codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 9 **CX/RVDF 09/18/9 Part 2**
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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Eighteenth Session

Natal, Brazil, 11-15 May 2009

DISCUSSION PAPER ON CURRENT PRACTICES AND NEEDS FOR FURTHER WORK BY THE COMMITTEE

(Report of the electronic Working Group on Risk Management Topics and Options)

SECTION I :

COMMENTS RECEIVED IN RESPONSE OF THE CIRCULAR LETTER CL 2007-37-RVDF PART 3 (UP TO AUGUST 25TH, 2008)

AUSTRALIA

Australia welcomes the opportunity to comment on these matters and we provide the following comments in response to Part C of CL2007/37-RVDF:

i. Use of the Estimated Daily Intake Concept (JECFA approach)

Australia supports the use of the Estimated Daily Intake concept by JECFA. The adoption of the approach together with estimates of the safety of short-term exposure (acute intake) is scientifically sound and brings the risk assessment approaches of JECFA and JMPR closer together. There is no scientific reason for the extent of the difference in dietary intake calculations between JECFA and JMPR, and Australia encourages an ongoing dialogue and exchange of ideas between the two committees.

In general terms, Australia also supports mechanisms to encourage better liaison and improved harmonisation between JMPR and JECFA in relation to risk assessment. Australia also supports harmonisation between JMPR/JECFA through consideration of all the recommendations from the FAO/WHO workshop on agricultural and veterinary drug residue risk assessments (Bilthoven 2005).

ii. Utilisation of the full ADI

In relation to use of the entire ADI in determining MRLs, Australia supports MRLs being developed that are relevant to appropriate use (i.e. Good Practice in the use of Veterinary Drugs [GPVD] rather than being theoretically calculated from the ADI). MRLs should be set at levels that can monitor GPVD. Australia notes that the JMPR takes into account MRL recommendations of JECFA when conducting its dietary risk assessments and that JECFA also notes the intake assessments of JMPR. Adoption of the EDI concept by JECFA will assist the two expert committees in reconciling their respective dietary risk assessments.

iii. Starter Cultures

Australia is not convinced that starter cultures need be considered by Codex in establishing MRLs that do not compromise the safety of consumers and can be used for trade purposes. Australia notes that for regulators this issue may form part of the assessment of a chemical product and in this context the Australian Pesticides and Veterinary Medicines Authority has developed a guideline in relation to dairy starter cultures.

iv. Appending Risk Management Recommendations to MRLs

Australia notes that this issue relates to whether additional recommendations on risk management could be provided by the Committee when it establishes MRLs. Australia does not support the use of such recommendations as these are matters that are to be addressed by national authorities within each individual country.

ISLAMIC REPUBLIC OF IRAN

Iran is not agreed with the use of EDI and full ADI. Although use of full ADI is scientifically justifiable within the current bases for Risk assessment however due to the possible extra-label use of veterinary drugs and possible uses in minor species it is recommended not to use full ADI to provide an extra safety margin.

Finally, it is suggested to extend establish MRLs for routine veterinary drugs in cattle, goat and sheep edible's offal such as rumen, abomasums and brain

UNITED STATES OF AMERICA

Use of the Estimated Daily Intake (EDI)

The EDI approach was discussed in detail during the 66th JECFA meeting in 2006. Historically, a theoretical maximum daily intake (TMDI) has been calculated based on MRL residues for each of the edible tissues. The residue concentrations were totalled and compared to the (toxicological or microbiological) ADI to assure that the human consuming each of the edible tissues containing residues at the MRL concentration would not be exposed to cumulative (all meats plus milk and eggs, where applicable) residues above the acceptable daily intake. The JECFA concluded that a median concentration of measured residues, rather than the theoretical MRL concentration (the upper one-sided 95% confidence limit over the 95th percentile for the same time point), represents a more realistic estimate of central tendency of the residue concentration over a prolonged period of time. As a result, the Committee decided to use the median of the residue distribution to substitute for the MRL in the intake estimate, and to call this value the "estimated daily intake" or EDI.

Recognizing the inherent assumptions, the delegation of the United States supports the EDI approach and agrees that it represents a more realistic estimate of the residue exposure over a prolonged period of time.

Utilization of the Full ADI

Utilization of the full ADI is, in the current context, a discussion of how the MRLs are recommended and compared to the ADI.

The general approach for the development of a maximum residue level (MRL) was discussed in detail as long ago as the 34th JECFA (1989) where the Committee noted that the MRL would depend on whether the ADI or Good Practice in the use of Veterinary drugs was used as the basis for calculation. By the 36th JECFA, the following process was described:

> *The first step in establishing a recommended MRL is the determination of an Acceptable Daily Intake (ADI) based on the available toxicological data. If the use of the veterinary drug according to good practice in the use of veterinary drugs yields concentrations of residues lower than those corresponding to the ADI, the MRL will be reduced accordingly. However if the residues cannot be measured using a practical analytical method under these conditions of use, the MRL will be raised so that compliance with the MRL may be checked analytically. In no instances, however, will an MRL be recommended at concentrations that significantly exceed the MRL based on toxicological considerations.*

This approach, and definition, has been refined over the years so that the 17th edition of the Codex Alimentarius Commission Procedural Manual provides the following:

> *Codex maximum limit for residues of veterinary drugs (MRLVD) is the maximum concentration of residues resulting from the use of a veterinary drug (expressed in mg/kg or µg/kg on a fresh weight basis) that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food.*
>
> *It is based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI) or on the basis of a temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects.*
>
> *When establishing an MRL, consideration is also given to residues that occur in food of plant origin and/or the environment. Furthermore, the MRL may be reduced to be consistent with good practices in the use of veterinary drugs and to the extent that practical analytical methods are available.*

It is noted here that under the current definition an MRLVD is first established "based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI)." This approach, if followed, would allow use of the full ADI in establishing the MRL. Under the current approach, MRLs recommended to Codex by the JECFA are typically further refined (reduced) by the consideration of good practices in the use of veterinary medicine, by other relevant public health risks, and by food technological aspects. Many of these refining criteria are not directly related to food safety.

The delegation of the US strongly emphasizes the importance of promulgating MRLs that are based on food safety. To that end, the US recommends additional discussion in the following areas:

1. Daily residue exposure, as determined through either the traditional TMDI or the recently elaborated EDI approach, if calculated based upon cumulative consumption of edible tissues to the full market basket amount, will overestimate true dietary exposure. The US proposes recommending MRLs using an exposure calculation that recognizes a more realistic daily consumption of meats, respecting that eggs and milk are separate commodities. It is more reasonable to presume that on any given day the consumer of a meal derived from muscle will not regularly also have a meal from kidney, and so forth; therefore it is appropriate to calculate daily cumulative exposure (preferably using the EDI approach) based on only one meat plus milk plus eggs (where applicable) with MRLs assigned accordingly.
2. The delegation of the US believes that the determination of the ADI represents an adequately conservative estimate of safety for consumption of veterinary residues in the human diet; therefore there is no additional food safety benefit gained by further restricting MRLs based on the residues that result under good veterinary practices. In addition, a restriction of residues below levels that are already deemed to be safe may adversely impact the availability of otherwise safe and effective veterinary drugs. Furthermore, recommending MRLs that are reflective of the performance limits of available analytical methodology, while facilitating adequate monitoring for residues, results in an analytical method more exacting than that needed to ensure food safety. As a consequence, such an approach may place developing/emerging countries at a technological disadvantage. Similarly, MRLs that are lower than needed to protect the public health may result in the discard of safe food in countries where available animal protein is limited.
3. The delegation of the US supports further discussions on the use of food technology considerations in risk management. However, the US maintains that food technology considerations are not, fundamentally, issues of food safety and, as such, they should not be used in the recommendation of MRLs. The US recommends that food technological aspect considerations are more appropriately provided as risk management recommendations to the member countries as was recently done in the 16th CCRVDF meeting[1].
4. Finally, the delegation of the US supports further discussions on the use of regional consumption values in developing MRLs and evaluating dietary exposure to veterinary drug residues. The US delegation encourages member nations to provide available consumption information to forward these discussions.

Starter Cultures

At the 16th Session of CCRVDF, the Committee agreed to advance a maximum residue limit (MRL) for pirlimycin in cows' milk that was based of human food safety and include the following footnote:

> *JECFA evaluated the effect of pirlimycin residues on starter cultures and for this reason recommended an MRL of 100 µg/kg of milk. Codex Members may therefore adapt national/regional MRLs in order to address this technological aspect for trade of fresh liquid milk intended for processing using starter culture*.[2]

As currently defined in the Codex Alimentarius Commission Procedural Manual, 17th ed., an MRL is set:

> *based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI), or on the basis of a temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects.*

Based on the Committees decision with regards to pirlimycin in cows' milk at the 16th Session, the United States would like to propose that the EWG on Risk Management Topics and Options recommend a revised definition of an MRL to the Committee. The United States proposes that the Codex definition of an MRL be revised to exclude food technological aspects as the basis for setting MRLs as they are not directly related to food safety. Instead, the United

[1] The 16th CCRVDF agreed to advance the MRL for Pirlimycin in milk to Step 8 based on the food safety consideration of 200 micrograms/kg with a footnote that allows Codex members to adopt a national/regional MRL to address the technological aspect for trade of fresh liquid milk intended for processing using dairy starter cultures.
[2] ALINORM 06/29/31 para 60.

States would support adding similar language, as was included with the MRL for pirlimycin, as a risk management statement.

In the "Discussion Paper on Risk Management Topics and Options for the CCRVDF" (CX/RVDF 07/17/13), it was noted that some members of the EWG would support the consideration of food technological aspects in the establishment of an MRL because the approach is used at their national levels. While United States appreciates these differences in processes, it is important to note that Member Counties are not excluded from elaborating on any established Codex MRL at their national level. By appending such risk management statements as was included for pirlimycin in cow's milk, countries will still receive guidance on food technological aspects. Setting an international standard based on reasons other than food safety, will result in lower MRLs, longer withdrawal periods, and, in the case of dairy products, unnecessary discard of milk.

Appending Risk Management Recommendations to MRLs

At the 14th Session of CCRVDF, the Committee added doramectin in cows' milk to the priority list of veterinary drugs for evaluation or re-evaluation by JECFA.[3] The 62nd JECFA recommended a new MRL for cows' milk, but noted that the necessary discard times are very long and unlikely to be consistent with good veterinary practice. At the 15th Session of CCRVDF, some delegations expressed concern over the inclusion of the additional footnote with the MRL for doramectin in cows' milk, stating that the footnote may raise unnecessary concerns for food safety and might give grounds to countries to deny product authorizations. Other countries were supportive of inclusion of the footnote, stating that it provided good guidance to countries where the drug was not authorized for use in lactating cows or it was recently introduced. The MRL was advanced to Step 5 with the attached footnote during that session.[4] At the 16th Session of CCRVDF, the footnote was simplified to read "Depending on the route and/or time of administration, the use of Doramectin in dairy cows may result in extended withdrawal periods in milk. This may be addressed in national/regional regulatory programmes." With the revised footnote, the Committee agreed to advance the MRL for doramectin in cows' milk to Step 8.[5]

The United States is in support of appending risk management recommendations to MRLs as a means of providing guidance on Good Veterinary Practice or, as in the case of pirlimycin in cows' milk[6], food technological aspects. As these factors are not directly related to human food safety, they should not be considered when setting MRLs. The United States supports further discussion within the electronic working group to determine when and how risk management statements should be appended or otherwise associated with an MRL.

IFAH

The International Federation for Animal Health (IFAH) submits the following information on current practices and suggestion for the scope of further work by CCRVDF on: i) Use of the Estimated Daily Intake (EDI); ii) Utilization of the full ADI; iii) Starter cultures; and iv) Appending risk management recommendations(s) to MRLs.

i) The Joint Expert Committee on Food Additives has historically made very conservative assumptions in calculating the MRLs in the various edible tissues of food producing animals. As evidence of this practice has been the suggestion by various governments and international organizations that Codex and JECFA should consider other procedures such as regional consumption factors (recommendation by the Bilthoven Workshop) and the full utilization of the ADI. At its 66th meeting in 2006, JECFA changed its procedures for calculating MRLs by calculating an Estimated Daily Intake (EDI) rather than the historical theoretical maximum daily intake (TMDI). The EDI uses the mean residue value in each of the tissues rather than the theoretical maximum residue concentration (the upper one-sided 95% confidence limit over the 95th percentile for the same time point). The EDI represents a much less conservative approach to establishing MRLs than the TMDI procedure. However, the EDI approach is still very conservative as it assumes an individual will consume all edible tissues containing residues at the MRL every day for a life time. This approach becomes even more conservative when the risk managers establish withdrawal periods that ensure every tissue in every animal will not contain residues in excess of the MRL. IFAH recommends that the CCRVDF Working Group on Risk Management Options and Topics consider methods for calculating the MRLs in conjunction with a full utilization of the ADI and develop procedures for calculating MRLs that are protective of human health but also recognize a more realistic consumption of edible tissues, eggs and milk.

ii) See discussion in i). The definition of an MRLVD is primarily "based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake

[3] ALINORM 03/31A para 113.
[4] ALINORM 05/28/31 paras 84-87.
[5] ALINORM 06/29/31 paras 62-63.
[6] The 16th CCRVDF agreed to advance the MRL for Pirlimycin in milk to Step 8 based on the food safety consideration of 200 micrograms/kg with a footnote that allows Codex members to adopt a national/regional MRL to address the technological aspect for trade of fresh liquid milk intended for processing using dairy starter cultures.

(ADI). MRLs are currently reduced using "good veterinary practice" arguments, other relevant public health risks, and food technological aspects. The working group should consider when issues not relating to food safety should be used in determining the MRLVDs.

iii) The 16th Session of CCRVDF made the decision to advance a maximum residue limit (MRL) for pirlimycin in cows' milk that was based solely on human food safety. This decision should set the precedent for determining all MRLVDs in milk. The working group should recommend to the Codex Committee on General Principles and the Commission that the consequential amendments to the Procedural Manual be made.

iv) IFAH supports the appending of risk management recommendations to MRLs; however, when the recommendations are not directly related to human food safety, they should not be considered when setting MRLs. IFAH supports further discussion on this issue within the working group.

SECTION II:

ADDITIONAL COMMENTS RECEIVED BY THE CHAIR OF THE ELECTRONIC WORKING GROUP

ARGENTINA

Argentina won't be making any comments on these topics on this occasion.

CANADA

Canada would like to offer the following comments on Part C, of the circular letter (CL 2007/37-RVDF) included with the Report of the 17th Session of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) (ALINORM 08/31/31):

Use of the Estimated Daily Intake (EDI)

Background:

Historically, a theoretical maximum daily intake (TMDI) has been calculated based on Maximum Residue Limit (MRL) for each of the edible tissues. The residue concentrations were totaled and compared to the (toxicological or microbiological) ADI to assure that the human consuming each of the edible tissues containing residues at the MRL concentration would not be exposed to cumulative (all meats plus milk and eggs, where applicable) residues above the acceptable daily intake.

The EDI approach was discussed in detail during the 66th JECFA meeting in 2006 and JECFA concluded that a median concentration of measured residues, rather than the theoretical MRL concentration (the upper one-sided 95% confidence limit over the 95th percentile for the same time point), represents a more realistic estimate of central tendency of the residue concentration over a prolonged period of time. As a result, the Committee decided to use the median of the residue distribution to substitute for the MRL in the intake estimate, and call this value as the "estimated daily intake" or EDI.

Comments:

The delegation of Canada proposes reconsideration of the new method "estimated daily intake" or EDI for the estimation of chronic dietary exposure of residues that had been implemented at the 66th JECFA Meeting in 2006 for the following reason:

Using the median of the residue data excludes the 50% of residue data higher than median. Furthermore, recognizing that MRL should cover the worst case scenario this approach will underestimate true dietary exposure over a prolonged period of time. The previous approach "theoretical maximum daily intake (TMDI), calculated based on the theoretical MRL residues for each of the edible tissues is more realistic than the new approach and it will cover the safety of 95th percentile of population with 95% confidence.

Utilization of the Full ADI

Utilization of the full ADI is, in the current context, a discussion of how the MRLs are recommended and compared to the ADI.

Background:

The latest definition for maximum residue limit can be found in the 17th edition of the Codex Alimentarius Commission Procedural Manual provides as follows:

> *Codex maximum limit for residues of veterinary drugs (MRLVD) is the maximum concentration of residues resulting from the use of a veterinary drug (expressed in mg/kg or µg/kg on a fresh weight basis) that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food.*
>
> *It is based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI) or on the basis of a temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects.*
>
> *When establishing an MRL, consideration is also given to residues that occur in food of plant origin and/or the environment. Furthermore, the MRL may be reduced to be consistent with good practices in the use of veterinary drugs and to the extent that practical analytical methods are available.*

Comments:

Canada utilizes an approach of using full ADI for individual tissues "based on the standard 500g meat" to establish MRLs. By definition a MRL is a level of residue that could safely remain in the tissue or food product derived from a food-producing animal that has been treated with a veterinary drug. This residue is considered to pose no adverse health effects if ingested daily by humans over a lifetime. However, JECFA uses actual residue levels (not maximum levels) based on good animal husbandry practices and calculate intake exposure of each tissue plus other food commodities (e.g. milk, egg, etc.) in a food basket concept by applying TMDI or EDI methods. Total calculated intake estimate is then compared to the full established ADI and must be lower. In case, the total intake estimate is higher than the ADI, JECFA reduces the MRL values to the levels at which intake estimate do not exceed the upper bound of the ADI (safe level).

JECFA does not use ADI (or portion of ADI) to set the MRLs but the total residue intake exposure must not exceed the ADI.

In fact, the actual levels of residue at an appropriate interval time determine the value of the MRLs. It means that there is a window for pushing up the MRLs higher and still meeting the ADI criteria as long as the total dietary intake value does not exceed upper bound of the ADI.

Canada believes that using the new method (EDI) which is based on the median of the actual data artificially widens this window and gives more space for increasing the MRLs. Since using median of the residue distribution for the intake estimate excludes 50% of the residue data higher than the median, this approach may not accurately reflect the safety of food.

The delegation of Canada supports the use of full ADI. With respect the observer's contention regarding using higher doses in harsh environment, Canada believes that this is a risk management issue for national/regional authorities and can be handled by modifying the withdrawal times

The delegation of Canada supports further discussions on the use of food technology considerations in risk management. However, Canada believes that food technology

considerations are not issues of food safety and, as such, they should not be used in the establishment of MRLs.

Also, the delegation of Canada supports further discussions on the use of national/regional consumption factors in deriving MRLs and evaluating dietary exposure to residues of veterinary drug. The delegation of Canada encourages member nations to provide available consumption information to forward these discussions.

Starter Cultures

Background:

At the 16th Session of CCRVDF, the Committee agreed to advance a maximum residue limit (MRL) for pirlimycin in cows' milk that was based of human food safety and include the following footnote:

> *JECFA evaluated the effect of pirlimycin residues on starter cultures and for this reason recommended an MRL of 100 µg/kg of milk. Codex Members may therefore adapt national/regional MRLs in order to address this technological aspect for trade of fresh liquid milk intended for processing using starter culture*.

As currently defined in the Codex Alimentarius Commission Procedural Manual, 17th ed., an MRL is set:

> *Based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI), or on the basis of a temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects.*

Comments:

Based on the Committees decision with regards to pirlimycin in cows' milk at the 16th Session, Canada would like to propose that the EWG on Risk Management Topics and Options recommend a revised definition of an MRL to the Committee. Canada would like to propose the revision of the Codex definition of an MRL to exclude food technological aspects as the basis for setting MRLs as they are not directly related to food safety.

Canada also would support adding similar language, as was included with the MRL for pirlimycin, as a risk management statement.

Canada agrees that setting an international standard based on reasons other than food safety, may result in lower MRLs, longer withdrawal periods, and, in the case of dairy products, unnecessary discard of milk.

Appending Risk Management Recommendations to MRLs

Background:

The 62nd JECFA recommended a new MRL for Doramectin in cows' milk, but noted that the necessary discard times are very long and unlikely to be consistent with good veterinary practice (approximately 240 hours for pour-on and 480 hours for injectable products). Committee noted that in milk containing 4% of milk fat, the residues in milk fat would be equivalent to 375 ppb (15 ppb/0.04 = 375 ppb). This value is much higher than the MRL of 150 ppb in tissue fat. At the 15th Session of CCRVDF, some delegations expressed concern over the inclusion of the additional footnote with the MRL for doramectin in cows' milk, stating that the footnote may raise unnecessary concerns for food safety and might give grounds to countries to deny product authorizations. Other countries were supportive of inclusion of the footnote, stating that it provided good guidance to countries where the drug was not authorized for use in lactating cows or it was recently introduced. The MRL was advanced to Step 5 with the attached footnote during that session. At the 16th Session of CCRVDF, the footnote was simplified to read "Depending on the route and/or time of administration, the use of Doramectin in dairy cows may result in extended withdrawal periods in milk. This may be addressed in national/regional regulatory programs." With the revised footnote, the Committee agreed to advance the MRL for doramectin in cows' milk to Step 8.

Comments:

Canada is in support of appending risk management recommendations to MRLs as a means of providing guidance on Good Veterinary Practice or, as in the case of pirlimycin in cows' milk, food technological aspects. As these factors are not directly related to human food safety, they should not be considered when setting MRLs. The delegation of Canada supports further discussion within the electronic working group to determine when and how risk management statements should be appended or otherwise associated with an MRL. Canada supports the JECFA position that implementation of the established MRLs and withholding time for milk should be addressed under national /regional regulatory programs.

EUROPEAN COMMUNITY

Please find attached the European Community comments which were prepared

by the Committee for Medicinal Products for Veterinary Use (CVMP) and which have been endorsed by the European Commission.

1. Reflection paper on the new approach developed by JECFA for exposure and MRL assessment of residues of VMP – **See Annex B**.

2. Reflection paper on injection site residues – **See Annex C**.

GERMANY

(B-1) Use of the Estimated Daily Intake (EDI) concept: The work should focus on two issues: (i) the means to improve communication between JECFA and CCRVDF on changes in risk assessment methodology, in advance of their implementation; and (ii) the impact on the risk management process of the changes, introduced by the 66th JECFA in its method for the evaluation of residues of veterinary drug in foods

- *Basically, I agree with the statement under B-1 of the discussion paper CX/RVDF 07/17/13. The EDI concept (= exposure calculations based on median residue levels) presents an appropriate approach to estimate long-term (chronic) exposure to veterinary drug residues. The estimates will be more realistic than previous estimates based on TMDIs. But, there seem to be some limitations in the proposed JECFA concept which I discuss below:*

- *One of the currently unresolved questions is whether the EDI approach provides adequate protection of consumers exposed to residue levels in animal derived food <u>which are higher than the typical median</u> (i.e., possible intake between the median and the MRL or even at the MRL). At such residue levels, the ADI will probably be exceeded. While the likelihood for this to happen on a daily basis can be considered relatively low, it is evident that an EDI based approach (tailored to mimic the average intake) would not cover this scenario. This point seems to be of particular importance for veterinary compounds: In many cases, pharmacologically active substances present an acute hazard (i.e., ADI/NOEL based on the acute pharmacological/ microbiological effect) and, thus, there is a relevant consumer risk from acute exposure. The current JECFA concept does not give an answer. JECFA may be requested to address these concerns and further develop its approach to cover short-term/higher residue intake scenarios. The acute reference dose ARfD approach might be one option to approach this but feasibility of this approach for assessment of pharmacologically active compounds has yet to be explored.*

- *The quantitative impact of the EDI concept on the MRls is difficult to assess as EDI calculations have only been performed for a very limited number of substances (see results from 66th JECFA meeting, 2006). At least in theory,*

there might be a considerable difference between the EDI based (= new JECFA concept) and TMDI based (= conventional concept) MRL assessments as the time points on the residue depletion curve at which residues are considered "safe" (EDI < ADI or TMDI < ADI) and at which, consequently, MRLs are usually selected can be quite different for the two models. JECFA may be requested to undertake a more systematic impact assessment and provide further information on the likely impact of its method on the size of the MRLs.

- *Further, JECFA has been repeatedly criticized for adopting and immediately using a fundamentally new MRL and intake calculation concept without any participation of regional scientific committees and authorities. There is apparently no mechanism for effective consultation with concerned parties before new scientific approaches are implemented at JECFA level. Some misunderstanding might have been avoided if formal consultation procedures were in place.*
- *It may be noted that the EDI approach proposed by JECFA is also an attempt to harmonize risk assessment approaches with the Codex and, in particular, to achieve greater consistency with the approach already used by JMPR for assessing chronic exposure to pesticide residues. Since a number of years, JMPR is using the results of supervised trials median residue (STMR) levels instead of the MRLs to estimate chronic intake in relation to the ADI.*

(C-1) Utilization of full ADI;

No specific comment at present

(E-2) Starter cultures. The work should be based on constructive comments to be submitted by members and/or observers before the next session of the Committee;

Assessment of effects on industrial starter cultures in milk is part of the normal MRL risk assessment for antibiotics in the EU („For milk, the MRLs should not exceed the concentration without effect on dairy starter cultures"7). . There is an option for lowering MRLs to take account of undesired effects on starter cultures.

(E-7) Appending risk management recommendation(s) to MRLs. The work should consider whether additional recommendations on risk management could be provided by the Committee when it establishes MRLs.

I think this is a very reasonable suggestion. MRL recommendations may be accompanied by recommendations on the use of the substance/product which can be expected to contribute to avoidance of non-compliant residues and give guidance to regulators in formulating adequate risk management phrases. For instance, restrictions of use in certain animals as laying hens or lactating cows, recommendations on appropriate injection volumes. In my opinion, effects on starter cultures would also fall into this category. Risk assessors (JECFA) could also be requested to give managers appropriate advice on health based guidance values allowing to assess possible acute health risks in case of positive residue findings/ acute exposure situations (the ADI as a guidance value reflecting possible health risk after lifetime exposure is often not very useful for this purpose). There may be more examples.

(2) Topics for which the Committee requested further clarification:

(B- 3) Use of Regional Consumption Factors (recommendation by the Bilthoven Workshop);

No specific comment. As far as I understand, the Bilthoven Workshop re-confirmed use of the traditional standard food basket for animal derived commodities, in the absence of better alternatives based on empirical consumption factors ("the theoretical food basket approach leads, in combination with the MRL, to over conservative estimates of the long-term exposure to veterinary drugs of "average eaters" and highly conservative estimates for the "preferential eaters"[8]). It was also noted that „the current data provided by GEMS/Food to conduct short-term intake assessments lack the detailed information needed for optimal assessment"[2]. However, the last word may not have been said on the subject. Some adjustments might be possible once new, more reliable empirical consumption data become available; adjustments might also be become necessary with a view to further harmonization of intake calculations between JECFA and JMPR (the two Committees seem to use different food baskets for animal derived commodities). Further, the development of more sophisticated acute and chronic exposure scenarios might require some adjustments of the intake assumptions (e.g., an acute exposure scenario in relation to an ARfD may require a food basket based on upper percentile consumption figures while average/median consumption data might be adequate for long-term daily intake calculations based on the ADI).

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[7] EU document: Volume 8: Notice to applicants and Guideline: Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-8/pdf/vol8_10-2005_.pdf and Guideline on Assessment of effect of antimicrobial substance on dairy starter cultures, http://www.emea.europa.eu/pdfs/vet/swp/027699en.pdf

[8] Updating the Principles and Methods of Risk Assessment: MRLs for Pesticides and Veterinary Drugs. FAO, Rome, 2006. http://www.fao.org/ag/AGP/AGPP/Pesticid/JMPR/DOWNLOAD/bilthoven_2005.pdf

(E-5) Old Drug Policy; and

No specific comment at present. It is my impression from several discussions that the term "Old Drug Policy" is a very vague term which does not suggest any specific method or meaning. What is the rationale behind this?

(E-6) Threshold of Toxicological Concern for Veterinary Drugs (CX/RVDF 07/17/13, para. 85). [See ALINORM 08/31/26 – para 129 – 4th indent]

No specific comment on this at present. I basically agree with the comment under E-6 of discussion paper CX/RVDF 07/17/13. The Threshold of Concern (TTC) appears to be a promising tool for establishing risk-based lower residue limits for substances that have no ADI/MRL (superior to the often used approach to use analytical performance limits as for instance detection/quantification limits) . One major limitation of the approach is that, at present, no suitable TTCs for pharmacological, hormonal or microbiological effects are availabl. Such effects often play a considerable role in the risk assessment of veterinary drugs. The following example may illustrate this: JECFA's pharmacological ADI for dexamethasone is as low as 0-0.000015 mg/kg bw or 0-0.015 µg/kg bw which gives as daily intake of 0.9 µg/person/day. This is much lower than most of the TTC values for toxicological endpoints established so far (except for the TTC for high potency genotoxins/carcinogens which was estimated with 0.15 µg/day).

I think the TTC concept needs to be further developed and expanded/validated before it can be used in the assessment of pharmacologically active substances.

(3) An update on the on-going activity of the VICH Expert Working Group on Metabolism and Residue Kinetics on harmonization of statistical methods for calculation of withdrawal period, if available [See ALINORM 08/31/26 – para 131 & 133].

The current status of work on "harmonization of statistical methods for calculation of withdrawal period" in the VICH EWG may be summarized as follows:

One of the 5 Topics the VICH EWG is (currently) dealing with is "Statistical methods for the determination of withdrawal periods". The objective is to provide a global comparison of differences in statistical (and possibly non-statistical) withdrawal time calculation tools and model assumptions and their impact on data requirements for residue studies in the different regions. If this exercise shows that the tools and assumptions can significantly affect residue study design (study would be accepted by authorities in one region and rejected in another), it could then be considered to harmonize the statistical approaches.

The project is still ongoing. The VICH EWG has discussed the issue on some occasions but a no final conclusion be reached up to now.

As an interim result the EWG noted that the greatest impact on current differences in withdrawal periods would probably not come from the statistical calculation tools but rather from differences in risk management policies in the VICH regions, such as MRL setting procedures, the use of different confidence limits/safety margins, injection site policy and some other issues primarily related to risk management, rather than the statistical tools themselves. It was agreed however that additional examples would be needed to further assess the impact of non-harmonized statistical tools.

(4)Possible changes in the status of the proposals listed in document CX/RVDF 07/17/13 [specifically the items listed in ALINORM 08/31/26 – para 129 – 2nd indent] and make appropriate recommendations to the Committee for further consideration and action [See ALINORM 08/31/26 – para 135], and

No specific comment at present

(5) Identification of new proposals with relevant background information and appropriate recommendations to the Committee [ibidem].

No specific comment at present

JAPAN

B-1: Use of the Estimated Daily Intake (EDI) concept

Currently, as a principle in Japan, TMDI must be calculated in exposure assessment for each veterinary drug as it provides sufficient safety margin to consumers. Where necessary or possible from data availability, EDI, which more realistically reflects the actual intake of residues, is also calculated.

Japan believes that if JECFA refines EDI estimation methodologies for better reflection of real intake situation and for uses in the whole world, these methodologies will greatly improve the exposure assessment and as a consequence, MRL setting.

C-1: Utilization of full ADI

MRLs should be established on a basis of residues arising from uses following good practice in the use of veterinary drugs. There might be some exposures to drug residues from non-animal foodstuff, *e.g.*, foods of plant origin, being contaminated with drugs from excreta released into the environment. Taking such exposures into account, MRLs determined by allowing exposure that is equivalent to the value of ADI (full ADI) will not be therefore appropriate for protecting the health of consumers.

E-2: Starter cultures

Codex MRLs should aim at protecting the health of the consumers and ensuring fair practices in the food trade as described in Article 1 of the Statutes of the Codex Alimentarius Commission. Codex MRLs should be established from food safety point of view based on results of the residue studies and the ADI. Japan does not support taking technological issues into account when establishing MRLs in the Codex. The issues should be settled among manufacturers, not by Codex.

UNITED KINGDOM

The UK is concerned about the apparent lack of communication between JECFA and the CCRVDF. It is suggested that any decision drafted or taken by JECFA should automatically be copied to the CCRVDF secretariat for immediate distribution to Codex contact points. In providing this to the CCRVDF, the JECFA secretariat should clearly identify any deadline for comments and to whom these should be sent. Passively putting information on a JECFA website requesting comments is inadequate communication.

Today I was shown a paper (CX/PR/08/40/7) being presented to the next CCPR meeting in China next month. This paper includes at Appendix II information that helpfully lays out the risk analysis principles applied by the CCPR, and which also details the role of the JMPR, CCPR the interaction between them, and the approach taken for establishment of MRLs. This could help us in our task and there may be sections of the text which we could adopt with minor word changes or refer to in our document. There are also specific comments about pesticide MRLs for commodities derived from animals and specifically for fat soluble pesticides in products such as milk which we should consider as there are clear implications for our work. I suggest that we study this document and also the report of the CCPR meeting to see how it was received and any comments made on it. I am attaching a copy of CX/PR/08/40/7 for your consideration.

The introduction of the EDI principle is a radical change in philosophy within JECFA and caught major regulatory authorities largely by surprise. To manage the implementation of the EDI principle by JECFA, the UK suggests that JECFA co-ordinates a workshop with other regulatory bodies to discuss in detail the current and proposed systems and agree in discussion with these regulators how to implement the new system, if this is the agreed way forward.

The full utilisation of ADIs depends on the outcome of the above discussions but it is again clear that the CCRVDF and JECFA do not agree on how to treat data used to set the ADI and this must be included in any discussions above.

The starter culture issue was highlighted by the discussions at CCRVDF on the controls set for pirlimycin. The precedent was set permitting Codex Members to adapt national/regional MRLs in order to address this technological aspect for trade of fresh liquid milk intended for processing using starter culture, provided the MRL proposed on safety grounds was not exceeded. The full range of uses of animal products from treated animals must be considered if there is a potential for use in starter cultures or similar.

Appending risk management recommendations has also been accepted in the past by the CCRVDF when conditional use of clenbuterol was agreed in the MRL. This should be considered on a case by case basis in the future and may permit the adoption of Codex MRLs which are currently the subject of disagreement by various Codex Members.

Information on regional consumption patterns within the UK could be provided by the Food Standards Agency in the UK. However, the UK has no comments to offer at this stage on “Old Drugs Policy” and “Threshold for Toxicological Concern for Veterinary Drugs”, but it is possible that EMEA and/or EFSA might have some comment on these issues.

The UK is about to begin a study to evaluate the incidence and fate of injection sites in the human food chain. Details of this study and the final report (on completion) can be provided to this group to assist in discussions.

INTERNATIONAL DAIRY FEDERATION - IDF

The IDF believes that in establishing MRL's in milk that are used for international trade purposes Codex does not need to consider the effect on starter cultures. MRL's should be based solely on levels that do not compromise the safety of consumers and technical processing issues for the specific dairy products that involve starter cultures can be managed effectively by processing controls by dairy businesses.

SECTION III:

COMMENTS RECEIVED ON THE 1ST DRAFT OF THE DISCUSSION PAPER FROM PARTICIPANTS TO THE WORKING GROUP (UP TO DECEMBER 31st 2008)

EUROPEAN COMMUNITY

The CVMP reviewed the Discussion paper on risk management topics and options for the CCRVDF circulated by France on 29 August 2008 to the electronic Working Group on the matter. The CVMP thanks France for preparing the draft and the Working Group members for their contributions. The CVMP wishes to offer the following comments:

Items identified for immediate consideration:

A.- Use of the Estimated Daily Intake (EDI) concept

The CVMP presented its scientific considerations regarding the EDI concept in its Reflection paper (EMEA/CVMP/SWP/138366/2008-Rev.1) that was submitted to the Working Group for consideration in July 2008, and was also submitted to JECFA for consideration by the Committee at its 70th meeting. For any further scientific comments on the concept as such, the considerations by the JECFA are awaited.

The CVMP fully supports the recommendations made in paragraph 17, but notes that under 17(i) the points to be forwarded to JECFA are 'concerns' as well as 'requests for clarification'.

Some specific comments and proposed revisions relating to the text in paragraphs 13, 14 and 15 are provided in the Annex to these comments, and in order to reflect the changes in the recommendations the amendment to paragraph 17(i) below is proposed.

17(i) forward the **concerns raised and** requests for clarification in para. **13 and** 15 to the next JECFA meeting for consideration and report at the next session of the Committee;

Additionally, as a more general comment, the CVMP considers that the consultation process should be improved regarding documents and approaches on methods and principles, allowing input from all CCRVDF members, and approval on new or revised methods and principles by the CCRVDF before implementation. Consideration should be given to a consultation process through website publication of draft proposals well in advance of a JECFA meeting allowing written comments and publishing an agenda providing information on the methods and principles that will be discussed (at the moment only information on the substances to be discussed is provided). Such consultation would help to allow concerned parties to develop their own positions on relevant issues and so submit comments to JECFA before a final JECFA position is adopted. Such procedure would facilitate acceptance of approaches and ultimately acceptance of MRLs proposed by JECFA, and help to speed up the Codex process. The CVMP proposes that an additional point should be added in the recommendations to reflect this view.

17(v) establish a consultation process regarding documents and approaches on methods and principles, allowing input from all CCRVDF members before a final JECFA position is adopted, and seek approval by the CCRVDF before implementation.

Furthermore, the CVMP notes the comments from Australia encouraging the further harmonisation of the approach of establishing MRLs for residues of veterinary drugs with the approach for pesticides. The need of harmonisation emerged a couple of years ago in relation to the establishment of MRLs for dual use substances. However, the problem related only to these few substances, and therefore attempts to harmonise assessment between JECFA and JMPR should be limited to those. The CVMP considers that there are sound reasons to differ in the approach of setting MRLs between veterinary drugs and pesticides, e.g. withdrawal periods are set for veterinary drugs on individual product basis while for pesticides standard pre-harvesting periods have been established that are taken into account in the MRL considerations. While harmonisation of approach is of course a noble goal, before any attempts in further harmonisation are made, a discussion at CCRVDF level should take place again to establish whether there would be still a need for such harmonisation.

B.- Utilization of full ADI

The CVMP supports the recommendations to the CCRVDF in paragraph 22 to defer consideration of this issue at this time until the Committee has reviewed JECFA's response on the EDI issue.

C.- Starter cultures

As stated in the document in the EU the consideration of the effect on industrial dairy starter cultures is part of a standard MRL assessment for antimicrobial substances, as this is considered essential for the overall consideration of allowed maximum residue levels of such substances in food. In fact, similar consideration could also be given to other technological aspects of food and feed production, if relevant, e.g. the processing of meat.

The CVMP agrees that the consideration of any such technological aspects are risk management considerations rather than food safety considerations. While the recommendation under paragraph 28 seems to offer a compromise, it is however feared that this approach will not provide a solution in practice, as the approach allows that Codex member countries set different MRLs, and for an antibiotic e.g. for the EU a different MRL as the one derived from the consumer safety data alone could be established depending on the data of effects on dairy starter cultures. Thus the recommended approach is likely to result in non harmonised MRLs, thus hindering trade.

D.- Appending risk management recommendation(s) to MRLs

The CVMP supports the recommendation under paragraph 32 to append risk management recommendations, where appropriate.

Items on which the Committee, at the 17th session, requested further clarification before its next session:

E.- Use of Regional Consumption Factors (recommendation by the Bilthoven Workshop)

The CVMP recognises that the current standard food basket used for elaborating MRLs overestimates the long-term exposure to residues of veterinary drugs of the "average eater" with the exception of some specific tissues under certain conditions. The approach has however also considerable advantages, i.e. it is simple and clear, and it provides for a harmonised approach for the exposure estimate, different to the use of regional consumption factors.

Therefore, the options and recommendations proposed are not supported as such, and the following comments are made.

On Paragraph 36: The CVMP is concerned of going in a direction of using regional consumption data in developing MRLs, as this would in all likelihood result in a complicated and intransparent method for calculating MRLs and be counterproductive in respect to the aim of setting harmonised MRLs.

On Paragraph 37(i): The proposal to gather regional consumption figures is questioned on the reasons outlined above. In addition, any compilation of consumption data is resource intensive and any such request by CCRVDF to member countries should be a targeted approach to ensure that the appropriate data are compiled. In addition, also the methods and resources needed for their assessment should be clear before starting such an activity. Therefore, before Codex countries should be invited to provide available consumption information to JECFA, a more structured approach data would need to be agreed, i.e. clarifying the aims and direction for the collection.

On Paragraph 37(ii): Before the discussion of the implementation of the concept "one meat, plus egg, plus milk" can be discussed, the concept and acceptability of the concept as such need to be discussed. The CVMP will review this concept; however, at present no comments can yet be provided if the concept would be acceptable in the EU. According to the Codex procedure, it is proposed that JECFA be asked to give an opinion, and input from CCRVDF members be allowed in the considerations, as outlined in the comments under point A.

F.- Old Drug Policy

The issues and comments discussed under this item seem not to be coherent.

IFAH proposed at the last CCRVDF meeting the reconsideration of an old drug policy. It is assumed that the proposal was meant in relation of establishing Codex MRLs for veterinary drugs that are on the market since long and patents and data protections have expired. However, the reference in this context to the group of "veterinary drugs without a Codex ADI/MRL" and the concepts discussed of assessing these substances is seen with great concern. Whilst formally of course any of this old drugs for which no JECFA assessment has been made and no Codex MRL has been set, is a drug without Codex MRL/ADI, however this term has been used primarily for substances for which it was not possible due to specific human health concerns to establish an ADI and MRL (such as chloramphenicol, nitrofurans) or for which in the past never an application was made but which are largely considered as unsafe (like malachite green) and these substances are often banned in Codex countries.

Paragraph 39 relates to these substances and the approach on how to deal with them. The approaches for assessment of the "veterinary drugs without a Codex ADI/MRL" as discussed by the CCRVDF WG on substances without Codex MRLs/ADI (CX/RVDF 07/17/13) were not meant for establishing MRLs, i.e. safe limits regarding ingestion over a lifetime, but to assist to find appropriate risk management measures to deal with unwanted substances for which often in addition only sparse data are available.

The CVMP is not opposed that an old drug policy is established. However, it needs to be carefully discussed, what constitutes any such old drug policy, and such policy needs to be endorsed by the CCRVDF before it can be applied. In this context consideration should be given how to better use existing assessment in Codex countries in regions for old veterinary drugs, and in how far these existing assessments could be used to establish Codex MRLs for these substances.

In summary the CVMP supports that the issues are discussed further, which could be either in the Working Group on risk management topics and options for the CCRVDF or the Working Group on Priorities.

G.- Threshold of Toxicological Concern for Veterinary Drugs (CX/RVDF 07/17/13, para. 85)

No further comments. The CVMP supports the recommendation.

Update on items to be taken up for consideration in the future:

H.- Residues at injection sites

The CVMP supports the recommendation to wait for the conclusions of the on-going work by VICH before taking up this matter again.

I**.- Harmonisation of withdrawal period's calculation**

The CVMP supports the recommendation to wait for the conclusions of the on-going work by VICH before taking up this matter again.

GERMANY

I would like to thank France for preparing a very clear draft Discussion paper on risk management topics and options for the CCRVDF (circulated in August 2008) and wish to offer the following comments:

Items identified for immediate consideration:

A.- Use of the Estimated Daily Intake (EDI) concept

The paragraphs 11-16 provide a good overview of the spectrum of different views and opinions regarding the use of the EDI. There is obviously considerable discrepancy among experts concerning the scope and implications of the concept and this discussion makes it very clear that further clarification is still needed. Therefore, I fully support the recommendations made under paragraph 17 (i-iv).

B.- Utilization of full ADI

One point not mentioned in this discussion is the use/partitioning of the ADI in case of dual use substances (veterinary/pesticide use) when both residues in plant and animal products contribute to the daily intake. Use of the full ADI for one usage (e.g. pesticides) would automatically preclude setting of MRLs for the other. The Bilthoven report is largely silent on this aspect. Another aspect is the a priori «reservation» of a certain portion of the ADI for MRls in milk, eggs or honey (if appl). As far as I know, this is common practice at national level when future uses of substances in lactating cattle or laying birds or bees are anticipated or at least considered possible.

I would support the recommendation under paragraph 22. I also agree that a decision to use the EDI or TMDI concept for intake estimates will clearly have a significant impact on this discussion.

C.- Starter cultures

I would support a recommendation to base the Codex MRL in milk solely on consumer risk assessment and food safety considerations and to manage technological aspects related to industrial processing of milk (effect of residues on starter cultures) at the national level.

Starter culture data may be assessed by JECFA (if such data are available) and a management statement on the appropriate residue levels not affecting starter cultures appended to the assessment report.

D.- Appending risk management recommendation(s) to MRLs

I support the recommendation under paragraph 32.

Items on which the Committee, at the 17th session, requested further clarification before its next session:

E.- Use of Regional Consumption Factors (recommendation by the Bilthoven Workshop)

The current standard food basket approach is reasonably conservative and safe (for most food commodities even in case of preferential eaters) and the underlying calculation procedure is well established, clear and relatively simple. The "food basket" is widely accepted in Codex member states and thus contributing to a harmonized approach for exposure estimates and MRL assessments. So any change should be well reasoned with implications considered and weighed.

On the other hand, some areas for improvement of the intake assessment have been noted (e.g., the standard basket may be too unrealistic regarding average/long-term intake, suboptimal for the evaluation of the acute/high consumption scenarios for certain commodities, non-harmonised with approaches used other areas as pesticides). It is however generally recognized that better and more complete food intake data must be available before any change/refinement, e.g. by using of regional consumption factors, can be envisaged. However, continuation of this discussion and review of new scientific developments is highly desirable and necessary, also with a view to a future harmonization of exposures assessments approaches between pesticides and veterinary residues, the use of the EDI concept and consideration of acute intake scenarios.

F.- Old Drug Policy

No specific comment

G.- Threshold of Toxicological Concern for Veterinary Drugs (CX/RVDF 07/17/13, para. 85)

I support the recommendation to keep the item on the agenda for further discussion. The discussion on the TTC is in a very early stage, and it is difficult to draw any conclusions already. The applicability and usefulness of this concept for the assessment of pharmacologically active substances is yet to be explored.

Update on items to be taken up for consideration in the future:

H.- Residues at injection sites

I support the recommendation.

I.- Harmonisation of withdrawal period's calculation

I support the recommendation.

UNITED KINGDOM

Para 12. …The residue concentrations were totalled and compared to the (toxicological or microbiological) ADI to assure that the human consuming each of the edible tissues containing residues at the MRL concentration would not be exposed to cumulative (all meats plus milk, honey and eggs, where applicable) residues above the acceptable daily intake.

Para 15. (i) … In fact, the actual concentrations of residue at an appropriate interval time determine the value of the MRLs.

Para 15. (iii) The concentration of the MRL would be very sensitive to …

Para 15 (v) … A more robust alternative approach will ~~probably~~ need to be developed to allow application and extension of the EDI concept to cover ~~a wider~~ the full range of substances.

Para 17 (iii) discuss with JECFA how to develop new approaches in collaboration with, and ensure a more effective consultation process with concerned parties before new scientific approaches are implemented by JECFA.

Para 17 (iv) suggest that JECFA co-ordinates a workshop with other regulatory bodies and concerned parties …

Para 21. ….MRLs should be set at concentrations that could monitor GPVD. ….

Para 23. …MRLs should be based solely on concentrations that did not compromise the safety of consumers and technical processing …

Para 24. …was used at their national/regional levels.

Para 26. …at their national/regional level.

34. …established for edible offals (other than liver and kidney) of cattle, goat and sheep, such as rumen, abomasums and brain.

UNITED STATES OF AMERICA

General Comments

There are a number of points that have been discussed that raise the issue of how an MRLVD is defined and derived. A common thread is found in the somewhat contradictory definitions of the MRLVD as a safety standard and the MRLVD as a standard for approved use.

The 17th Codex Procedural Manual defines the MRLVD both in terms of legally permitted use-

"…the maximum concentration of residue resulting from the use of a veterinary drug (expressed in mg/kg or µg/kg on a fresh weight basis) that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food."

And in terms of safety –

"…It based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI) or on the basis of a temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects."

While the current practice assures that residues below the MRLVD are safe and reflect approved use of the veterinary drug, a consequence can be that residues above the MRLVD, while not reflecting approved or permitted use conditions, may be safe for human consumption but not, as a Codex standard, permitted in international trade.

It is suggested that the Working Group consider this issue when considering other comments regarding the ADI and MRLVD.

In addition, the US Delegation proposes to provide a paper to talk about the ADI and MRLVD for discussion by the electronic Working Group. The discussion paper is anticipated to be provided in December, but no later than January.

Specific Comments

Para 12, second sentence.

Suggest edit the sentence to read (changes in bold):

The residue concentrations for each edible tissue were presumed to be at the MRL concentration, and were totalled and compared to the (toxicological or microbiological) ADI.

Para 13, last sentence Suggest add the following sentence:

As the MRLs are set in accordance with residues resulting from Good Practice in the Use of Veterinary Drugs, additional conservatism is practiced by allowing no more residue than needed in accordance with GPVD

Para 15 (i)

The first paragraph makes a number of statements that are questionable. It is noted that :

1. Using the median of the residue data also excludes 50% of the residue data lower than the median – such is the definition of a median value.

2. The use of the median value is intended to represent a more accurate estimate of the population exposure rather than a worst case estimate..

The TMDI is NOT a more realistic approach, as it ignores the actual residue values. It is, however, more conservative.

The second paragraph appears to misunderstand that the EDI is only proposed for chronic exposure.

Acceptability of the current EDI approach is predicated on the chronic nature of food consumption. The use of the median value to estimate the EDI is felt (as discussed above) to more accurately reflect the chronic residue comparison to the ADI.

Para 15 (ii)

There is always a disconnect between the derivation of the MRL and the ADI. MRLs are established based on residue levels resulting from the GPVD and are not directly derived from the ADI. The TMDI, and later EDI, are used to assure that when following this approach the human consumer is not chronically exposed to residues above the ADI. Please refer to the 66th JECFA for a discussion of this topic.

The JECFA very clearly states that the EDI approach is currently intended for chronic toxicity/exposure and that future work will be done to look at what would be needed for acute toxicity/exposure.

Para 15 (iii and iv) It seems odd to state that the EDI approach will require increased numbers of animals and at the same time state that it will reward poor data. I can see no basis to believe that the use of the EDI would “reward” poor data quality. In addition, this statement regarding concern for the quality of the data can be made for any data driven decision by JECFA or the Codex. The JECFA has historically declined use data of insufficient quality. In addition, it is reasonable to anticipate that the JECFA would use other approaches to assure that the human consumer does not exceed the ADI if the data are not suitable for an EDI estimate.

Para 15 (vi)

It is presumed that GVP refers to GPVD. Considerations of Good Veterinary Practice have been a part of the JECFA evaluation since the 32nd meeting of the JECFA (see p.11 of the 1988 report). This is not a new practice by JECFA and has consistently been part of its approach to recommending an MRL.

In addition, the Codex Alimentarius Commission Procedural Manual, 17th edition, clearly discusses the use of GPVD in developing the MRLVD, and states (bold added for emphasis) :

“Codex maximum limit for residues of veterinary drugs (MRLVD) is the maximum concentration of residue resulting from the use of a veterinary drug (expressed in mg/kg or µg/kg on a fresh weight basis) that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food.

It is based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI), or on the basis of a temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects. When establishing an MRL, consideration is also given to residues that occur in food of plant origin and/or the environment. Furthermore, the MRL may be reduced to be consistent with good practices in the use of veterinary drugs and to the extent that practical analytical methods are available. Good Practice in the Use of Veterinary Drugs (GPVD) is the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions."

Para 16

Please note the actual derivation of the MRL has NOT been changed by 66th JECFA, rather only the mechanism that is used to assure that the derived MRLs do not result in a consumption of residues that exceed the ADI. In addition, the 66th JECFA presented both TMDI and EDI calculations for transparency in its report to the Codex.

The use of the EDI has been discussed in a number of venues outside of the JECFA sessions, including the FAO/RIVM/WHO joint workshop, Updating the Principles and Methods of Risk Assessment: Maximum Residue Levels (MRLs) for Pesticides and Veterinary Drugs.

Finally, it is noted that the JECFA provides a recommendation of an MRL to Codex – the MRLs have not been altered. The alteration is only in the risk-management evaluation that JECFA has routinely performed to verify that the ADI is not exceeded by the MRL.

Para 20

The use of the full ADI for Codex MRLs moves the MRLs to be more reflective of the safety of the residues– however, it is noted that this approach would also require acceptance of the concept that on any given day only one edible tissue is likely consumed (muscle, liver, kidney, or skin/fat) and that the individual MRLs should not be combined.

Para 21

This argument for the use of GPVD in the development of an MRL runs diametrically opposed to the argument presented above (see 15 (vi)).

The WG should clearly state whether it is in agreement with the use of GPVD as a consideration in the setting of MRLs or not, and provide discussions consistently on that basis.

Para 22 A more appropriate recommendation would be to initiate a dialog between the JECFA for veterinary drugs and CCRVDF as the risk assessment and risk management bodies and engage in a thorough discussion of the issue.

Para 35

The recommendation in this paragraph is consistent with that in paragraph 20 above.

This is essentially the approach used by the US for tolerances and it is a key to the ability to use the full ADI. This approach bases the MRL more firmly of safety rather than as a tool to establish legal use of the veterinary product.

Para 37 (ii)

This is a significant recommendation and consistent with some of the discussions earlier in the document (Para 20, 35). It does, however, bring in significant differences in approach internationally (e.g., US tolerance vs. EC MRL). The WG should make a stronger recommendation for broader discussion of this issue.

Para 47

I do not agree with this recommendation.

At the 17th CCRVDF meeting, the issue of residues at the injection sites was discussed and at the time, correctly assigned as a topic to be taken up in the future. This was primarily due to the efforts underway at VICH, particularly by the Steering Committee and the Metabolism and Residue Kinetics Expert Working Group.

However, there have been two recent developments that effect this decision. First, the 2008 Steering Committee failed to agree to the re-establishment of the Safety Expert Working Group, which would have had the mandate to develop guidelines for establishing an acute reference dose for veterinary medicinal products. The development of a concept paper will continue (led by industry) but final acceptance, in reality, appears doubtful. Secondly, the MRK-EWG has discontinued development on its "Topic 5 Guideline" related to the statistical analysis of residue data for establishing withdrawal times due to a lack of consensus on methodology and considerations that this activity was beyond the initial terms of reference for this group. The intent of this guideline (in part) was to propose strategies for management of injection site residues. Thus, it is clear that workable solutions for the injection site residue issue will not appear in the foreseeable future from the activities of VICH.

As such, and because this remains a critical food-safety issue, and this topic should be elevated in priority and included in the list of topics to be taken up immediately for consideration by the Committee .

INTERNATIONAL DAIRY FEDERATION (IDF)

The IDF would like to submit the following comment on Item C. Starter Cultures (paragraphs 23-28):

The IDF believes that there is no need for Codex to consider the effect on starter cultures when establishing MRL's in milk for international trade purposes for the following reasons:

- MRL's should be based solely on the levels that do not compromise the safety of consumers.
- Technical processing issues for specific dairy products that involve starter cultures can be managed effectively by processing controls by dairy companies.
- Raw milk for further processing into cultured products is generally not an internationally traded product.
- While MRL's in milk that consider the effect on starter cultures may be established at the national level, Codex and JECFA should address MRL's only at the international level.

As such, the IDF does not agree with the recommendation in paragraph 28 that makes reference to JECFA evaluating residues for their effect on starter cultures nor establishing national/regional MRL's in order to address this technological aspect.

The IDF suggests removing the reference to starter cultures as it relates to the evaluation by JECFA and establishing MRL's by Codex.

JECFA SECRETARIAT

The JECFA Secretariat would like to reiterate the comments made in CRD 6 of the 17th Session of CCRVDF in response to REPORT OF THE PHYSICAL WORKING GROUP ON RESIDUES OF VETERINARY DRUGS WITHOUT ADI/MRL, as well as comments made orally during the 17th Session.

Items identified for immediate consideration

A. Use of the Estimated Daily Intake (EDI) Concept

General comments

The 70th JECFA noted the history of the development of the EDI and discussion of how it fits into JECFA's evaluation of residues of veterinary drugs, as reported by the sixty-sixth JECFA. The sixty-sixth JECFA identified the EDI as one of a number of issues that are being addressed as part of the Joint FAO/WHO Project to Update and Consolidate Principles and Methods for the Risk Assessment of Chemicals in Food http://www.who.int/ipcs/food/principles/en/). This history includes that an international workshop was held within the framework of the project in Bilthoven, the Netherlands in November 2005 (Report available at ftp://ftp.fao.org/ag/agn/jecfa/bilthoven_2005.pdf). It was this workshop, to which international experts in the field of veterinary drug and pesticide residues were invited, including experts from the European Commission, the EMEA, FDA and other regulatory agencies as well as experts from academia and industry, that agreed that the principles and methods for the estimation of exposure for chemicals used as veterinary drugs and pesticides should be harmonized to the extent possible and agreed on a set of recommendations to JECFA and JMPR. One of these recommendations to JECFA, was recommendation no. 14: JECFA should consider using the median value of the distribution of residue concentrations from which the MRL is derived for the calculation of conservative estimates of long-term (chronic) intakes.

JECFA at its 70th meeting confirmed the utility of the EDI as a tool to ensure that intakes of residues resulting from use of veterinary drugs in accordance with Good Practices in the Use of Veterinary Drugs and the recommended MRLs do not exceed the ADI. The Committee acknowledged that the use of the EDI is currently applicable only to the evaluation of chronic toxicity of, and chronic exposure to, residues as reflected by the ADI. The Committee also reconfirmed that it requires an adequate data set to estimate the EDI. When data are not adequate to estimate the EDI, other conservative approaches to ensure that the ADI is not exceeded are applied. Future work will address considerations to identify the appropriate measures of hazard, consumption and exposure for issues of acute toxicity and acute exposure, as might be appropriate for an acute reference dose (ARfD). As noted by the sixty-sixth JECFA, the EDI should not be applied when there is concern for acute toxicity or acute exposure. For this purpose, appropriate tools and approaches will need to be developed.

The final Expert consultation on the FAO/WHO joint Project to Update and Consolidate Principles and Methods for the Risk Assessment of Chemicals in Food, held in Seoul, Republic of Korea 11-14 November 2008, confirmed the suitability of the EDI as an estimate of chronic dietary exposure. However, again, it was pointed out that the EDI is only applicable to the assessment of chronic exposure to residues of veterinary drugs evaluated on the basis of chronic toxicity. The EDI should not be applied when there is concern for acute toxicity or acute exposure. Additional work is required to address acute exposure for comparison with an acute reference dose (ARfD).

In addition, the JECFA secretariat would like to refer the Risk assessment policy for CCRVDF on the Role of JECFA as adopted by the 30th session of CAC (Codex Procedural Manual, 17th Ed. p. 147), and in particular point e) referring to that fact that risk assessment should be based on realistic exposure scenarios. It must be pointed out that scientific principles and method developed and used in risk assessment are independently developed by international experts in the relevant fields and are not subject to approval by risk management bodies.

Thus, in conclusion, the process by which the new exposure method for chronic intake of veterinary drug residues has been transparent and necessary consultations with international expertise in the field have been held. In addition, explanations were provided to CCRVDF at the 17th meeting. Thus, none of the recommendations in paragraph 17 are in our view valid.

Specific comments

The MRLs are points on a withdrawal time - tolerance limit curve. JECFA uses the upper on-sided 95% confidence limit of the 95th percentile of the distribution of residues, in keeping with the internationally accepted method for determination of MRLs. MRLs for the four standard edible tissues are estimated at the same time point which has to be compatible with the (range of) official waiting period(s). The following additional criteria are to be met: Realistic Intake estimates at that time point have to range below the ADI; and suitable validated analytical methods are available for enforcement. The process to arrive at recommendations for MRLs by JECFA is a scientific, data driven process. It is also clear that the derivation of MRLs are driven by the available data from residue depletion studies and official withdrawal time and not directly related to the ADI. With reference to this and to the general comments above, the JECFA Secretariat thus finds that none of the statements made in paragraphs 14 and 15 are correct. We provide specific comments on some of them below.

- Regarding paragraph 14, as indicated previously, EDI is not for acute toxicity. It should be corrected. In addition, it is not understood why certain points of view are only provided as footnotes and other appear in the text. This adds to the text being rather imbalanced towards certain specific views.

- Regarding paragraph 15 (iii), this is not correct as JECFA always checks the suitability of the data set for the approach used. In particular, the characteristics of the residue distributions and the consequences of extremely variable data on intakes are examined.

- Regarding paragraph 15 (iv), this statement as such is not correct and rather misleading.

- Regarding paragraph 15 (v), this statement is not correct. The statistics behind the approach are equivalent to those proposed by the EMEA/CVMP for the determination of withdrawal times.

- Regarding paragraph 15 (vi), the JECFA Secretariat would like to refer to the definition in Codex and guidance on the Good Practice in the Use of Veterinary Drugs, which members of Codex have to follow. It is difficult to envisage an alternative approach, as exposure has to be estimated on the basis of some use pattern. In the Codex description of maximum limit for residues of veterinary drugs (MRLVD), it is indicated that the MRL may be reduced to be consistent with good practices of in the use of veterinary drugs. Good Practice in the Use of Veterinary Drugs (GPVD) is officially recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions. This is also the agreed approach adopted by JECFA.

- Regarding paragraph 16, this statement is clearly incorrect. As already stated at the last session, the EDI approach was developed based on request of CCRVDF to develop a more realistic exposure assessment and to base risk assessments on such realistic scenarios. In addition, in paragraphs 34 – 37, that even the more realistic, but still conservative exposure estimate represented by the EDI approach, may over estimate exposure. The JECFA Secretariat would like to point out that the food basket approach has been retained by JECFA, as it represents a further conservative estimate to protect eaters of the specific foods in the population. This food basket was originally drawn up based ion information gathered and agreed by CCRVDF.

B. Utilization of full ADI

General comments

This has been discussed in detail at several previous occasions and it is unclear to the JECFA Secretariat what in addition should be considered in this context. Please refer to the 66th JECFA report on the rounding of the ADI (General considerations 2.3 where it is clearly stated that the ADI is not directly used in the derivation of the MRL, attached in Annex 1).

C. Starter cultures

General comments

To consider effects of antimicrobial residues on starter culture is a risk management decision and CCRVDF needs to give clear guidance to JECFA to what extent it wants the JECFA to consider and report on such effects.

Items on which the committee, at the 17th session, requested further clarification before its next session

E. Use of regional consumption factors (recommendation by the Bilthoven workshop)

General comments

This is in fact not a recommendation for the Bilthoven workshop. The recommendation form the workshop on this matter is recommendation No. 13: To improve the international food consumption information data base, national governments should be encouraged to submit their consumption data to FAO and WHO. In the international context, it would be and important gaol to improve the database for consumption patterns of food, the GEMS/Food Diets, in order to arrive at realistic figures for consumption of foods of animal origin, with respect specifically to acute intake of residues.

F. Old Drug Policy

General comments

As the JECFA Secretariat explained at the 17th Session of the CCRVDF, an 'old drug policy' has never existed. According to the terms of reference for this working group (see CX/RVDF 09/18/## page 1 paragraph 4) members should identify risk management issues and their rationale. The JECFA Secretariat would like to point out that there is no reference to what meeting of JECFA is referred to and no detailed reference is made as to what entails this so-called 'old drug policy'.

The JECFA Secretariat would like to provide the following information and clarification to what we understand under this point. JECFA at its 40th meeting developed an approach for evaluating veterinary drugs with a long history of use that takes into account concerns about incomplete data packages and defines in principle minimum data requirements. For details please refer to the report of the 40th meeting http://whqlibdoc.who.int/trs/WHO_TRS_832.pdf .

Specific comments

- Paragraph 40: As for all other evaluations a minimum of adequate data is required for JECFA to perform an evaluation. The point is not in which part of the world compounds are used, it is rather the question if sufficient data are available to allow an evaluation and who will submit the data.

G. Threshold of Toxicological Concern for Veterinary drugs

General comments

The JECFA Secretariat would like to remind the CCRVDF that the application of different approaches in the hazard characterization (and exposure assessment) is a risk assessment issue. Based on recommendations by the 66th JECFA and subsequently by the 17th session of the CCRVDF, JECFA at its 70th meeting has started discussion on the development of a decision-tree approach for the evaluation of veterinary drugs which includes application of the TTC concept. The development of this decision tree approach will take several years and close interaction between JECFA and CCRVDF is required. With regards to the TTC concept and its application to veterinary drugs further work is necessary. It has to be pointed out that for the application of the TTC concept always some compound specific data needs have to be available for the assessment, both in relation to chemical and toxicological data as well as for data on exposure.

Paragraph 43 seems to cover another issue and is not related to the TTC.

Annex A:

Excerpt from the 66th JECFA Report – Annex I. 2.3 Expression of the ADI and derivation of the MRL – (WHO TRS 939, 2006)

General considerations at the current meeting

One of the functions of JECFA is to establish health-based guidance values for residues of veterinary drugs, most often an ADI. The ADI is an output of a risk assessment of the compound, following application of the first two steps of the risk assessment paradigm: hazard identification and hazard characterization. As such, it represents a health-based guidance value, where exposure is considered to represent a negligible risk to consumers if it does not exceed this value. The ADI has a number of uses in risk assessment and risk management, only one of which is in helping to derive the recommended MRLs.

The MRL and the ADI are separate outputs of the risk assessment process and serve different purposes.

The ADI is derived from the NOEL or lowest-observed-effect level (LOEL) from the appropriate toxicological studies, using a safety factor. Given that there are assumptions and uncertainties in deriving the ADI, such as the use of safety factors, the use of a range of doses in toxicological studies and normal biological variation, it is more meaningful to express the ADI to only one significant figure to avoid any inference of inappropriate precision. The general rounding rule for mid-way values (x.5) is to round up, in line with common convention (see, for example, Australian Standard AS 2706-2003 (*7*)). Examples for rounding to one significant figure are as follows: 1.25 becomes 1, 0.73 becomes 0.7 and 1.5 becomes 2.

The MRL recommendation procedure is an iterative process. The MRL is not derived directly from the ADI. If the ADI is based on toxicological end-points, all residues of toxicological relevance are considered; if the ADI is based on microbiological end-points, all residues of microbiological relevance are considered. The MRL recommendation procedure also takes into account the conditions of use (e.g. use of the veterinary drug according to good practice in the use of veterinary drugs, or GPVD) and the residues that result from such use (e.g. residue depletion studies). It also considers results of radiolabel residue studies, the bioavailability of bound residues, the identification of target tissues and a marker residue, the availability of practical analytical methods, estimated exposure resulting from recommended MRLs and consideration of extension of the MRLs to tissues, eggs and milk of other species.

The initial consideration in recommending an MRL is whether it is sufficiently protective of human health. If the use of the veterinary drug yields an estimated intake of veterinary drug residues consistent with the ADI, the recommended MRLs may then be adjusted accordingly when taking into account the other factors noted above. As a general principle, the Committee will not normally recommend an MRL that results in residue levels that lead to dietary intake exceeding the ADI based on toxicological or microbiological considerations. To protect consumers in all segments of the population, historically the Committee has based its recommendations on intakes estimated using a conservative model diet consisting of 300 g of muscle, 100 g of liver, 50 g of kidney and fat, 1.5 kg of milk and 100 g of eggs. Previously, the Committee estimated intakes by using MRLs to derive a theoretical maximum daily intake (TMDI). At the current meeting, the Committee modified this procedure and is now using the median residue levels to derive an estimated daily intake (EDI) to better reflect estimates of chronic (lifetime) exposure (see section 2.4.1). Figure 1 is an update of the figure prepared during the Bilthoven MRL workshop (*4*).

Conclusions

The Committee confirmed that the rounding practices used in expressing the ADI are scientifically and mathematically sound. In addition, since the ADI is not directly used in the derivation of the MRL, the JECFA rounding practices have no direct consequence on the MRL.

Annex B:

EC COMMENTS ON THE NEW APPROACH DEVELOPED BY JECFA FOR EXPOSURE AND MRL ASSESSMENT OF RESIDUES OF VMP

Executive summary

At its 2006 meeting the Joint FAO/WHO Expert Committee on Food Additives (JECFA) agreed upon a new approach for the estimation of chronic dietary intake for use in MRL assessments for veterinary drugs[9]. The new approach uses median residue levels in animal derived food for the calculation of a so-called Estimated Daily Intake (EDI) from a model daily food basket. Previously exposure was estimated using the Theoretical Maximum Daily Intake (TMDI) and a model daily food basket. The TMDI represents a 'worst case' assumption in which residue levels are at the maximum permitted level (i.e. the MRL) in each food commodity consumed.

JECFA considered the EDI to be the most reliable and accurate estimate of the actual long-term exposure to residues and therefore a more appropriate tool in determining whether residues pose any chronic (lifetime) risks.

The CVMP, having thoroughly examined the new JECFA approach, agreed that median residue values would be an appropriate model for estimating chronic dietary exposure. However, the CVMP concluded that a change of the 'chronic' model would automatically imply consideration of a complementary approach to address 'acute' scenarios based on the assumption of short-term 'high residue exposure'. As this necessary second element of the model has not yet been developed, the CVMP considered the new JECFA proposal to be unfinished. A full evaluation of the EDI approach and its use in MRL assessments is not possible until information is available on how the acute exposure assessment will be made.

The new JECFA approach of estimating the MRL involves an apparent disconnection of the link between the MRL derivation and ADI (i.e., the proposed MRL will no longer need to lead to exposure below the ADI when exposure is calculated using the TMDI). The CVMP considered that this approach can only be accepted when the ADI is based on chronic exposure data AND data has been provided to demonstrate that acute exposure scenarios do not represent a safety concern.

A further serious concern raised by the CVMP was that with the new approach the size of the MRL would be very sensitive to variability and extreme values in the data, which in turn, are to a considerable degree dependent on the design and quality of the residue study performed. It was noted that weak data (i.e. few data points or data showing high variability) would be rewarded with higher MRLs and that the spread between median and extreme values in a single residue trial could determine the size of the MRL, which could represent a concern for consumer safety.

Alternative approaches need to be investigated to overcome this issue and to reward the production of robust data. One way this might be achieved would be to use the lower confidence limit of a percentile instead of the upper confidence limit of a percentile as the point of departure in the MRL calculation (see figure 4).

The CVMP also noted that it is likely that an increased number of animals would be required in order to use the new approach compared to those given in current international guidelines. Other parameters such as the number of time points and the frequency of time points may also need to be adjusted.

Another point of concern was that the presented approach relies to a great degree on the applicability of a specific statistical model of linear regression and tolerance limit determination. Practical experience has shown that the statistical assumptions underlying this model are not met for a considerable number of data sets.

To deal with data that cannot be assessed using the proposed statistical approach, a robust alternative approach will probably need to be developed to allow application and extension of the EDI concept to a wider range of substances.

A further concern of the CVMP is that JECFA reports that before an MRL recommendation is made the candidate value is checked against Good Veterinary Practice (GVP) data, and is altered to make it consistent with this data. However, GVP is a poorly defined term and the effect of incorporating GVP data into the approach may be enormously variable. The use of GVP data is not considered to be scientifically robust and its incorporation into a method that is argued to be scientifically superior is inappropriate.

The CVMP agreed that practical experience with this approach is very limited (only very few substances have been assessed with the new approach) and that the methodological and statistical questions raised in this paper need to be addressed before any definitive conclusions can be drawn.

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[9] Joint FAO/WHO Expert Committee on Food Additives (JECFA), 66th meeting (Residues of veterinary drugs), Rome, 22 - 28 February 2006, Evaluation of certain veterinary drug residues in food. WHO TRS 939
http://whqlibdoc.who.int/publications/2006/9241209399_eng.pdf ; Summary and Conclusions
ftp://ftp.fao.org/ag/agn/jecfa/jecfa66_final.pdf

In addition, the CVMP strongly suggests that a strategy should be agreed upon that addresses the objectives of the approach, its scope of application, and the implementation of the new approach. This should take into account current limitations of the approach, the major impact it has on the setting of MRLs, and the fact that it is significantly different to the approach used over the last decades. This could be addressed by both JECFA (in respect to scientific) as well as CCRVDF (regarding risk management issues).

1. Background

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) agreed at its 66th meeting (2006)[1] a new approach for the estimation of chronic dietary intakes for use in MRL assessments for veterinary drugs. The elaboration of this new approach followed up recommendations from the FAO/RIVM/WHO Workshop in Bilthoven (2005)[10]. The CVMP reviewed the new approach developed by JECFA in 2007. The comments of the European Community at the 17th Session of the Codex Committee on Residues of Veterinary Drugs in Foods in September 2007 presented under point 3a, Report of the 66th JECFA meeting (see CRD 13 of 17th CCRVDF meeting), which were based on the CVMP considerations, summarized the first findings and concerns regarding this approach.

In the meantime a further in depth review has been undertaken by the CVMP and its Safety Working Party (SWP-V). In this review the SWP-V held a dedicated workshop in February 2008 to discuss the approach with Dr Dieter Arnold (Vice-Chairman of the 66th JECFA meeting on residues of veterinary drugs) and Dr Annika Wennberg (JECFA Secretariat). The workshop aimed to clarify commonalities and differences between the CVMP and JECFA approaches for assessing the safety of residues, and to evaluate possible implications that would arise from the new JECFA principle for estimating exposure if it were endorsed by the EC.

Having completed the review the CVMP supported by the SWP-V prepared this document detailing their findings. In this document the JECFA approach is described followed by the discussion and conclusions of the CVMP.

2. Exposure scenarios

2.1 Chronic exposure

At its 66th meeting the JECFA Committee[1] modified its procedure for estimating chronic exposure to residues of veterinary drugs. The new concept is to use median residue levels in animal derived food for the calculation of a so-called Estimated Daily Intake (EDI) from a model daily food basket. JECFA considered the EDI to be the most reliable and accurate estimate of the actual long-term exposure to residues and therefore a more appropriate tool in determining whether residues pose any chronic (lifetime) risks.

In the past, exposure was estimated using the Theoretical Maximum Daily Intake (TMDI) which represents the 'worst case' assumption of maximum permitted residue levels (i.e. at the MRL) in each food commodity consumed. This important change of model was initiated because the TMDI approach was thought to grossly overestimate the true chronic level of exposure of the population. JECFA considered that, if good veterinary practice is observed, there is a relatively low statistical probability that residues in edible tissues will approach the MRL.

The calculation of the EDI is based on the same equation as used previously for the calculation of the TMDI (including use of standard consumption figures and corrections for ratios of marker/total residues) with the one exception of using median residues instead of the MRLs as the point estimate of the residue concentration in animal derived food.

The modified chronic model proposed by JECFA is consistent with the approach already used by JMPR in the assessment of chronic exposure to pesticide residues. In this area the TMDI concept was reviewed in 1997 and it was proposed to use supervised trials median residue (STMR) levels instead of the MRL to estimate a chronic intake[11]. Thus, the new JECFA proposal contributes to a better harmonization of Codex residue assessment procedures for chemicals in food. The CVMP is currently using TMDI estimates in relation to chronic exposure.

The new JECFA proposal is schematically shown in Figure 1, taken from the report of the 66th JECFA meeting)[1].

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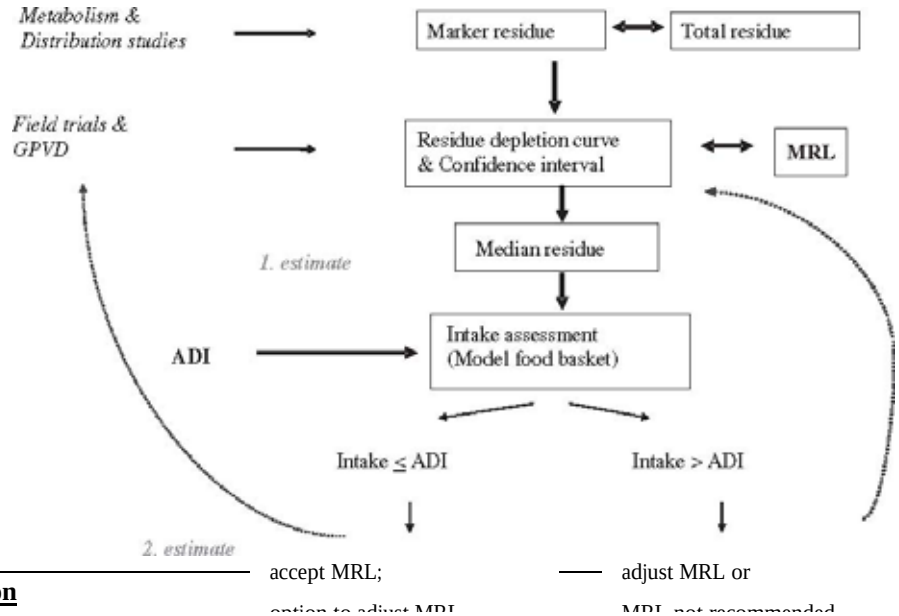
[10] FAO/RIVM/WHO Workshop: "Updating the Principles and Methods of Risk Assessment: Maximum Residue Levels (MRLs) for Pesticides and Veterinary Drugs (2005)
http://www.fao.org/ag/AGP/AGPP/Pesticid/JMPR/DOWNLOAD/bilthoven_2005.pdf

[11] WHO 1997: Guidelines for predicting dietary intake of pesticide residues (revised); Prepared by the Global Environment Monitoring System - food contamination monitoring and assessment programme (GEMS/Food) in collaboration with the Codex Committee on Pesticide Residues, WHO/FSF/FOS/97.7., WHO, Geneva, Switzerland.
http://www.who.int/foodsafety/publications/chem/en/pesticide_en.pdf

Figure 1: The JECFA residue evaluation process

JECFA Residue Evaluation



CVMP conclusion

The CVMP was in agreement with JECFA that median residue values would be an appropriate model for estimating chronic dietary exposure.

2.2 Acute (short-term) exposure

Replacement of the 'worst case concept' by 'median values' can be expected to considerably lower exposure estimates and, consequently, the estimates of risk. This inevitably raises the question of whether the EDI approach would provide a sufficient degree of protection for consumers exposed to residue levels higher than the median, on occasions when food baskets containing higher than average residues are consumed (e.g. residues at MRL levels in a single meal/over the course of day). While the likelihood of this happening on a regular basis was considered relatively low, there was consensus that the EDI does not cover the scenario of a 'short-term/high-concentration' exposure.

In addition, acute exposure scenarios are of particular interest for pharmacologically active substances which, in many cases, present a relevant acute hazard (i.e., ADI/NOEL is based on an acute effect). In relation to acute effects a separate exposure assessment would be needed to ensure that there is no relevant acute risk at the MRLs established.

JECFA has currently no established procedures for addressing acute intake scenarios. JECFA recognized, however, that further work is necessary to adequately address concerns related to short term hazard and exposure assessment[2]:

"[..] JECFA should consider the use of the concept of the acute reference dose (ARfD) in addition to the ADI, when a veterinary drug being considered exhibits acute toxicity. JECFA should develop procedures to discriminate between ADI and ARfD for cases where it would be appropriate to estimate short-term (acute) intakes."

CVMP conclusion

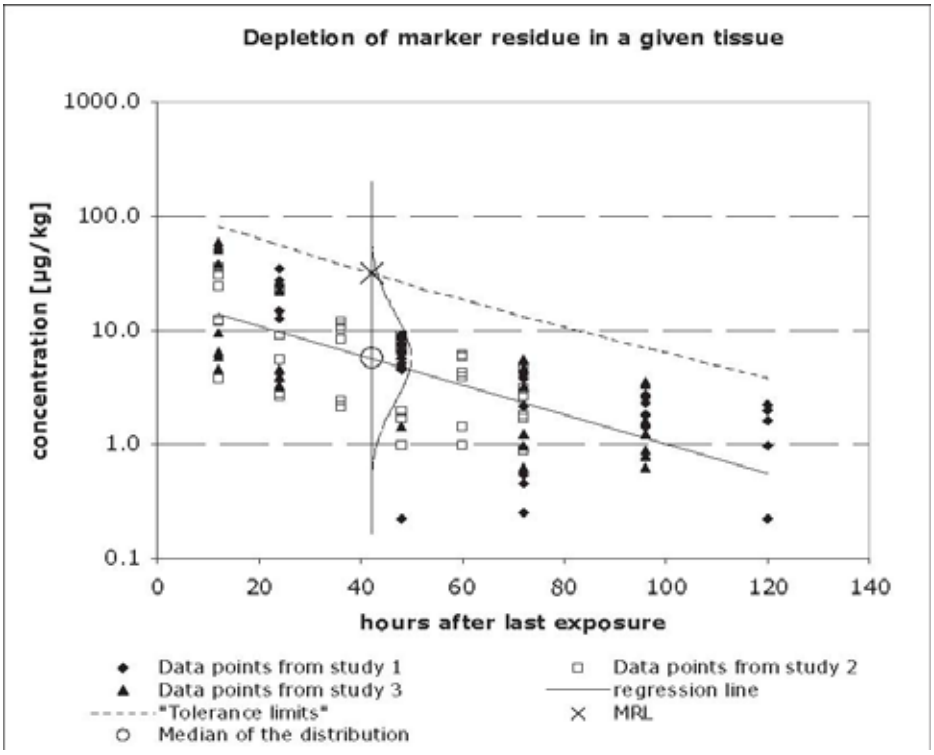
While the logic for using the EDI in relation to chronic exposure was clearly understood, the CVMP reconfirmed its previous conclusion that a change of the 'chronic' model would automatically imply consideration of a complementary approach to address 'acute' scenarios based on the assumption of a short-term 'high residue exposure'. As this necessary second element of the model has not yet been developed, the CVMP considered the new JECFA proposal to be unfinished. A full evaluation of the EDI approach and its use in MRL assessments is not possible until information is available on how the acute exposure assessment will be made.

3. Previous JECFA and current CVMP approaches

The previous JECFA approach was based on the concept that the TMDI calculated using the MRLs does not exceed the ADI. This principle has also been and is still applied in the EU.

4. New JECFA approach

The new approach described in the 2006 JECFA report for the 66th meeting defines the link between MRL and daily residue intake (as expressed through the EDI) as follows[1]:



Explanation of the relationship between MRL and the median concentration used for the calculation of the estimated daily intake (EDI)

"*The MRL and the median concentration are derived from the same time point of the depletion data of the marker residue. The MRL is a point on the curve describing the upper one-sided 95% confidence limit over the 95th percentile. The median is the corresponding point on the regression line for the same time point. Both figures are obtained from a statistical evaluation of the data*"

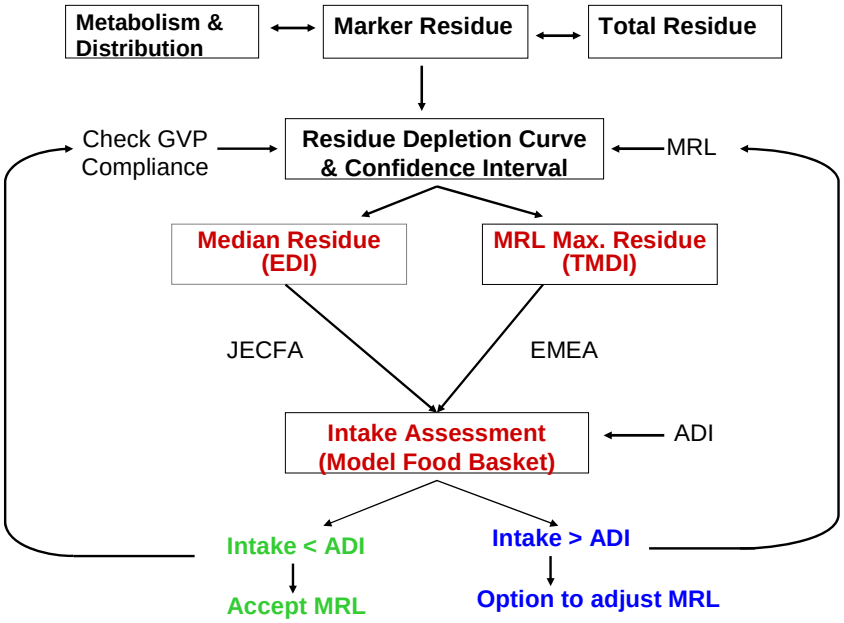
This relationship between MRL and EDI is illustrated in Figure 2 (taken from the JECFA report[1]). The point at or beyond which the predicted median intake (EDI) equals the ADI is used as the point of departure (POD) for the derivation of MRLs. In this first approximation the MRL represents the upper tolerance limit for the marker residue concentration in the edible tissue at $t_{EDI/ADI}$[12].

Figure 2: Statistical approach to determine MRL based on the EDI concept

JECFA also considers the likely level of residue that can be expected in edible tissues after use of the veterinary product under field conditions (i.e. in accordance with the principles of Good Veterinary Practice) and the MRL may be further reduced if suitable analytical methods are available that allow for routine monitoring at lower levels. After taking account of such factors, the resultant MRLs would usually be lower than the maximum value (first approximation) that can be estimated solely on the basis of an acceptable dietary exposure.

Figure 3 provides a comparison of the new JECFA method and the CVMP method. Figure 3: Comparison of new JECFA and CVMP method (Figure taken from JECFA report[1] and modified)

[12] tEDI/ADI = time point when the EDI reached the level of the ADI



CVMP conclusions

Apart from open questions related to the selection of appropriate exposure scenarios (chronic versus acute), the new approach of estimating the MRL involves an apparent disconnection of the link between the MRL derivation and ADI (i.e. the proposed MRL will no longer need to lead to exposure below the ADI when exposure is calculated using the TMDI). This approach can only be accepted when the ADI is based on chronic exposure data AND data has been provided to demonstrate that acute exposure scenarios do not represent a safety concern.

A main concern was that with the new approach the size of the MRL would be very sensitive to variability and extreme values in the data, which in turn, are to a considerable degree dependent on the design and quality of the residue study performed. It was noted that weak data (i.e. few data points or data showing high variability) would be rewarded with higher MRLs and that the spread between median and extreme values in a single residue trial could determine the size of the MRL, which could represent a concern for consumer safety.

Alternative approaches need to be investigated to overcome this issue and to reward the production of robust data. One way this might be achieved would be to use the lower confidence limit of a percentile instead of the upper confidence limit of a percentile as the point of departure in the MRL calculation (see figure 4).

It was also noted that it is likely that an increased number of animals would be required in order to use the new approach compared to those given in current international guidelines. Other parameters such as the number of time points and the frequency of time points may also need to be adjusted.

Another point of concern was that the presented approach relies to a great degree on the applicability of a specific statistical model of linear regression and tolerance limit determination. Practical experience has shown that the statistical assumptions underlying this model are not met for a considerable number of data sets.

To deal with data that cannot be assessed using the proposed statistical approach, a robust alternative approach will probably need to be developed to allow application and extension of the EDI concept to a wider range of substances.

JECFA reports that before an MRL recommendation is made the candidate value is checked against Good Veterinary Practice (GVP) data, and is altered to make it consistent with this data. However, GVP is a poorly defined term and the effect of incorporating GVP data into the approach may be enormously variable. The use of GVP data is not considered to be scientifically robust and its incorporation into a method that is argued to be scientifically superior is inappropriate.

The CVMP agreed that practical experience with this approach is very limited (only very few substances have been assessed with the new approach) and that the methodological and statistical questions raised in this paper need to be addressed before any definitive conclusions can be drawn.

In addition, the CVMP strongly suggests that a strategy should be agreed upon that addresses the objectives of the approach, its scope of application, and the implementation of the new approach. This should take into account current limitations of the approach, the major impact it has on the setting of MRLs, and the fact that it is significantly different to the approach used over the last decades. This could be addressed by both JECFA (in respect to scientific) as well as CCRVDF (regarding risk management issues).

Figure 4: Ways to overcome the problem of variation should be explored. One way could be to use a lower confidence limit of the selected percentile instead of the upper confidence limit. In this way, the resulting MRL will become lower in case of weak data and become higher with strong data. If there is a concern that the MRLs will become too low, then a higher percentile could be selected (e.g. P99 instead of P95).

Annex C :

EC COMMENTS ON INJECTION SITE RESIDUES

Problem Statement

Establishing maximum residue limits (MRLs) in muscle for long-acting injectable products poses a particular problem. For these products residue levels at the injection site tend to be high while depletion of residues is slow. Residue levels at the injection site tend to be dramatically higher than those in non-injection site muscle, or fat, liver or kidney. Consequently, withdrawal periods for these products are typically determined by residue levels at the injection site and tend to be particularly long.

Industry argues that as long-acting injectable products require less frequent dosing than their short acting counterparts they offer improved convenience, compliance and consequently improved consumer safety and animal welfare. However, the extended withdrawal periods for these products discourages their development and use, and represents a burden for farmers.

The CVMP considers that withdrawal periods for these products should be no longer than absolutely necessary based on scientific and consumer safety considerations.

The Committee has explored a number of ways of achieving this goal. A number of the proposals investigated would require non-injection site muscle and injection site muscle to be treated differently, both during the CVMP assessment and possibly also during residue surveillance/control. Residue surveillance/control may need to be able to distinguish between non-injection site muscle and injection site muscle.

The CVMP has, therefore, discussed the issues with those involved in residue surveillance/control in order to (1) better understand the requirements of residue surveillance/control, and (2) further explore the possibility of introducing changes to residue surveillance protocols. Furthermore, a discussion with industry representatives took place to better understand the industry's concerns regarding the current approach and their proposals for the future. This document describes the approaches considered and their strengths and weaknesses.

Possible approaches that would lead to decreased withdrawal periods for long-acting injectable products

Suggestions explored by the CVMP for addressing the injection site residue issue include:

NO.	PROPOSAL	COMMENT
1	Always use the same tissue (e.g., neck) for injections and then discard that tissue	▪ May be impractical for vets and farmers ▪ May be impossible for large volume injections ▪ Wasteful of meat
2	Make injection sites exempt from the MRL	▪ Risk for consumer safety
3	Calculate withdrawal periods for injection sites without using a statistical method, but by establishing a time point at which residues at injection sites from all animals are below the MRL	▪ Uncertainties mean that the impact would be inconsistent and unpredictable
4	Establish injection site residue limits at an increased level relative to muscle MRLs using a standard factor (e.g., 10)	▪ Questionable scientific rationale ▪ Potential risk for consumer safety, particularly if ADI[1] is based on an acute endpoint ▪ Residue surveillance would need to be able to distinguish between non- injection site muscle and injection site muscle
5	Use non-edible tissues as injection sites	▪ May be impractical for vets and farmers ▪ May not be possible in many cases due to lack of appropriate non-edible tissues
6	Develop formulations that decrease the impact of injection site residues / phase out the use of those formulations that lead to the most significant injection site residues	▪ Desirable solution for the long-term but will not help in short-term
7	Recommend lower than necessary MRLs for tissues other than muscle in order to allow for increased muscle MRLs	▪ Tissue distribution relationship would be disrupted with the effect that it could not be inferred that because a compliant result is obtained in one tissue other tissues would also be compliant

NO.	PROPOSAL	COMMENT
		▪ Decreasing MRLs for non-injection site tissues could be viewed as penalising products administered by routes other than injection
8	Establish injection site residue limits based on an Acute Reference Dose rather than the ADI[1]	▪ May be useful if it can be shown that exposure to injection sites is rare ▪ Would only be applicable if the ADI[1] were based on chronic exposure ▪ Residue surveillance would need to be able to distinguish between non- injection site muscle and injection site muscle
9	Use the 'unused' portion of the ADI[1] to maximise muscle MRLs	▪ May be useful in cases where there is a large 'unused' portion of the ADI[1] ▪ Tissue distribution relationship would be disrupted with the effect that it could not be inferred that because a compliant result is obtained in one tissue other tissues would also be compliant
10	Reconsider the standard food basket – question the position that a person may consume 300g of muscle, 100g liver, 50g fat and 50g kidney on a daily basis	▪ Might allow MRLs for all tissues to be increased ▪ Would represent a major change to an internationally endorsedrisk assessment approach ▪ Could potentially lead to revised MRLs for most substances
11	Amend the intake calculation so that exposure resulting from ingestion of each individual tissue type may reach the ADI[1] (minus a proportion of the ADI[1] allocated for milk).	▪ Approach followed in USA ▪ Incompatible with the internationally accepted food basket approach

[1] ADI = Acceptable Daily Intake

The proposals in the table above can be divided into those that require residue surveillance/control to be able to distinguish between non-injection site muscle and injection site muscle (proposals 4 and 8), and those that do not (proposals 1, 2, 3, 5, 6, 7, 9, 10 and 11).

Proposals that do not require residue surveillance/control to be able to distinguish between non-injection site and injection site muscle

From the comments in the table it can be concluded that proposals 1 to 3 are unlikely to represent appropriate solutions. Proposal 5 (use non-edible tissues as injection sites) could provide a solution for some products (for example, the ear has previously been proposed as a non-edible injection site and may be appropriate for products for individual animal treatment with small volume injections).

For options 1 (always use the same tissue and discard that tissue) and 5 (use non-edible tissues) there is a risk of abuse as injections could be given at sites that are unlikely to be tested. However, it should be borne in mind that the current system cannot exclude abuse either.

Proposal 6 (develop formulations that decrease the impact of injection site residues) is the most desirable option of all, but unfortunately it is unlikely to represent a solution in the immediate future.

In its considerations the CVMP has taken care, when establishing MRLs, to consider tissue distribution relationships as, in theory, these allow residue levels detected in any one target tissue to be used to predict the compliancy of other tissues. Residue surveillance/control experts have confirmed that it is unusual to routinely test all four tissues – the most common approach for antibiotics seems to be to sample only kidney and/or muscle. The fact that not all tissues are always tested indicates that the tissue distribution relationship is used in practice. However, residue control experts have also confirmed that a non-compliant result for an antibiotic in kidney is not necessarily reflected by a non-compliant result in muscle, and so muscle testing must be performed before non-compliancy can be concluded for this tissue. This indicates that the tissue distribution relationship used in the setting of MRLs is not entirely effective for extrapolating compliancy from one tissue to another. If the CVMP were prepared to disregard the tissue distribution relationship, then proposal 7 (recommend lower than necessary MRLs for tissues other than muscle in order to allow for increased muscle MRLs) could be used. However, for substances to be administered by more than one route, establishing lower than necessary MRLs for muscle may be beneficial for the injectable product while representing a serious disadvantage for non-injectable formulations. Industry representatives have reported that, from their perspective, this disadvantage is

easily outweighed by the advantage gained from increasing the muscle MRL. It is also worth noting that in its MRL recommendations, JECFA is increasingly seeking to ensure that the tissue distribution relationship is maintained, so by disregarding tissue distribution the CVMP would be out of step with other internationally accepted approaches.

Like proposal 7, proposal 9 (Use the 'unused' portion of the ADI to maximise muscle MRLs) would disrupt the tissue distribution relationship. However, it may be of some use in those cases where there is a large 'unused' portion of the ADI.

Proposal 10 (reconsider the standard food basket) would represent a major change to an internationally accepted approach to evaluating the safety of veterinary medicinal products for food producing animals, and given that the existing methodology has demonstrated itself to be safe, may be questioned on consumer safety grounds.

Proposal 11 (Amend the intake calculation so that exposure resulting from ingestion of each individual tissue type may reach the ADI (minus a proportion of the ADI allocated for milk)) is already used by the FDA and may be responsible, in large part, for the shorter withdrawal periods typically allocated by the FDA. However, such an approach is inconsistent with the internationally accepted use of a standard food basket for calculating potential consumer exposure.

It is also worth noting that in a small number of its MRL assessments the CVMP has recommended that no MRL for muscle be established, based on low residue levels seen following administration of the substance. When this is done withdrawal periods for the subsequently marketed product are established based on calculations that demonstrate that ingestion of a standard food basket in which the muscle portion is made up entirely of an injection site, does not lead to exposure greater than the ADI. However, the absence of an MRL for muscle represents a regulatory problem for residue surveillance/control as increasingly meat is imported into the EU as lean muscle and while MRLs may have been established for fat, lean meat may not contain sufficient fat to test. The absence of an MRL for muscle may therefore mean that there are no reference values against which to test such consignments. Furthermore, as muscle is the tissue most commonly eaten, the absence of an MRL for muscle may be difficult to justify to consumers. Consequently, the CVMP considers that in all but exceptional cases, MRLs should be established for muscle.

Proposals that would require residue surveillance/control to be able to distinguish between non-injection site and injection site muscle

Proposal 4 (establish injection site residue limits at an increased level relative to muscle MRLs using a standard factor) is not a favoured option given the questionable scientific rationale and potential risk for consumer safety.

Proposal 8 (Establish injection site residue limits based on an Acute Reference Dose rather than the ADI) may be justifiable on scientific and consumer safety grounds if it can be shown that the ingestion of injection sites is a rare event. A major barrier to the introduction of this proposal is the fact that it would require residue surveillance to be able to distinguish between non-injection site muscle and injection site muscle.

The only way to be able to distinguish between non-injection site muscle and injection site muscle would be for a second muscle sample to be taken (from the same animal but a different muscle group) and tested in the event of a noncompliant result in the first sample. In the EU, residue surveillance programmes generally rely upon a single sample being taken of the relevant target tissue (e.g., muscle). A scheme that used two muscle samples was previously proposed in the Codex draft guideline for residues at injection sites (1999). The draft guideline proposed that the second sample would be analysed if the first sample was found to contain residue levels above the MRL for muscle but below the injection site residue limit. If analysis of the second sample revealed residue levels in accordance with the MRL for muscle then it could be assumed that the first sample had contained an injection site. Only if both samples exceeded the MRL for muscle would the carcass/consignment be condemned. Additionally, it would seem reasonable to condemn the carcass/consignment if one sample contained residue levels above the injection site residue limit.

The proposed draft Codex guideline was never adopted as agreement could not be reached by the various stakeholders. One of the barriers to agreement was the difficulties that would result for residue surveillance. The EU commented that the proposals would result in practical problems for sampling protocols:

- Injection sites may not be easily identifiable as such and tissue sampling may result in only part of an injection site being sampled, leading to results which are difficult to interpret [although it should be noted that this is presumably a problem under existing residue surveillance protocols]
- Additional validation of the analytical method may be required in some cases
- An additional analytical method may be needed if the marker residue at the injection site differs from the marker residue in non-injection site muscle

If the 'two samples of muscle' model was adopted, an additional problem for residue surveillance could occur if there is no access to a second sample, a situation that may arise with retail sampling and at import, particularly if the produce is in the form of cuts of meat rather than whole carcasses. It is unclear how a residue level greater than the MRL for muscle would be interpreted in such circumstances as this could potentially be because of an injection site being inadvertently sampled.

From discussions with residue surveillance/control experts it is clear that across the EU there is considerable variation in the sampling protocols and analytical methods used for residue control/surveillance. Considering residues testing for antibiotics alone, the approach taken in the different Member States is not harmonised. The detection capabilities and the range of screening tests vary widely and there are differences in which tissues are selected (kidney and/or muscle) and the number of tissue samples taken from each carcass. Any changes to MRL setting procedures that would require parallel changes to sampling and testing protocols must take this lack of harmonisation in residue control/surveillance into account. At present any proposal to introduce a harmonised double sampling approach across the EU would be likely to meet strong resistance as such a requirement would have substantial resource implications resulting from the need to take, store, test and analyse the additional samples as well as to set up and validate additional analytical methods where necessary (residues present at the injection site will be of an order of magnitude greater than in non-injection site muscle and well outside the working range of a typical quantitative chemical confirmatory method). If it is not realistic to envisage the introduction of such a harmonised approach, then any changes to current MRL-setting procedures must be practicable in terms of residue control/surveillance in the existing non-harmonised environment.

Comment on the approach used in the USA

In some instances the FDA Center for Veterinary Medicine has established an allowed residue level at the injection site that is distinct from the allowed residue level in non-injection site muscle. In these cases the allowed residue level at the injection site has been based either on a default value of 10 times the target tissue tolerance limit (MRL) or on the ARfD. Regardless of which of these options has been used, the applicant has had to demonstrate that at the proposed withdrawal period residue levels in the target tissue (typically liver or kidney) comply with the established tolerance limits and that residue levels at the injection site comply with the relevant allowed residue level. If residue levels at the injection site are seen to exceed the allowed level, then the target tissue tolerance limit is adjusted downwards to a level that ensures that when it is met then the allowed injection site residue limit will also be met. Note that this means that the tolerance levels for tissues other than muscle are reduced which, as mentioned in relation to proposal 9, could have the effect of penalising non-injectable formulations.

As detailed in relation to proposal 4, the CVMP would not be supportive of a proposal to establish an increased injection site residue limit using a standard multiplication factor. The CVMP does consider that it may be scientifically valid to use the ARfD to establish a safe level for residues at the injection site if it could be shown that the ingestion of injection sites is a rare event. The main problem with this approach would be that residue surveillance/control authorities would be faced with the need to distinguish between non-injection site and injection site muscle.

Discussion and conclusions

The CVMP has investigated a number of options for assessing injection site residues but no single proposal has emerged as a clear favourite. Without the introduction of double muscle sampling for residue surveillance/control the only approaches identified that could be used are:

Proposal 5: use non-edible tissues as injection sites;

Proposal 6: develop formulations that decrease the impact of injection site residues / phase out the use of those formulations that lead to the most significant injection site residues;

Proposal 7: Recommend lower than necessary MRLs for tissues other than muscle in order to allow for increased muscle MRLs;

Proposal 9: Use the ‘unused’ portion of the ADI[1] to maximise muscle MRLs.

Proposal 5 is only likely to be applicable in a small number of cases. Proposal 6 is attractive but the responsibility for the development of such formulations lies primarily with industry. Proposal 7 may be an option in a number of cases but it does not respect the tissue distribution relationship. Furthermore, it could be viewed as an approach that penalises products that are not administered by injection. Proposal 9 will only be useful in those instances where there is a large ‘unused’ portion of the ADI and, like proposal 7, it does not respect the tissue distribution relationship. Additionally, it should be borne in mind that it may be necessary to leave a portion of the ADI unused in order to allow for the establishment of MRLs in other tissues (milk and eggs) and possibly for residues that occur as a result of the use of the substance in pesticides.

With regards to options that would require double sampling of muscle at residue surveillance/control, only proposal 8 (establish injection site residue limits based on an ARfD rather than an ADI) is considered scientifically justified, and only if it can be shown that ingestion of injection sites is a rare event. However, it is clear that implementation of this option would require close cooperation with residue surveillance/control authorities, and it is acknowledged that implementation of appropriate residue surveillance/control procedures may represent a significant challenge.

The CVMP concludes that it may be possible to increase the permissible level of residues at injection sites by implementing one or more of the above approaches on a case by case basis but considers that, at present, none of the proposals investigated stand ready to make a dramatic impact on withdrawal periods. From the CVMP’s perspective, the most desirable proposal is the development of formulations that decrease the impact of injection site residues

(proposal 6) as such formulations would bring clear benefits to farmers, animals, consumers and industry. The CVMP notes that other proposals investigated offer limited applicability and/or would have limited impact. For example, recommending lower MRLs for tissues other than muscle in order to allow for increased muscle MRLs (proposal 7) and using the 'unused' portion of the ADI to maximise muscle MRLs (proposal 9) would, in most examples examined, lead to only small increases in the muscle MRL. With regards to the use of the ARfD to establish an injection site residue limit (proposal 8), the CVMP notes that for the majority of existing long acting injectable products this approach would not be appropriate as the established ADI is based on acute endpoints.

This reflection paper is now published with the aim of stimulating discussion on this topic, of attracting comments on the views expressed in this paper, and in the hope of receiving new proposals for possible ways to reduce the impact of injection site residues without compromising consumer safety.