European Medicines Agency
Veterinary Medicines and Inspections

London, 13 January 2005
EMEA/CVMP/209865/2004

OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON INJECTION SITE RESIDUES (EMEA/CVMP/542/03-FINAL)

Background

The guideline on injection site residues was agreed by the SWP-V on 28 November 2004, and released by the CVMP for consultation on 14 January 2004. On 18 June 2004 a Focus Group with Interested Parties to discuss the guideline under consultation took place at the EMEA. On 17 September 2004, the SWP-V revised the guideline under consultation taking into account the comments received. On 13 October 2004, the CVMP finally adopted the guideline that will be implemented on 13 April 2005.

During the consultation process comments were received from:

Table 1: Organisations that commented on the draft Guideline as released for consultation

Organisation
Animal health industry organisations
European Group for Generic Veterinary Products (EGGVP)
IFAH-Europe
Research organisations
Farma Research BV
Harlan Bioservice for Science GmbH
Pharmaceutical company
Norbrook

The enclosed document provides an overview of the comments received on the draft guideline on injection site residues (EMEA/CVMP/542/03-CONSULTATION) and the considerations by the Committee for Medicinal Products for Veterinary Use and its Safety Working Party.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 47
E-mail: mail@emea.eu.int http://www.emea.eu.int

Table 2:Discussion of comments

GENERAL COMMENTS
Comments on "Assessment Approach" Comments on the general assessment approach were mainly received from industry organisations. These comments were mostly related to the use of the ADI/MRL as standard reference points for the establishment of withdrawal periods at injection sites. Industry expressed the view that use of an ADI/MRL concept was inappropriate for injection site residues because the basic assumption of daily intake, which is inherent in this concept, would grossly overestimate the real exposure. The approach was considered by the industry too restrictive, leading to disproportionate measures if applied as blanket approach to all injectables. Instead of a standard approach based on ADI/MRL, industry would have preferred more flexible and targeted approaches on a product-by-product basis. In this regard, it was suggested that the guideline could have benefited considerably if the EMEA/CVMP had allowed the option of using alternative concepts based on short-term exposure scenarios and acute reference doses. Industry felt that this was more in line with procedures accepted by international regulatory bodies and in other areas of risk assessment of food contaminants. One of the industry organisations explained in detail the rationale for preferring alternative concepts and recommended a statement on this issue to be included in a revised draft guideline. In support of their arguments, the same organisation also presented data and calculations concerning a probability analysis of injection site intake. It was underlined that a European consumer would consume a piece of injection site not more than four times in a year. Also comments from the other industry organisation mainly centred around the issues of applying short-term exposure approaches and acute reference doses in the assessment of injection site residues.
Comments on the treatment of injection sites as muscle tissues Further subjects of industry comments were related to the suggestion to treat injection sites as muscle tissues when establishing withdrawal periods. The use of statistical approaches to calculate withdrawal periods based on linear regression and 95/95 % tolerance limits was challenged as being inappropriate for many data sets due to high variability of data. It was obvious that industry preferred non-statistical approaches based on conventional safety spans.
Comments on "Technical Guidance" There were several, partly very detailed, comments and questions on sampling, sampling techniques and chemical analysis of injection site residues (shape of the sample, sample weight, homogenisation/storage of samples, need for a control sample etc). Industry organisations consistently argued against the requirement for a second sample at the injection site as this would mean additional demands for studies and extra expenses without any benefit on the side of safety. It was reasoned that proper marking and sampling techniques would already ensure adequate sampling. In contrast, there were comments from two research laboratories in which the proposal for an additional control sample was explicitly acknowledged as this would improve reliability of sampling. However in these comments from practitioners it was pointed out that an extra "surrounding" sample of 300 g is probably not feasible in many cases, considering the neck anatomy of medium or even large size animals.

The above-mentioned argumentations are discussed in the comments below.

SPECIFIC COMMENTS	CONSIDERATION BY CVMP/OUTCOME
Acute Reference Dose (acute RfD) The ADI, as now defined, however, does not and should not apply to injection site residues. Consumption of these tissues happens infrequently at best and cannot be considered to occur on a chronic basis. The industry organisations prefer the acute RfD approach and argue that since the injection site residues do normally not present a hazard, the injection site should not be treated as standard muscle tissue.	A considerable part of the ongoing discussion on "ADI" *vs* "acute RfD" derives from the common assumption that if a certain degree of exposure to a veterinary drug residue is "safe" on a daily basis (ADI), then a higher level of exposure is automatically acceptable on an occasional basis. This assumption rests on a misunderstanding about the precise ADI definition for many pharmacologically active compounds used in veterinary medicines. Such compounds are normally developed and designed to treat acute medical problems in mammals. Thus, in most cases, the desired acute pharmacological or antimicrobial effects rather than "chronic" toxicological effects, represent the sensitive endpoints which determine the overall NOEL and ADI. Therefore, a clear-cut distinction between a "classical" ADI derived from "chronic" studies and an additional acute reference value (acute RfD) based on acute/short-term endpoints is not possible for most veterinary drugs. Most veterinary ADIs already represent an upper acceptable safety limit for acute exposure. In addition, the CVMP did not propose the acute reference dose concept for the assessment of injection site residues, because of the following reasons: 1. It is difficult to define acute reference doses for pharmacologically active compounds. Very few compounds have ADIs solely based on chronic studies. 2. Probabilities of exposure is not a concept used in setting MRLs and withdrawal periods for veterinary medicines. Fixed food consumption figures are being used for all tissues, even when exposure could be low (e.g. in kidney). 3. Reliable data on exposure to injection site residues is lacking. For example, the fate of injection sites in the food chain is largely unknown. Meat processing of injection site may influence the residue concentrations as well as the exposure of consumers to residues. Apart from that, for most Annex I or III substances the relevant reference point to be considered for the determination of withdrawal times is the MRL (not the ADI). The proposal to apply an acute RfD concept for substances having a MRL (in muscle) necessarily implies that residues exceeding MRLs are tolerable if exposure is only rare. The SWP-V/CVMP have thoroughly examined this approach and reached the firm conclusion it would be unacceptable in the EU to exceed legally binding MRLs in any food to be marketed (including injection sites), irrespective of the likely exposure level and underlying safety endpoint (ADI or acute RfD).

Paragraphs 5/6 **Statistical requirements** One of the industry organisations did not support use of the "Note for guidance: Approach towards Harmonization of Withdrawal Periods (EMEA/CVMP/036/95)" for injection site data. The statistical requirement within this guideline were considered far too conservative, an approach, which does not achieve an appropriate level of consumer protection commensurate with the risk of consumption of injection site residues.	Analysis of several randomly selected data sets presented to the SWP-V/CVMP showed that the statistical approach described in the mentioned Guideline (EMEA/CVMP/036/95) is a useful and applicable approach for injection site data as well (this is also well known from experience with numerous product files). Where standard statistics are not applicable other statistical methods may be used, and the alternative, non-statistical, approach for data sets that do not sufficiently meet statistical criteria is available.
Paragraphs 6/7/8/9: **MRL and ADI approach** Even if it would be considered appropriate to use the ADI approach for all injection sites, since in most cases this would result in more realistic withdrawal times, it is clear that when applying the ADI approach to the injection site, one could encounter a problem with residues surveillance. Although out of scope of this guideline, it is clear that this would be unwanted. Therefore a fixed and higher MRL, should be set for the injection site only.	The CVMP has thoroughly considered the idea of a separate MRL for injection sites. The CVMP however concluded that this approach is (a) not practicable in residue control (it is not/not always possible to clearly identify the injection site) and (b) consumer confidence problems may arise when there are two MRLs for one and the same tissue (i.e., muscle).
Paragraphs 6/7/8/9: **MRL and ADI approach** For products exceeding the dose in the summary report, simple calculations (e.g. injected amounts compared with ADI's using the in the summary report established absorption, metabolism, excretion data) may demonstrate that supplementary residue determinations are not required or that, alternatively, a safe withdrawal period may be proposed. A "case by case" approach could therefore be followed and the general guidance, as indicated in these paragraphs (complete depletion studies) should be restricted to those cases where further data are required to establish a suitable withdrawal time.	Possible injection site residues are normally not considered during the MRL procedure. Injection site residues are highly product specific and it is therefore indispensable that product specific data are available when assessing the withdrawal period, also for Annex II compounds.

Paragraph 10: **Alternative exposure limits (for substances with no MRL and ADI)** The scientifically justified basis for the determination/calculation of the alternative exposure limit will be difficult to establish. It is not clear if acute or chronic toxicity or tolerable levels would be appropriate exposure limits. According to the comments received, the very low incidence of consuming an injection site should be taken into account, leading to a focus on the acute effects of a substance. And for products included in Annex II of the Council Regulation 2377/90 and for which it was not even considered necessary to establish an ADI, the requirement to perform residue studies should definitely be an exemption. Only in rare cases and following a valid and scientific justification by the assessor, applicants can be required to perform such studies.	General guidance on determination of alternative exposure limits cannot be given within the scope of a guideline on injection site residues. There are several Annex II substances for which it was not possible/appropriate to establish a formal ADI. These compounds include normal food constituents or substances of endogenous origin (vitamins, selenium, natural hormones etc). However, the absence of an ADI does not imply that these compounds are safe at any dose level, or at any residue concentration at the injection sites. Some of these substances have the potential to leave high residues at the injection site. Usually, potential alternative exposure limits have already been assessed in the MRL procedure and are mentioned in the CVMP Summary Report (e.g. tolerable daily/weekly intake, recommended dietary intake for nutrients etc).
Paragraph 13: **Separate studies on metabolism at the injection site** One of the industry organisations did not support the requirement for separate metabolism data to be collected from the injection site. As injection site is not a "tissue". It is a heterogeneous collection of various tissues, primarily muscle and fat, with the specific contribution of each tissue varying from animal to animal. That is why residue levels vary so greatly at the injection site. In the same manner, metabolic profiles will vary greatly. It would be scientifically unsound to try to determine a metabolic profile at the injection site because it is a composite of tissues. It could vary considerably from animal to animal.	The metabolic composition of residues at the injection site may be quite different from that in other tissues and, therefore, information on the metabolic pattern is indispensable.
Paragraph 14: **Generic veterinary medicinal products** This paragraph is in contradiction with art.13 of the new Directive 2004/28/EC where it is explicitly mentioned that "*... the applicant shall not be required to provide results of . . .residue tests ... if he can demonstrate that the medicinal product is a generic of a reference product...*"	The term "generic" is confined in the new Directive 2004/28/EC for specific products and used in a much narrower sense than it is meant in the guidelines. To avoid confusion with this term, the first sentence of para 14 of the guidelines has been changed as follows: "For ~~generic~~ products <u>containing known substances with known</u> <u>,</u> ~~where the~~ composition of the residues (of the active ingredient) at the injection site ~~are known~~, radiometric residue depletion studies are normally not necessary ...."
Paragraph 16: **Study Design and Sampling** For cattle sheep and pigs the rump is the prime cut of meat and therefore to reflect meat industry guidance this site should not be used for administration.	It is beyond the scope of the guideline to exactly prescribe the sites of injection to be used for individual products. The most common injection site in residue studies in the past (and meat industry's preference) was the neck, but there were also a number of studies where rump injection was used.

Paragraph 17: **Study Design and Sampling** Guidance as to the maximum volume which can be applied to each of the food producing species would be advantageous	As before, this would be outside the scope of the guideline.
Paragraph 19: **Study Design and Sampling - homogenisation** Guidance as to the timeframe within which homogenisation has to occur should be provided as the current understanding is that samples should be frozen for 72 hours prior to homogenization in an effort to minimize degradation caused by enzymatic action.	Recommendation of a timeframe on how quickly homogenisation should occur after sampling is not possible. Handling of injection site samples is essentially not different from that of other tissue samples, except that the injection site should be homogenised as a whole (not only an aliquot) to account for possible inhomogeneous residue distribution. If samples are stored prior to homogenisation it is advisable to demonstrate storage stability in the presence of matrix material (as for other tissues).
Paragraph 20: **Surrounding sample** Some of the comments received did not support the collection of the surrounding sample. It was argued that the guideline clearly emphasises that proper marking and sampling techniques need to be followed and if this is done, the probability of proper collection of the injection site tissue is high. The extra assurance obtained by collection and assay of a surrounding tissue sample does not justify the extra analytical expense.	From analysis of several data sets presented to the SWP-V/CVMP it was concluded that residues are present in surrounding samples as well. The examples showed that in 30-50% of individual injection sites residues were similar or even higher outside the core sample. These examples clearly indicate that consumer safety assessment could profit from this additional information on the distribution of residues in the injection site area.

Paragraph 20 **Surrounding sample** It is the opinion of one of the Industry organisations that 500 g already contains the available surrounding tissue, moreover, 500 g + 300 g would equal (even in adult cattle) the whole neck region. Furthermore taking a surrounding cylindrical sample of the injection site immediately after excising the core sample, may prove almost impossible for the reason stated above. The requirement to take a core and surrounding sample in small animals, roughly proportional to the 5:3 ratio for large animals (footnote 7), may lead to overestimation of the residues levels in smaller animal species (especially sheep and goats). Taking two samples from one side of the neck will lead to core samples of 200 g or less, resulting in a relative increase of the residue level. Sampling an extra tissue (the injection site surrounding tissue) would increase the variability since many factors, as mentioned in the first page of the guideline, influence the distribution of residues in and around the injection site (even the position after slaughter and the influence of gravity). It seems that the surrounding tissue is sampled as a control for the core sample. It is however very doubtful that the obtained data will contribute to the evaluation of the results obtained on the core sample. Especially if there are several injection sites per side of the neck (large volume products or short injection-intervals), injection sites close to surrounding tissue may occasionally also behave erratic. The injection site as a single tissue will be sufficient to establish a reasonable withdrawal time for this tissue, certainly when taking into account that the risks are already overestimated due to not adapted MRL's or ADI's.	The guideline already takes account of the fact that sampling of 500 g is not always possible ("where the size of the animal allows it"). The 500 g standard sample represents an internationally accepted recommendation (numerous residue studies world-wide have been conducted on this basis). As stated in the guideline, in small animals smaller sample sizes are acceptable as well. It should, however, always be ensured that sampling is representative and includes the maximum possible residues concentration. The recommendation to take a second (surrounding) sample was not made because the core sample was considered not to be large enough to contain the injection site. The surrounding sample is requested to obtain additional information on the quality/reliability of sampling, the degree of dispersion of residues at the injection site and the concentration gradient. There were data sets which clearly indicated that this information can be beneficial to the assessment of consumer safety. Considering the numerous injectable substances/products on the market and the possible animal species related differences, it is nearly impossible to define an optimum sample size for the surrounding sample. The value of 300 g for the surrounding sample mentioned in the guideline should be considered as "default" value and the proposed 5/3 ratio (core/surrounding sample) should not be taken as fixed rule. It is however important that injection site studies and sampling are accurately recorded and described, in particular the injection technique and equipment used, depth of injection (intramuscular), measures taken to allow precise location and identification of the injection site at slaughter, relevant technical details on sample collection procedures and sample preparation techniques etc. Also expert judgement on the appropriateness of the chosen sampling approach should be provided (see para 27 of the guideline). In case a company chooses to deviate significantly from the proposed approach, it is recommended to seek scientific advice.
Paragraph 20 **Surrounding sample** Approximate dimensions of the second concentric ring sample could be provided.	This would be overly prescriptive. The surrounding sample is mainly taken to control for sampling quality of the core sample. Its precise dimension is secondary.

Paragraph 20 **Surrounding sample** Specific guidance for veterinary medicinal products, parenterally administered in the neck region should be provided since applying the method suggested in the guideline (cylindrical core + control samples) for products administered parenterally in the neck region of animals might lead to results that: 1. do not necessarily represent a worst case estimate (i.e. dilution of sample with blank material or completely missing the analyte. 2. can not be used to determine the withdrawal time (i.e. concentrations in core lower than in control sample and subsequent elimination of the sample) A suggestion to sample injection site tissue from the neck region by means of dissection of the muscles in individual animals was made (assuming that the direction in which the injection fluid has been dispersed is visible and can be followed through tissue lesions). The amount of sample to be collected should be related to the age and size of the target species. As general guidance 300-400 grams (if animal size allows it) should be used.	The suggested cylinder sampling method assumes, as a simplifying approximation, that dispersion of injection fluid is uniform to all directions within the injection site area. This is not always the optimal model. It is also known that injections given intramuscularly in the neck region can be deposited intra- as well as intermuscularly and that this may have an impact on the dispersion pattern in individual animals. The concept of a second (quality assurance sample) has been introduced the guidelines as a means to minimise biased sampling. It seems that the dissection method proposed has been specifically developed for irritating substances where contaminated tissue is visible through tissue lesions. This procedures assumes that residue containing tissue is directly correlated with lesions and, therefore, predictable by pathological examination (where no irritation is visible, no residues are present). It is highly unlikely that this is true for all veterinary compounds and that this also applies to very low substance concentrations in the ppt range. So the dissection approach has its obvious limitations when residues are not visible. Certainly, it is interesting for research purposes, but it is not useful as general technique since, most probably, it can only be applied to a very limited number of compounds. Dispersion of a drug at the injection site is dependent on many different parameters as animals species, anatomical site of injection site, injection technique, needles/equipment used, angle and depth of injection etc, and the drug itself and its formulation. In consequence, the exact dispersion geometry is nearly unpredictable and may vary considerably from experiment to experiment and animal to animal. Therefore, it was assumed as a default that a 3-dimensional cylindrical sample would approximately reflect average dispersion behaviour around the point of injection. Results of numerous residues study show that this sampling technique works quite well and reproducibly.

	The 500 g core sample is already a large portion of tissue, even in medium size animals. The SWP-V/CVMP is aware of the difficulties to samples 500 g in all animals and therefore states that this sample size is only required in cases where "the size of the animal allows it". However, it is also recommended in the guideline to use animals of an upper weight range of the target population (large enough) so that the maximum injections volumes can be investigated. Where the optimum sample size is not possible due to anatomical reasons, the guideline recommends to use a modified sampling approach. In any case, the chosen sampling approach and sample target weight should be adequately reported and justified. As a general rule, it is advisable to reduce sample diameter but retain depth, if possible. Also in this case a second sample around the excised core sample should be collected to confirm reliability of the approach. The proportions of core and surrounding sample should be kept, if possible. It is also recognised that the size for the surrounding sample of an additional 300 g is comparatively large and sampling of a total of 800 g (500 g core plus 300 g surrounding sample) is hardly possible in many animals. It should be noted that the recommendation of 300 g for the surrounding sample is to be understood as "orientative" rather than a rule. This sample can be reduced if the experimental situation requires it. It should be kept in mind, that the purpose of the surrounding sample is to check validity of sampling for the core sample. It is rather the concentration value that matters, not the absolute size or absolute mass of residues recovered. An indispensable requirement is, however, that the material collected around the core sample is enough to perform an analysis. As a results of the consideration of this comment the following amendment at paragraph 20 of the draft guideline was included in the guideline: *"The size of 300 g for the surrounding sample should be seen as orientation. It is recognised that sampling of an extra 300 g amount of tissue can not always be achieved, in particular with neck injections. If the experimental situation requires it, the surrounding sample weight may be reduced as is necessary. It is essential, however, that the material collected is enough to perform an analysis"*

Paragraph 21 **Study Design and Sampling** Should core and the surrounding samples be removed in a single sampling? Is it acceptable to add to the core sample to ensure the injection site weight meets the required limits of 500 g +/- 20 %.	The sequence in which samples are collected is not important. However, subsequent adding of any material to the core sample to obtain the target sample weight might be interpreted as an attempt to bias results and is not advisable. Sample weighing less than the proposed target weight should not be automatically rejected, provided there is founded and plausible justification for deviating from the recommended approach.
Reactions in the injection site Clarification is required in the instance where reactions may occur outwith the dimensions of either the core or surrounding sample: should such reactions be sampled as part of the surrounding sample described but not sampled neither described or sampled as out with the sampling area for injection site residues	It is advisable to describe the entire sampling procedure as detailed as possible, including the appearance of the injection site and any lesions which were observed. It is also advisable to sample all potential or suspected residue containing material for (later) analysis in case of difficulties with the interpretation of results.
Page 8 (first paragraph) **Glossary, Injection site definition** It is said that the injection site should not include a portion of skin. This seems to be in clear contradiction to Volume 8 of the Rules governing Medicinal Products in the European Union, Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin stating that fat and skin in natural proportions are edible tissues in pigs. Thus, the intramuscular injection site in pigs corresponds to a cylinder-shaped sample of approximately 10 cm diameter and 6 cm depth of muscle, fat and skin.	Following in-depth discussions, it was concluded by the SWP-V/CVMP that it is not necessary to collect an additional fat/skin sample at the site of injection as the most relevant injection site sample is muscle including adhering fat/fascia in natural proportions (as defined in the "glossary"). This should however not be interpreted as no necessity for a fat/skin sample in case of pigs (or poultry).