

Residues of veterinary drugs in food

WHO procedural guidelines for the Joint FAO/WHO Expert Committee on Food Additives

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1. Introduction

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) is convened by both Organizations under their respective terms of reference for Expert Committees. This document describes the procedures used by WHO in its evaluation of veterinary drug residues in food; a separate document that is available at the web site given below describes the procedures used by FAO. While common procedures are used in most instances, separate guidelines for the two Organizations have been prepared because they have differing rules and regulations for expert committees and because the expertise required and the work done by experts invited by the two Organizations is different.

JECFA is convened according to WHO regulations for expert advisory panels and committees, the text of which was adopted by the Thirty-fifth World Health Assembly (resolution WHA35.10). The text is available at http://policy.who.int/cgi-bin/om_isapi.dll?softpage=Policy42 under "Basic Texts". The World Health Assembly and the Executive Board have authority to establish and dissolve Expert Committees, the Members of whom are selected by the Director-General from one or more Expert Advisory Panels, taking into account the need for adequate representation of different trends of thought, approaches, and practical experience in various parts of the world, as well as appropriate interdisciplinary balance. In selecting Members, account is also taken of the desirability of achieving gender balance.

The Committee evaluates substances in response to requests by FAO and WHO Member States and the Codex Alimentarius Commission. Separate meetings are held to assess either (i) residues of veterinary drugs in food or (ii) food additives and contaminants. Because the procedures are significantly different for the two types of assessments, separate guidelines have been prepared for food additives and contaminants, which are available at the web site given below.

Through the publication of reports and monographs (called evaluations), JECFA advises FAO, WHO, their Member States, and the Codex Alimentarius Commission (through the Codex

Committee on Residues of Veterinary Drugs in Foods, CCRVDF) regarding the safety of veterinary drug residues in edible products of animals. The reports of the meetings, which outline general considerations and summarize the evaluations of the veterinary drugs on the agenda, are published by WHO in the *Technical Report Series*. Toxicological monographs, which are based on working papers prepared by WHO Temporary Advisers, are published in the *WHO Food Additives Series*. Residues monographs, which are prepared by participants invited by FAO, are published in the *FAO Food and Nutrition Paper* series.

These notes are designed to provide guidance to the WHO Joint Secretary, Temporary Advisers, Members, and sponsors relating to the submission of data and their roles and responsibilities in dealing with the evaluation of residues of veterinary drugs in food. The guidelines outline the structure of the WHO Secretariat and its role in servicing JECFA, timetables to be followed in preparing for meetings, the appropriate handling of data, and appropriate relationships with sponsors, which in most cases are drug companies. Supplemental material is included that outlines the procedures by which veterinary drugs may be placed on the agenda (Annex 1) and procedures for issuing the call for data (Annex 2).

Close adherence to these guidelines by everyone involved will ensure that the concerns and views of all interested parties will be taken into account in the decisions of JECFA and that the independence and integrity of the evaluations are maintained, both in appearance and in actual fact.

2. Structure

Committees consist of 'Members' and 'Secretariat'. Members are responsible for making the decisions based upon their expertise and experience, the scientific information before them, and advice provided by the Secretariat. The Secretariat consists of the WHO and FAO Joint Secretaries, other employees of WHO and FAO who assist with preparation for the meeting, and WHO Temporary Advisers and FAO Consultants.

Experts who participate as WHO Members must be Members of a WHO Expert Advisory Panel. Although these are 'standing panels', JECFA is not a standing committee. Therefore, JECFA exists and can make decisions only during the time of the meeting itself. The Secretariat conveys the decisions of the Committee to the executive heads of FAO and WHO and to interested institutions, including the Codex, and individuals. The Secretariat cannot modify or amend the interpretation of data by JECFA. The only modifications to reports and monographs that may be made by the Secretariat are those of an editorial nature; changes of a substantive nature can only be referred to a subsequent meeting for consideration.

3. Selection procedures

WHO chooses Members on the basis of their scientific expertise in the areas under consideration, which include toxicology, pharmacology, metabolism, microbiology, pathology, epidemiology, veterinary medicine, and molecular biology. A balance between academic and regulatory experience and geographical distribution are important. Members are invited directly by the Secretariat as independent scientific experts, and they do not represent their employers, governments, or other institutions. Their travel expenses are paid by WHO; honoraria are not provided.

Several sources are used for identifying appropriate scientists to serve as Members of JECFA. These include direct solicitations by WHO to governments and other organizations for nominations, unsolicited recommendations to WHO, experience in working with scientists at previous Expert Committee or other scientific meetings, and reviews of scientific publications.

Members of the Committee invited by WHO must be Members of an Expert Advisory Panel, most of whom are appointed to the Food Safety Panel. Members of Panels are considered for

appointment after consultation with relevant national authorities. They are appointed by the Director-General, in consultation with Panel secretaries, Regional Directors, and WHO programme coordinators, giving consideration primarily to their technical ability and experience, but also endeavouring to ensure that panels have the broadest possible international representation in terms of diversity of knowledge, experience, and approaches in the fields for which the panel has been established. Appointment is for a maximum of four years, but membership can be renewed.

WHO enlists the help of relevant agencies in its Member States and academic and research institutions to identify scientists to serve as Temporary Advisers. Temporary Advisers must be given time during working hours by their employers to perform the large amount of preparatory work that goes into the evaluations, which is a contribution of the institution to WHO.

Criteria that are used by WHO for the selection of Temporary Advisers include:

- < The person must be a toxicologist (or expert in a related field) as evidenced by suitable training and adequate relevant experience.
- < He or she must have practical experience in reviewing, analyzing, evaluating, and extrapolating mammalian biological data on toxic chemicals to humans.
- < The person must have ready access to other experts and must be able to obtain and utilize information from a variety of scientific specialties to assist in resolving differences among advisers, consultants, Members, and industry personnel.
- < Because the meeting is conducted in English and the vast majority of the relevant literature and reports are published in English, a good working knowledge of English is required.
- < Adequate time must be made available to him or her for preparing working papers.
- < The scientist must be able and willing to maintain the security of confidential data.

Both Members and Temporary Advisers are required to disclose in writing all circumstances that could lead to potential conflicts of interest. When an interest is declared on a particular substance, the scientist does not participate in its evaluation.

4. Responsibilities

The International Programme on Chemical Safety (IPCS) is responsible for servicing the WHO Secretariat of JECFA.

4.1. WHO Joint Secretary

The WHO and FAO Joint Secretaries have overall responsibility for organizing the meeting, inviting participants, ensuring that the appropriate documentation is prepared, servicing the meeting while it is in session, and editing and the publishing the report and evaluations in a manner that faithfully reflects the conclusions of the Committee. Specifically, the WHO Joint Secretary:

- schedules meetings and develops the agenda in collaboration with the FAO Joint Secretary;
- prepares and publishes, both in print and on the FAO and WHO web sites, requests for data for the meeting, in collaboration with the FAO Joint Secretary;
- identifies and arranges for the selection and invitation of Members and Temporary Advisers;
- solicits and coordinates the submission of data and their distribution to appropriate Members and Temporary Advisers;

- coordinates the preparation of working papers, ensuring liaison between the authors and peer reviewers;
- represents the WHO Secretariat at JECFA meetings;
- works with CCRVDF to ensure that as many priority substances as possible are evaluated by JECFA and to explain the basis for the evaluations after they have been performed;
- prepares summaries of the conclusions as soon after the meetings as possible in collaboration with the FAO Joint Secretary and places them on the WHO web site;
- oversees technical editing of the reports (in collaboration with the FAO Joint Secretary) and toxicological evaluations and arranges their publication;
- provides information about JECFA and its evaluations to governments, organizations and individuals and at scientific meetings;
- maintains an up-to-date roster of experts on veterinary drug residues from which future Members and Temporary Advisers can be drawn; and
- updates the *Summary of evaluations performed by JECFA*.

4.2. Temporary Advisers and Members

Working papers are prepared by Temporary Advisers in coordination with the WHO Joint Secretary. Temporary Advisers are members of the Secretariat during the time that they are preparing working papers and attending JECFA meetings. The general responsibilities of Temporary Advisers and Members include:

- acting in their individual capacities as experts and not as representatives of any organization;
- maintaining the integrity and security of all commercial data to which they have access as part of their work for JECFA;
- performing literature searches on the substances for which they have responsibility;
- abiding by the terms set out in the instructions provided for the declaration of interests; and
- working closely with each other to prepare working papers in the form of summaries of the data (Temporary Advisers) and draft evaluations (Members) in sufficient time for distribution and review before the meeting.

4.3. Sponsors

COMISA (Confédération Mondiale de l'Industrie de la Santé Animale) assists the Secretariat in disseminating the agendas for JECFA meetings and helps ensure that the manufacturers of veterinary drugs know that their products are on the agenda. COMISA routinely provides names of relevant individuals with whom to correspond relating to the substances on the agenda.

Manufacturers have the responsibility to submit all relevant published and unpublished data, including individual animal data, that are available on the veterinary drugs on the agenda, except for those data previously evaluated by the Committee, as described in the request for data issued by the FAO/WHO Secretariat. Confidential information pertaining to manufacturing trade secrets (such as manufacturing processes), if submitted, should be clearly identified so that this information will not be published in the monographs.

5. Procedures

The Temporary Adviser summarizes the available data and provides comments on the relevance and significance of the data when preparing his or her working paper. All sections are prepared except for the **Toxicological evaluation** section (see the companion document, *Guidelines for the preparation of working papers on veterinary drugs*, which is available on the WHO web site provided on the first page of this document). The working paper is sent to the Member who has been assigned to peer review it, with instructions to comment on it and propose an evaluation. A **consolidated** working paper is then prepared by the Temporary Adviser, based on the Member's comments and proposed evaluation.

5.1. WHO Joint Secretary

The Joint Secretaries distribute a call for data on the compounds on the agenda 10-12 months in advance of the meeting, both in paper form and on the internet. The compounds are selected on the basis of priority lists established by CCRVDF, requests by FAO and WHO and their Member States, and recommendations of earlier meetings of JECFA (see Annexes 1 and 2). The deadline for submission of data is ordinarily 6-7 months before the meeting.

Before the deadline for receipt of data, the WHO Joint Secretary will assign individual veterinary drugs to scientists who have agreed to serve as Temporary Advisers, taking into account their wishes, experience, and expertise. The Joint Secretary will then provide to the data sponsor (manufacturer) the name and address of the scientist who will be reviewing the data in this capacity. [The sponsors either identify themselves directly to the Joint Secretary or they are identified through other means, with primary coordination through COMISA.] The sponsor is requested to send one copy of its dossier to the Temporary Adviser and one copy to the Joint Secretary at WHO Headquarters for use as a reference copy at the meeting. The Joint Secretary will ask the sponsor to prepare and send a third copy of the dossier to the Member who will be assigned to peer review the working paper 3-4 months before the meeting.

The Joint Secretary will provide guidelines for the preparation of working papers and procedural guidelines to the Temporary Advisers and Members, along with other information and instructions, at the time that the assignments are made or shortly thereafter.

The WHO Joint Secretary, in coordination with the FAO Joint Secretary, will provide the scientists involved with the evaluation of a particular veterinary drug contact information on the other scientists involved with its review, i.e. the WHO Temporary Adviser and Member and the FAO scientist preparing the residues monograph. The Temporary Adviser and WHO Member will be encouraged to work together to prepare a consolidated working paper and to work with the FAO scientist on cross-cutting issues relating to toxicology and residues.

The WHO Joint Secretary will ask Temporary Advisers to submit legible written copies or electronic files of their consolidated draft working papers to the WHO Joint Secretary in sufficient time so that they are received no later than 1.5-2 months before the meeting. The Joint Secretary will then distribute working papers to the sponsor (without the evaluation section), who will be asked to review it for its technical accuracy, and to participants of the upcoming meeting for review. Shortly before the meeting the Joint Secretary will produce a sufficient number of the draft or revised working papers for all participants and will distribute them at the meeting.

When a sponsor makes available unpublished proprietary data for evaluation, the Joint Secretary safeguards the data from unauthorized disclosure. To ensure that the copies that are sent to the Temporary Adviser and Member are safeguarded, they are requested to acknowledge in writing that they accept the conditions that have been laid out for their use and storage. When the data are no longer needed, the Secretariat either returns the data file at the manufacturer's expense or destroys it, depending upon the wishes of the sponsor.

5.2. Temporary Advisers

The Temporary Adviser must safeguard all proprietary data. He or she may not make copies of any part of the file or share or use the data for any purpose other than the JECFA assignment. Upon completion of the assignment, the Temporary Adviser should either return the data file to the sponsor or destroy it, depending upon the wishes of the sponsor. Non-adherence to these procedures will result in removal of the Temporary Adviser from the activity.

The Temporary Adviser should perform a literature search on the compounds assigned to him or her. ***It is extremely important that literature searches are performed***, especially on veterinary drugs that have been in use for a long time in human and/or animal medicine.

The Temporary Adviser will contact the sponsor and request submission of studies that he or she knows have been reported elsewhere but have not been included in the data package if they are likely to be relevant to the evaluation. If the sponsor is unresponsive to this request, the Temporary Adviser should note the potential impact of the missing data on the evaluation.

If full reports of studies are not submitted, the Temporary Adviser will request them, including individual animal data, from the sponsor as soon as possible.

The Temporary Adviser will work closely with the Member assigned to peer review the draft to ensure that the comments and proposed evaluation of the Member are considered and included. The Temporary Adviser will submit a legible printed or electronic copy of the consolidated working paper to the WHO Joint Secretary 1.5-2 months before the Joint Meeting. ***It is extremely important that this timeframe is met***, because this amount of time is necessary to distribute the working paper to participants, give them an opportunity to review it, and provide comments to the author. If significant comments are submitted, the Temporary Adviser will revise the working paper and submit it to the WHO Joint Secretary in sufficient time so that copies can be produced before the meeting. To avoid the possibility of improper influence on the author by the sponsor, the draft working paper should not be sent to the sponsor by the Temporary Adviser; it will be sent to the sponsor by the WHO Joint Secretary (without the evaluation section), with a request to verify its accuracy and to provide a copy of comments to the Temporary Adviser at the time that they are submitted to the Secretariat.

After the meeting the Temporary Adviser will modify those working papers that will be published as toxicological monographs or monograph addenda to accurately reflect the decisions of the Committee. The Temporary Adviser will be invited to stay for a day after the meeting to make these modifications, as they should be made before the Temporary Adviser leaves the meeting site.

5.3. Members

Members of JECFA are the decision-makers, and as such are responsible for conducting the meeting. As noted earlier, Members invited by WHO must be Members of a WHO Expert Advisory Panel. The chairman, vice-chairman, and rapporteur must be Members of the Committee.

Members of the Committee will be assigned as peer reviewers of working papers prepared by Temporary Advisers and to propose evaluations. They will be expected to work with the Temporary Advisers during the last stages of the preparation of the working papers. Copies of the dossiers on the substances on which they will be reviewing the working papers will be sent to the Member by the sponsors.

The Member will inform the Secretariat of relevant unpublished studies that he knows have been reported elsewhere but have not been included in the data package submitted by the sponsor. He should note the potential impact of the missing data on the evaluation.

Members should attend the entire meeting, because they are the ones who make the final decisions concerning the evaluations.

5.4. Sponsors

Submission by sponsors of summaries of data using the working paper format described in the *guidelines for the preparation of working papers*, which are available on the WHO web site provided on the first page of this document or by request from the WHO Joint Secretary, is encouraged, but such summaries are not sufficient in themselves for a full evaluation. All reports must be complete and supported by the detailed data generated during the experimental phase of the study.

Dossiers should be submitted in triplicate, one copy going to the Secretariat at WHO Headquarters, one to the Temporary Adviser who is preparing the working paper, and the other to the Member who has been assigned to peer review the working paper. The sponsor should contact the Secretariat to learn the identities of the Temporary Adviser and Member before sending data. If the sponsor would like to have the dossiers returned (at his expense) after they have been used by JECFA, it should be so indicated at the time of submission. If such instructions are not received, the files will be destroyed.

Data should be submitted by the deadline established by the Secretariat. Late submission may result in a delay in the preparation of the working paper or may even delay consideration to the following JECFA meeting devoted to the evaluation of residues of veterinary drugs in food.

When data on veterinary drugs having temporary ADIs are not provided for consideration at the meeting in the year in which the temporary ADI expires, the temporary ADI is unlikely to be extended by the Committee unless the Secretariat is supplied with an adequate explanation for the need for extra time to generate the information.

Working papers are sent to the sponsors for the exclusive purpose of verifying their accuracy and they are not to be distributed or used in any other way.

6. Relationship between the Secretariat and sponsors

It is important that sponsors' information and views relevant to their submissions are fully taken into account, while at the same time it is important that JECFA's evaluations of the data are not influenced or inhibited by actions of the sponsors, either in fact or in appearance. To accommodate these requirements, the following procedures for the interaction of Temporary Advisers with sponsors have been established:

- < The Temporary Adviser may contact the sponsor for clarification of issues, at the Temporary Adviser's discretion. If the Temporary Adviser does not wish to communicate directly with the sponsor, he may communicate through the WHO Joint Secretary. However, direct interaction is encouraged.
- < Copies of all exchanges of information and correspondence, including memoranda of telephone conversations, should be sent by the Temporary Adviser to the WHO Joint Secretary. The Joint Secretary will file these communications and will make them available to the Committee upon request.
- < The sponsor will not contact the Temporary Adviser except to inform him that additional information is available. Any other information that the sponsor wishes to convey should be sent to the WHO Joint Secretary.
- < The Temporary Adviser should report to the WHO Joint Secretary any undue industry pressure. Industry abuse will be reported by the Secretariat to COMISA.

- < Temporary Advisers not adhering to these procedures regarding interactions with sponsors may be removed from the activity.

To ensure that sponsors' views are taken into account, they will be given the opportunity to participate in a scientific dialogue in association with the submission of their data at the time of the JECFA meeting. COMISA and the Secretariat will, between them, make the necessary arrangements for the participation of the sponsors at a time when the Committee goes out of session for this purpose.

Annex 1. Procedures for placing veterinary drugs on the agenda

Requests for the evaluation of certain veterinary drugs and consideration of issues of a general nature by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) may come from a number of sources:

1. Codex committees

The Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) refers substances to JECFA based on priorities that it establishes using criteria that it has developed that are in accord with accepted procedures of the Codex Alimentarius Commission.

2. FAO and WHO Member States

FAO and WHO Member States may request the inclusion of veterinary drugs on the agenda of JECFA through a direct request to the FAO and WHO Secretariats. Such a request must be accompanied by a commitment to provide the necessary data 6-7 months before the meeting.

3. Sponsors

For veterinary drugs not previously evaluated by JECFA, an industry sponsor may forward a request for evaluation through the government of a Member State to CCRVDF, with a commitment to provide the relevant data. Requests for the re-evaluation of a veterinary drug that has been reviewed by JECFA previously may be forwarded directly to the JECFA Secretariat. As with all other substances on the agenda, the Joint Secretariat includes the substance in the call for data for the meeting to ensure that all interested parties have the opportunity to submit data.

4. JECFA Secretariat

The JECFA secretariat may place a veterinary drug on the agenda for re-evaluation even though no outside request has been received.

5. JECFA itself

The Committee often establishes a temporary ADI or recommends temporary MRLs, with a request for further data by a certain time. These veterinary drugs, which have the highest priority for evaluation, are placed on the agenda of the appropriate meeting by the Joint Secretariat.

Annex 2. Procedures for issuing the call for data

The Joint Secretariat issues a call for data on the veterinary drugs on the agenda 10-12 months before the meeting, which is posted on the FAO and WHO web sites and is sent to Codex and other contact points. The substances are selected on the basis of priority lists that are established as outlined in Annex 1. The deadline for submission of data is normally 6-7 months before the meeting. The late submission of data may result in the postponement of the evaluation to a future meeting.

Before inclusion of a substance on an agenda for the first time, the JECFA Secretariat will have received a positive indication that there will be one or more submitters of data for the evaluation, or that the data are available from other sources such as a government organization or the published literature. For substances that are being re-evaluated, for example those that have a temporary ADI, the Secretariat assumes that the sponsor of the original evaluation will be providing the necessary data unless informed otherwise.

The Joint Secretary will provide those submitting the data with the names and contact details of the individual(s) that have been assigned the responsibility to prepare the working paper. When for any reason the data submitter does not send information to the scientists preparing the working paper, the Joint Secretary will ensure that copies of the data that were sent to WHO Headquarters are sent to them.

When a sponsor makes available unpublished proprietary data for evaluation, the Joint Secretary and Temporary Adviser will safeguard the data from unauthorized disclosure. Temporary Advisers are required to acknowledge that they accept these conditions. When the data are no longer needed the Joint Secretary and Temporary Adviser will either return the data file to the submitter at his/her expense or will destroy them, depending upon the data submitter's wishes. Those submitting data are requested to inform the Joint Secretary and Temporary Adviser at the time that they submit them whether they wish data to be returned. In the absence of guidance, the data will be destroyed.

The JECFA Secretariat sometimes receives requests to include substances on the agenda that have been evaluated previously after the initial *call for data* has been issued. Such requests are considered in the light of (a) the time schedule of the meeting and (b) whether addition of the item on the agenda is urgent. Such late requests are generally discouraged, and the veterinary drug will not be placed on the agenda if notice is given so late that publication of a supplemental call for data is impractical, unless it is an emergency situation. Under this circumstance the veterinary drug will normally be placed on the agenda of a later meeting for evaluation.