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Revised reflection paper on injection site residues: considerations for risk assessment and residue surveillance

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1. Introduction

In June 2008 the CVMP published a first version of this reflection paper for consultation (a copy of that document is provided in annex I). As detailed in the problem statement presented in original reflection paper, residues in injection site muscle for some products tend to be dramatically higher than residues in non-injection site muscle (as well as in fat, liver and kidney). The result is that a single carcass may contain muscles with very different residue levels of injectable substances, and these differing levels of residues in a single tissue type make setting an appropriate MRL very challenging.

The CVMP considers that, to be considered 'appropriate', an MRL (i) must ensure consumer safety and (ii) should result in a withdrawal period that is not longer than necessary in order to ensure consumer safety. MRLs set in the conventional way can result in extended withdrawal periods for injectable substances that do not meet the second of these criteria.

The CVMP's 2008 reflection paper, which followed on from discussions with residue surveillance authorities and industry representatives, enumerated a number of options that could be used in order to maximise the appropriateness of the muscle MRL. However, in its conclusion the paper acknowledged that while one or more of the options presented might be applicable on a case by case basis, none of the options could be applied consistently to result in a significant impact on withdrawal periods. The aim of the reflection paper was to stimulate discussion on the topic of injection site residues and to attract further comments and views to be considered in the development of an approach that would allow the establishment of appropriate MRLs for injectable substances.

Following publication of the reflection paper several stakeholders submitted comments. While the Committee appreciated the constructive nature of the comments received, it remained unable to identify an overall approach that could be consistently used in the development of MRLs for injectable substances. The Committee has therefore continued to engage in discussions on the topic of injection sites and in October 2012 agreed to work concertedly towards the development of an approach that would be used consistently to develop appropriate MRLs for injectable substances.

In July 2013 the Committee agreed on an approach to be used. This reflection paper describes that approach and stakeholders are now invited to comment on it.

2. Discussion

The Conventional approach

According to the conventional approach for setting MRLs residue depletion data for non-injection site muscle, fat, liver and kidney are examined to establish residue levels in these tissues at the time point at which the Theoretical Maximum Daily Intake (TMDI) falls below the ADI. The residue levels at this time point represent tentative MRLs that may be amended to account for other factors (e.g., the need to keep a portion of the ADI available to account for consumer exposure to residues from other sources) before final MRLs are proposed. When a veterinary medicinal product (VMP) is subsequently developed the withdrawal period is derived in such a manner as to ensure that residues in edible tissues deplete to below the MRLs before slaughter.

For some products administered by intramuscular or subcutaneous injection there is a depot formed in (or, in the case of subcutaneous injections, adjacent to) the muscle which is the injection site. The withdrawal period for such a product must be long enough to ensure that residues in the depot have declined to the MRL before slaughter. As a result of the high levels of the active substance in the depot, the time taken for residues at the injection site to deplete to the MRL will be longer than the

time taken for residues in other tissues to deplete to the MRL. In the case of long acting formulations, the depletion of residues from the depot is particularly slow, with the result that the withdrawal period may be extensive. In practice, these extended withdrawal periods may not be justified based on consumer safety considerations and may act to unnecessarily reduce the availability of veterinary medicinal products.

Lessening the impact of residues in muscle on the withdrawal period

In some cases, although residues may be present at high levels in injection site muscle, in non-injection site muscle residue levels are very low (sometimes below the limit of quantification of the analytical method) even shortly after administration. The CVMP considered that, for such substances, a tissue other than muscle should be used for residue monitoring purposes and therefore, the establishment of an MRL for muscle for these substances would not be critical. Consequently, for a small number of injectable active substances, the CVMP has chosen not to recommend an MRL for muscle. For products containing active substances for which no muscle MRL has been established, withdrawal periods have been calculated using the "ADI approach", which ensures that at the selected withdrawal period, residues in a food basket including 300 g of injection site muscle are below the ADI, so ensuring consumer safety. This approach had the added benefit of allowing any unused portion of the ADI to be allocated to the injection site for the purpose of deriving the withdrawal period, and so lessened the impact of the injection site on the overall withdrawal period.

Problems at residue control

For many residue control authorities muscle is the tissue of choice for residue monitoring. The approach of not establishing a muscle MRL therefore represents a difficulty as it leaves residue control authorities with no legal value against which to control residue levels in their preferred tissue sample. In order to monitor residue levels in the carcass samples from one of the other edible tissues have to be collected and analysed. Furthermore, meat imported into the EU often takes the form of lean cuts of muscle – residue control in this meat is not possible in the absence of an MRL for muscle. This represents a serious concern, particularly as muscle is the most commonly ingested animal tissue.

An alternative that would not work

An alternative approach would be to set the muscle MRL based on the residue depletion profile seen in injection site muscle rather than on that seen in non-injection site muscle. This could lead to higher muscle MRLs and correspondingly shorter withdrawal periods. However, a muscle MRL derived in this way would be of little relevance for residue control authorities. This is because injection sites are scarce (and in many cases not easily identifiable by eye) while non-injection site muscle is abundant and consequently, except on rare, chance occasions, non-injection site muscle will be the muscle sampled by residue control authorities. It should be expected that residues in non-injection site muscle would comply with an MRL set on the basis of residues in injection site muscle, even if the withdrawal period were not respected (i.e. monitoring residue levels in non-injection site muscle provides no information on residues in injection site muscle).

In addition, if the muscle MRL were set in this way, residues in other tissues would often be below the limit of quantification at the timepoint by which residues in injection site muscle reaches the MRL (i.e. it would not be possible to establish a tissue distribution relationship between residues at the injection site and residues in other tissues). Monitoring of residues in non-injection site muscle would therefore not normally provide information on whether residues in other tissue types comply with the MRLs established for those tissue types.

Moreover, for substances that are also administered by routes other than injection, a muscle MRL based on residue depletion at the injection site would be of no practical value.

The CVMP's preference

From the CVMP's point of view, the preferred approach would be to establish 2 residue limits for muscle – one limit for residues in non-injection site muscle and a second limit for residues at the injection site. From a residue monitoring point of view this would require authorities to take muscle samples from 2 physically separate parts of the carcass. If analysis of the first sample revealed that neither of the 2 residue limits were exceeded, then it could be concluded that the carcass was compliant with the MRLs. If the analysis revealed that the lower of the 2 limits was exceeded but that the higher limit was not, then the possibility that an injection site had been sampled would need to be addressed. This would be done by analysing the second muscle sample. As it is extremely unlikely that both muscle samples would be injection sites, this second sample should comply with the lower (non-injection site) residue limit. If it did not, then the carcass would be considered non-compliant.

Problems with the CVMP's preference

Residue control authorities have indicated that the cost of routinely taking 2 muscle samples would be prohibitive. In the absence of a second muscle sample for residue monitoring this approach cannot work, as residue control authorities could not rule out the possibility that an injection site had been sampled and that consequently the higher of the 2 limits should be applied. Furthermore, for meat being imported into the EU, residue monitoring authorities may not have access to two muscle samples from physically separate parts of an individual animal.

A compromise

The CVMP accepts that for residue monitoring purposes there is a need to always establish a single muscle MRL (except in those cases where a "No MRL required" classification is justified).

The CVMP considers that this muscle MRL should be derived in the conventional way but that it should not be used as the sole reference value in the setting the withdrawal period needed for muscle. An alternative value that corresponds to the maximum level of residues that would be expected at the injection site at the anticipated withdrawal period should also be derived.

This second value (hereafter referred to as the Injection Site Residue Reference Value – ISRRV) would not be published in Regulation (EU) 37/2010 and would not be used for residue monitoring purposes. The ISRRV would be published only in the EPMAR.

The ISRRV is derived as follows: the theoretical maximum daily exposure is calculated on the basis of recommended MRLs for liver, kidney and fat (skin+fat in the case of pig) and the resulting value is compared to the ADI. The ISRRV is then derived in a manner that would allow for residues in 300g of muscle to correspond to the remaining portion of the ADI (minus any portion of the ADI required to allow for consumer exposure from milk or other sources). The withdrawal period for the VMP is then derived in a manner that ensures that residues at the injection site will be below the ISSRV and that residues in non-injection site muscle, liver, kidney and fat will be below the MRLs for these tissues.

This approach provides residue monitoring authorities with a single MRL for muscle while also allowing withdrawal periods to be derived that ensure consumer safety but which are not longer than necessary in order to do this.

Consequences of the compromise

Annex I of Regulation (EC) No 854/2004 laying down specific rules for the official controls on products of animal origin intended for human consumption, in Section II, Chapter V, indicates that "*meat is to be declared unfit for human consumption if it: …(i) contains residues or contaminants in excess of the levels laid down in community legislation*" (ie above the MRL). If a muscle MRL is established to reflect the maximum amount of residues that should be allowable in non-injection site muscle, then at the withdrawal period residues at the injection site are likely to be present at levels above the muscle MRL. This means that, in line with Regulation (EC) No 854/2004, injection site muscle (containing residues above the muscle MRL) should be considered as a non-edible tissue.

In practice, while efforts may be made to remove injection sites, these will not always be easily identifiable and it cannot be assumed that they will always be removed from the food chain. Consequently, the CVMP considers that, even if injection sites should be formally considered as non-edible tissue, it is important to ensure that residues at the injection site are not present at a level that might represent a consumer safety concern. Compliance with a withdrawal period that ensures that residues at the injection site are below the ISRRV will ensure that even if an injection site is ingested, it will not represent a consumer safety concern.

While residues at the injection site will not represent a consumer safety concern, the chance sampling of an injection site by a residue control authority could lead to a non-compliant residue finding and possible punitive action against the farmer. Such action would be unfair given that the non-compliant finding would not represent non-compliance with the withdrawal period.

The CVMP considers that the likelihood of chance sampling of an injection site is very low as animals receive a limited number of injections during their lifetimes and consequently the proportion of muscle tissue into which an injection will have been administered will be very small and the chances of sampling that tissue will be correspondingly small. Furthermore, residues in many injection sites are likely to be below the non-injection site muscle MRL as it is known that almost all injected active substances deplete to below the non-injection site muscle MRL within 3 months of being administered and many animals will not be administered injectable veterinary medicinal products during the last 3 months of life.

Nevertheless, the CVMP considers that measures should be introduced to further minimise the possibility of sampling of an injection site by residue control authorities.

Follow up actions

In order to further minimise the possibility of sampling of an injection site the CVMP would like to see injections consistently administered into one part of an animal while residue sampling, wherever possible, should use muscle from a different part of the carcass. The CVMP therefore recommends that product literature should specify the area of the animal into which injections should be administered. Where possible this should be a non-edible tissue. Where use of a non-edible tissue is not possible injections should be administered into the neck for cattle, swine, sheep, goats and horses. Cattle may also be injected immediately in front of the shoulder blade, and horses in the breast (pectoral muscles). Finally, subcutaneous injections to piglets may be given in the skin fold between the hind leg and the abdomen). This should be specified in product literature.

The CVMP will liaise with residue control authorities in order to encourage consistent sampling from a part of the animal other than those named above. Some residue control authorities already sample diaphragm muscle. From the CVMP's point of view (and from the farmer's perspective) this is ideal as it ensures that the injection site is not sampled. However, the CVMP is aware that many residue control

authorities do not consider diaphragm to be a convenient muscle with which to work (based on the fact that it has a high density of tendons and that in some species the amount of muscle available from the diaphragm may be insufficient) and that for imported meat (where the whole carcass is not available) use of the diaphragm does not represent a possibility.

Weaknesses of the compromise

The level of the ISRRV will be dependent on the size of the portion of the ADI that remains available once the MRLs for other commodities (and any other sources of exposure) have been taken into account. For substances for which the available portion of the ADI is very small, establishing an ISRRV will have a correspondingly small impact on the withdrawal period.

For some injectable substances residues in non-injection site muscle will be measurable over a considerable period of time. For these substances it may be possible to set an MRL for non-injection site muscle and an ISRRV for injection site muscle that would be reached at approximately the same withdrawal period. Compliance of non-injection site muscle with the MRL would then provide assurance that the injection site complies with the ISRRV. However, for other injectable substances, residues in non-injection site muscle will be very low from very early time points. The MRL for muscle for these substances will be based on the limits of quantification for the analytical method. For such substances compliance with the muscle MRL would not necessarily ensure compliance with the ISRRV and the overall withdrawal period. For these substances muscle is simply not an ideal tissue to sample (as residues are always low in non-injection site muscle) and the CVMP considers that, if an entire carcass is available, then a tissue other than muscle should be monitored in preference over muscle.

3. Conclusion

There is a need to always establish a single MRL for muscle (except in those cases where a “No MRL required” classification is justified) and this MRL should be derived in the conventional manner, i.e. reflecting residues in non-injection site muscle. A second residue value, referred to as the ISRRV, should be derived reflecting residues at the injection site. However, this second value will have no legal value and so will not be used for residue monitoring purposes. It will be published only in the EPMAR and it will be used only as a reference value in the derivation of withdrawal periods to ensure that, in the unlikely event of the ingestion of an injection site, residues in the injection site would not represent a safety concern for consumers.

As the ISRRV will invariably exceed the MRL at the withdrawal period, injection sites may contain residues at levels above the MRL. This means that, in line with Annex I of Regulation (EC) No 854/2004, injection sites should, in principle be considered as non-edible. However, in practice, it may not always be possible to identify injection sites by eye and consequently the possibility that injection sites may sometimes enter the food chain cannot be ruled out. By ensuring that residues at the injection site comply with the ISRRV the ingestion of an injection site would not pose a threat to consumer safety.

The chance sampling of an injection site by residue monitoring authorities could lead to a non-compliant residue finding. While the likelihood of sampling of an injection site containing residues above the MRL is very small, in order to minimise this risk further the CVMP considers that injections should be administered into one part of the animal while sampling for residue monitoring should, wherever possible, focus on a physically separate part of the animal. The CVMP therefore recommends that the administration site is specified in product literature and will liaise with residue monitoring authorities to encourage sampling from parts of the animal that are unlikely to have been injected.

4. Acknowledgements

With a view to better understand the practices and concerns of veterinarians in the field, of the meat processing industry and of residue monitoring authorities the CVMP, assisted by the Federation of Veterinarians in Europe and the European Commission (FVE), circulated requests for information to representatives of these groups. The CVMP would like to acknowledge the input provided by responders as well as the assistance of FVE and the Commission in collecting these.

ANNEX I

ORIGINAL CVMP REFLECTION PAPER AS PUBLISHED IN JUNE 2008

European Medicines Agency
Veterinary Medicines and Inspections

London, 23 June 2008
Doc. Ref. EMEA/CVMP/520190/2007-CONSULTATION

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

REFLECTION PAPER ON INJECTION SITE RESIDUES: CONSIDERATIONS FOR RISK ASSESSMENT AND RESIDUE SURVEILLANCE

ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	19 June 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 September 2008

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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 ▪ 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

No.	Proposal	Comment
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 endorsed risk 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.