaffirm and use as needed the policy approaches associated with products that have "*a long history of safe use*" and the setting provisional MRLs.

Lengthy timelines

13. The overall timeline to develop an MRL, including the full step process after scientific assessment, is unduly long. Although there are exceptions, JECFA/CCRVDF timelines can take many years. The length of the process does not encourage sponsors to put forward compounds.

14. Following an initial submission of a sponsor dossier, and especially in cases where JECFA was unable to arrive at a positive conclusion, the period between JECFA meetings and uncertainty of when the next meeting might be held, creates uncertainty for the product, and that may persist for some time. If more data are requested by JECFA, and with JECFA meetings 1 to 1.5 years apart, then a published JECFA "negative opinion" remains in the public domain and is available for citation by consumers, authorities and competitors, with no opportunity for the sponsor to resolve the outstanding issues until the next JECFA meeting.

15. Even when JECFA has finished its assessment, the Codex step process means that an international food standard can take years to establish. This issue becomes even more problematic, and further uncertainty is created, if CCRVDF refers an assessment back to JECFA. Depending on the timing with respect to the next JECFA meeting, this can add a further year or longer to the process.

Recommendations for consideration

4) JECFA/Codex could consider ways of reducing the overall time for assessments, including the timing of the Codex multi-step process, actively seeking where efficiencies can be gained. For example, tools such as ad-hoc meetings and/or electronic meetings may be used more to consider specific substances.

5) It may be appropriate for Codex to appoint a "*chief trouble shooter*" from amongst the members, whose remit would be to work with the members, secretariat, sponsors and others to analyze timelines/processes and make recommendations how these can be reduced, without changing the multi-step process.

Risk that JECFA/Codex outcomes negatively affect existing markets

16. For sponsors, there is a significant risk in passing a product through the Codex process. The main uncertainty is that a positive assessment will not be completed (no ADI/MRL) or that a conclusion will be reached whereby the result does not facilitate commercial use (i.e. an ADI/MRL that is too low). Sponsors believe JECFA has an overly cautious approach regarding compounds already assessed for MRLs in leading competent regulatory authorities. Many times, MRLs could be set higher, consistent with an ADI that would facilitate trade while protecting human health.

17. CCRVDF rarely refines or overrules JECFA evaluations. In this way, CCRVDF de facto gives responsibility for MRL setting to JECFA. It is important for JECFA to propose the most practical MRLs possible, and in cases where they strongly differ from MRLs set in national markets, in cases where the ADI is not fully utilized, and when recommended (i.e. low) MRLs would prejudice international trade, CCRVDF should carefully consider these and adjust if needed.

18. Lack of predictability can also take the form of a referral from Codex back to JECFA for re-evaluations. This creates uncertainty and increases the time to establish MRLs. Or it can take the form of complete opposition to a substance or class of substances by a country/block of countries in the later steps of the Codex process on grounds other than consumer safety. Both negatively impact uptake of products authorized in multiple markets, and it increases reticence to submit future products to JEFCA/Codex process to establish MRLs.

19. On occasion, JECFA expresses concerns about products approved by leading global regulatory authorities, thereby implicitly questioning the authorities' competence. A negative assessment can cast doubt on the validity of existing national or multinational MRLs and their associated product licenses and could, at least in some circumstances, lead to marketing authorizations being suspended or even revoked, or new demands from regulatory authorities for the sponsor to address the points raised by JECFA.

20. Hence, a JECFA assessment can increase regulatory uncertainties, jeopardize existing authorizations and result in considerable expense or loss of market share (especially as competitors are likely to take advantage of this, e.g. by informing clients of a negative JECFA assessment).

Recommendations for consideration

6) Reserve should be taken by JECFA in expressing concerns over the safety of a drug which has already been evaluated and approved by the leading regulatory authorities. Like these regulatory authorities, attention should be given to consideration of the 3Rs policy (replace, reduce and refine) so that requests for data involving the use of experimental animals are only made when appropriate. If JECFA proposes a MRL that may have a negative impact on approvals by competent authorities, it should consider a discussion with the sponsor and the authorities prior.

7) In cases where public health and consumer protection are the issue, JECFA can request additional data, but requests for data over and above those already submitted to the world's leading regulatory authorities should only be made in exceptional circumstances. JECFA/Codex could draft a protocol of under which exceptional circumstances additional data request is warranted.

8) The possibility of allowing a sponsor to withdraw a drug from the process without adverse publicity, if the drug is likely to have an adverse JECFA assessment, that is not related to public health, should be available. In addition, JECFA could consider no publication of a recommendation until a final decision is reached.

Prohibitive cost

21. Cost is a concern with respect to submission. While dossiers from the available national major market submissions form the basis of the JECFA dossier, personnel-related costs are incurred within sponsor companies. When resources are stretched, as they frequently are, additional staff/consultants must sometimes be hired to construct the JECFA dossier. A JECFA submission is in competition with other development projects, and only the most interesting products with promising markets will be put forward. Given the cost, only large global companies can afford this.

22. The generation of data by a sponsor to achieve a JECFA assessment and Codex MRLs without any contribution, financial or otherwise, from generic suppliers, is a demotivator, and not equitable as the pioneer may not have the market share to support the generation of data. The benefits of JECFA/Codex standards are enjoyed by generic companies, but all the costs are carried by the large R&D-based companies – not a fair or tenable situation.

Recommendations for consideration

9) Sponsors could give indications of the financial costs of potential delays in the process as part of their submissions. In so doing, they will create awareness of the cost of delaying decisions to farmers, animal health, etc.

10) Suggest that means be found for national authorities to "*encourage*" generic suppliers to take their fair share of the cost burden.

Limited resources at FAO/WHO/Codex

23. The FAO component of JECFA is not adequately resourced. The secretariat has not received adequate resources to process products (in all sectors) through the JECFA process in the timely fashion desired. This will hopefully improve with the granting from unspent FAO funds in December 2017, of an additional $1.5 million to Codex scientific advice. It is hoped that this much-needed funding will be used to support additional resources to address workload issues at the secretariat, in the veterinary and other sectors. It is hoped this will help to accelerate processes.

Recommendations for consideration

See recommendations 4 and 5.

Changing food-animal market dynamics

24. The lower number of submissions is partly due to fewer products for food-producing animals coming to market. The reasons for this are: a) An increase in development time, substantial increases in cost, and sponsor recognition of the economic risks of pursuing new products that makes new investment more difficult to justify. b) Increasing regulatory requirements, most notably the required completion of additional studies and generation of more data, have significantly increased the overall cost and uncertainty of getting products to market. c) There are less incentives and therefore lower investments and less innovation in the food-animal market. There is an increasingly attractive market in selling generic products, the effect of which is to draw investment away from new product development. The companion animal health market has significantly increased over the last decade and has become comparatively rewarding. d) In animal health, the political climate for the commercial release of new antibiotics, variations of existing antibiotics, or production technology is unpredictable and therefore unattractive.

Recommendations for consideration

There are no recommendations because Codex has little influence on such market dynamics, but it would be helpful if Codex reiterated the importance of science-based decision-making.

Uncertainty regarding national application of Codex standards

25. Countries' lessening adherence to Codex adopted standards is a trend in many sectors, not just in veterinary medicine. In addition, the political approach of some countries - post-JECFA, in CCRVDF and CAC - towards products they deem undesirable, is problematic.

26. If a product with a positive JECFA assessment is rejecting or stalled in CCRVDF/CAC for political considerations, this casts doubt on the overall scientific credibility of the Codex process, though not on JECFA itself. Codex should seek a way forward that is: 1) not divisive, 2) but respects scientific assessment. Failure to do so will erode Codex credibility and relevance.

Recommendations for consideration

11) For Codex to be able to move forward with scientifically accepted standard-setting, Codex could consider ways in which it can strengthen countries adherence to collective and consensus-based Codex outcomes.

Old compounds

27. A separate yet related issue brought up by at CCRVDF23 relates to old compounds which are still widely used and for which there is no pharmaceutical sponsor. The challenge is to find innovative ways to use old data and thus accelerate the inclusion of these compounds in the priority list for JECFA evaluation. There is a need for innovative approaches to fill data gaps. Such novel approaches could be: systematic literature reviews, a requirement by the countries in question to try to collect data, in tandem with a recommendation that the top suppliers by volume contribute to collecting data.

28. Recognition and agreement to adopt national standards could be another approach (without a formal JECFA review or with only a limited review). As an example, JECFA conducted extensive reviews recently for amoxicillin and ampicillin and the results were identical to the European Union values used for many years. This outcome was generally predictable. Countries are reminded that they can always adopt other countries' MRLs if they are based on science.