EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for medicinal products for veterinary use

Concept paper on the revision of the Note for guidance on the approach towards harmonisation of withdrawal periods

Agreed by SWP-V	September 2013
Adopted by CVMP for release for consultation	10 October 2013
Start of public consultation	18 October 2013
End of consultation (deadline for comments)	31 January 2014

The proposed guideline will replace the CVMP Note for guidance: approach towards harmonisation of withdrawal periods (EMA/CVMP/036/95).

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

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1. Introduction

The CVMP Note for guidance: approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95 FINAL) sets out a standard statistical approach to be used across the EU in the analysis of residue depletion data for the purpose of establishing withdrawal periods. In relation to data points at which residues are present below the limit of quantification the Note for guidance indicates that a value of ½ of the limit of quantification should be applied to the data point.

2. Problem statement

The CVMP Note for guidance: approach towards harmonisation of withdrawal periods was published in 1996. While the approach recommended for dealing with residues below the limit of quantification is simple and easy to apply, more sophisticated methods for dealing with data below the limit of quantification are now available. Residue levels below the limit of quantification tend to occur mainly in terminal residue depletion phases, which are of particular relevance when assessing the depletion of residues below the MRL. The treatment of these data may have a considerable impact on the derived withdrawal period. It is therefore considered that the SWP should review these alternative methods and, if appropriate, incorporate these into the CVMP Note for guidance: approach towards harmonisation of withdrawal periods.

3. Discussion (on the problem statement)

Statistical approaches are the most recommended and commonly used methods for the analysis of residue depletion data and the estimation of withdrawal periods of veterinary drugs in the EU and world-wide.

The EU recommended method is described in the CVMP Note for Guidance Approach towards Harmonisation of Withdrawal Periods (EMEA/CVMP/036/95-FINAL). It is based on a linear regression analysis and the calculation of an approximate 95 % tolerance limit with 95 % confidence using equations by Stange (1971) and Graf et al. (1987). The data set used for this analysis needs to fulfil four statistical assumptions, namely: linearity of log concentrations versus time, independence of the data, normality of errors on a log-scale, and homogeneity of variances. The theoretically minimum number of data points/number of animals to conduct this calculation is 3 sampling time points with a minimum number of 3 animals at each point.

There are a number of both experimental and data processing factors that can affect the quality and accuracy of withdrawal time results obtained. These may include on the experimental side, among many others, the overall number of animals (data points) used in the experimental phase which is, in a statistical sense, relatively small[1], the positioning of the slaughter time points on the residue depletion curve, sampling and sample storage, and the LOD/LOQ and other performance characteristics of the analytical methods. With the new VICH guidelines 48 (Marker residue depletion studies to establish product withdrawal periods – EMA/CVMP/VICH/463199/2009) and 49 (Validation of analytical methods used in residue depletion studies – EMA/CVMP/VICH/463202/2009) there is now detailed guidance on the design of residue studies and validation of analytical methods available which is expected to improve the data collection process to become more reliable and consistent between studies.

[1] VICH GL 48 recommends that "the number of animals used should be large enough to allow a meaningful assessment of the data. From a statistical point of view, residue data from a minimum of 16 animals with four animals being euthanized at four appropriately distributed time intervals are recommended. Higher numbers of animals should be considered if the biological variability is anticipated to be substantial as the increased numbers might result in a better defined withdrawal period".

While the CVMP Note for Guidance Approach towards Harmonisation of Withdrawal Periods gives quite clear directions on the acceptable consumer protection level (i.e. 95 %/95 % tolerance limit) and acceptance criteria for the statistical assumptions, it is not very detailed on data treatment prior to the analysis and, in particular, the techniques to deal with "less than" values (censored/missing data) or outliers at the upper end of the data points. While there is some general consensus that removing of outliers should be done, if at all, very cautiously and - given the typically limited number of animals - based on both statistical and strong causal reasoning, there is no uniform agreement on the most appropriate method(s) for dealing with censored data such as omission of such data points/slaughter points, imputation of half the quantification limit for "less than values", using instrument-generated data below the LOQ/LOD or other statistically based estimations. This has been an issue of inconsistent data use and constant debate over the last number of years. As censored data are due to the inherent limitation of the analytical techniques to measure very low concentrations (limit of quantification) they occur mainly in terminal (late) residue depletion phases which are of particular interest when assessing the depletion of residues below the MRL. The method of using these data can, thus, have a considerable impact on the length of the withdrawal period.

The intention of this project is to explore the currently recommended method (using imputation of 1/2 LOQ) to deal with left censored data against more sophisticated alternatives such as (not exhaustive):

- maximum likelihood approach (i.e. determining the depletion curve that would maximize the likelihood of the observed data),
- simulation of data (e.g. bootstrapping),
- use of data "as measured",

in order to compare the performance and robustness of each method and their relative merits for achieving a most efficient and effective use of the available information.

4. Recommendation

The CVMP recommends a review of the options available for dealing with data below the limit of quantification and an update to the CVMP Note for Guidance Approach towards Harmonisation of Withdrawal Periods to incorporate new method(s) as appropriate.

5. Proposed timetable

31 January 2014	Deadline for comments on concept paper
February – December 2014	Consider comments received, review available approaches and publish an updated draft guideline for consultation
January – June 2015	Public consultation on draft updated guideline
July – December 2015	Consider comments received and develop a final updated guideline
June 2016	CVMP adopts the final guideline

6. Resource requirements for preparation

A rapporteur from the CVMP SWP will be responsible for the review of available methods and updating the existing Note for Guidance as appropriate and will require input from a statistician for this work.

The EMA secretariat will coordinate the public consultation. Time at plenary CVMP SWP and CVMP meetings will be required to discuss and adopt the various drafts of the guideline.

7. Impact assessment (anticipated)

The updated draft guideline should provide clear guidance to industry and regulators on the appropriate method(s) for dealing with residue levels below the limit of quantification. It is expected that the updated guidance will make better use of the available data and so allow the setting of withdrawal periods that better reflect the depletion profile of veterinary medicinal products.

8. Interested parties

Consumers, regulators, veterinary medicines industry.

9. References to literature, guidelines, etc.

Stange, K (1971) Angewandte Statistik, vol. II, Springer Verlag, Berlin, Heidelberg, New York.

Graf U, Henning HJ, Stange K and Wilrich PT (1987) Formeln und Tabellen der angewandten mathematischen Statistik (3rd edn)Springer Verlag, Berlin, Heidelberg, New York, London, Paris, Tokyo

VICH GL48: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: Marker residue depletion studies to establish product withdrawal periods - February 2011

VICH GL49: Guidelines for the validation of analytical methods used in residue depletion studies - February 2011