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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

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

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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.