Report to the

VICH OUTREACH FORUM

Withdrawal periods for veterinary medicinal products - Approach by VICH members and observers

Background

Within the discussions at several VICH Outreach Forum (VOF) meetings questions regarding the establishment of withdrawal periods (defined under 'General principles' below) were raised and it was observed that the withdrawal periods set in VICH countries and regions can vary. VICH has developed several harmonised guidelines on the design and conduct of studies related to residue depletion and the methods to analyse residues, but the evaluation approach is outside the scope of VICH and the responsibility lies within the individual countries/regions. However, VICH members agreed to present their approaches and the calculation methods used by the EU, Japan and USA were explained at the 12th VOF meeting. The VICH Steering Committee agreed to prepare a document summarising the approaches to determine withdrawal periods for the 13th VOF meeting.

Introduction

A major pillar in the authorisation of a veterinary medicinal product for use in food producing animals in respect to its safety is the setting of withdrawal periods providing that food of animal origin does not contain residues that may represent a health risk for the consumer. The withdrawal period is linked to the maximum residue limits (MRLs) (in the USA tolerances) established for the active ingredient(s) included in the product. Adequate instructions relating to the withdrawal period after use of the product must be contained on the product label.

VICH guidelines (GLs) exist for the conduct of residue studies to determine withdrawal periods in tissues for pigs, cattle, sheep and poultry, including milk and eggs (VICH GL48), aquatic species (VICH GL57) and honey (VICH GL56) as well as validation of analytical methods used for the residue studies (VICH GL49).

These VICH guidelines ensure that the requirements for residue studies are the same in all countries that are members of VICH. Thus, the approaches for establishing the withdrawal periods become also largely similar. However, the evaluation by the authorities in the different countries/regions may result in withdrawal periods that can differ due to some differences in the assessment approach or algorithms used, due to differences in the MRLs/permitted concentrations established on national/regional level or other considerations.

This document provides an overview on how VICH members and observer countries determine withdrawal periods. The document also provides links to guidance documents

available by authorities of VICH members and observers and to software for calculating withdrawal periods. A summary table on the approaches used is provided in the Annex.

General principles for the determination of withdrawal periods

A withdrawal period (also called withholding period[1], or for milk or eggs sometimes discard time) is the minimum period between the last administration of a veterinary medicinal product to an animal and the production of foodstuffs from that animal, i.e. slaughter, taking milk or eggs or honey for human consumption, which is necessary to ensure that the foodstuffs do not contain harmful residues that may represent a risk to the health of the consumer, i.e. the residues have fallen below the MRLs (or tolerance). The withdrawal period relates to the normal use of the product as stipulated in the marketing authorisation. The exact wording of the definition of a withdrawal period differs between the VICH countries/regions, but the principle is always the same.

The aim of VICH GLs 48 and 57 (Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: Marker-residue-depletion studies to establish product withdrawal periods) is to demonstrate the depletion of the marker residue upon cessation of drug treatment to the regulatory safe level (e.g. MRL or tolerance) and to generate data suitable for elaboration of appropriate withdrawal periods to address consumer safety concerns. Animal treatment in the study should be consistent with the intended product label. The guidelines recommend a study design and number of animals used large enough to allow a meaningful statistical evaluation of the data and assessment of the results. Withdrawal periods are calculated for all animal tissues/food commodities for which MRLs (or tolerances) have been established. The use of statistical models for the calculation of withdrawal periods is based on pharmacokinetic principles assuming exponential elimination of the residues and the residue concentration being a function of time after the last administration of the product.

Plotting the logarithmically transformed concentration versus time should lead to a linear relationship and a linear regression analysis can be performed provided that key parameters for a regression analysis (homogeneity of variances, linearity and normally distributed errors) are met. From the results of the regression analysis the one-sided upper tolerance limit for the 90^{th}, 95^{th} or 99^{th} percentile of the population with 95% confidence is calculated. This is identical to calculating a one-sided 95% upper confidence limit on the 90^{th}, 95^{th} or 99^{th} percentile of the population sampled[2]. The withdrawal period is determined from the time when the one-sided upper tolerance limit with a given confidence is below the MRL/permitted concentration (Figure 1).

[1] The term 'withdrawal period' is used throughout the text for ease of readability independent of the preference of terminology in the different jurisdictions.
[2] For further details see section: Differences in establishing withdrawal periods between VICH countries/regions

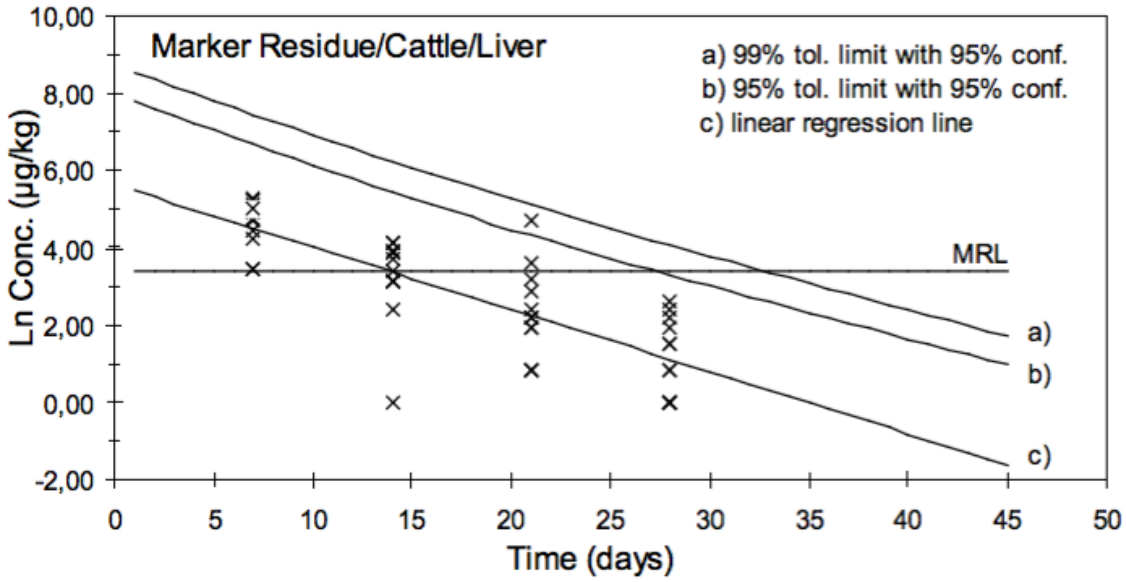

Figure 1: Example plot of withdrawal period calculation[3]

For the derivation of withdrawal periods in milk (or eggs) other approaches are used in some jurisdictions. These are based on a statistical evaluation of the distribution of time points for samples to reach the MRL (or other legal limit) or the assessment of the statistical evaluation of individual data time points. Also here, the decision is based on one-sided upper tolerance limits.

While wherever possible the statistical evaluation approach is used, there may be cases where the data available do not allow this, and an alternative approach is considered so that a withdrawal period can be established based on the study data that has been provided.

Withdrawal periods are expressed in days (for tissues, milk and eggs), milkings (normally based on 12 hour milking intervals) or degree days (for fish). Where the calculated withdrawal period is a fraction of a day or milking, it is rounded up to the next full day or milking. In New Zealand withdrawal periods over 14 days are applied at weekly intervals, and the value is rounded up to the next full week.

Residues at the injection site may persist much longer than in other tissues, which is reflected in the instructions for sampling related to injection sites in VICH GL48 and specific considerations for establishing withdrawal periods may be required in relation to the safe concentration they relate to. Therefore, countries/regions use different approaches to determine withdrawal periods for injectable products, which are often described in their published guidance documents.

Detailed descriptions of the approach recommended for withdrawal period calculations by authorities are available (EMA (tissues, milk, both with examples), FDA, JMAFF, APVMA, Health Canada). Standard statistical software or spreadsheets with statistical functions can be used for the calculations. Also, software and tools for the statistical analysis are available by the authorities to facilitate the calculations (EMA, FDA, JECFA tool (intended for MRL calculations)).

[3] From EMA: Guideline on determination of withdrawal periods for edible tissues (EMA/CVMP/SWP/735325/2012) (6).

Differences in establishing withdrawal periods between VICH countries/regions

When comparing withdrawal periods for veterinary medicinal products with the same active ingredient it should be borne in mind that withdrawal periods are product specific, as the processes of absorption, distribution and elimination are dependent on the formulation and its pharmacokinetics, including the active ingredient's binding properties, the product's excipient profile as well as the administration route.

For new studies the recommendations of the VICH guidelines should be followed. However, it should be borne in mind that despite the application of the guidelines several parameters such as the design and conduct of the actual study, e.g. the animals used (i.e. their breed, age, bodyweight or diet) or the timepoints chosen can still have a significant impact on the outcome and the suitability for a statistical analysis. Equally, the application of (different) analytical measurement uncertainty impacts on the results of the residue depletion studies, i.e. in the case of shortcomings with regard to the validation data for the analytical method used or in the case of instability issues of the analyte in a certain matrix.

Differences in withdrawal periods derived for the same veterinary product by different authorities can be due to a number of reasons, for which the main ones are listed below.

- Differences in the MRLs (or tolerances) established: As a withdrawal period is related to the permitted residue levels set, it will depend on the MRLs (or tolerance) established by the authorities in each country/region.

- Differences in use and interpretation of data:

    - In general, statistical analysis derived withdrawal periods on a set of data based on the same residue study for the same veterinary medicinal product showing linear regression do normally not lead to very large differences in the resulting withdrawal period by the different authorities assuming the MRLs/tolerances are similar. Differences in the calculations are:

        - Algorithms used: While the principles for the statistical analysis used are the same there is not one single set of algorithms describing the process that is applied and therefore the specific algorithms recommended by the authorities or used by sponsors can lead to differences in the resulting withdrawal periods.

        - Confidence limit and percentile of population: While consistently the 95% confidence limit is used, there is no consistency regarding the percentile of the population used for the calculation, with the USA, Japan and Canada using the 99^{th} percentile, the EU and Australia using the 95^{th} percentile, and New Zealand using the 90^{th} percentile for ruminants, horses and honey, the 95^{th} percentile for poultry, pigs, emus, farmed fish and eggs, and the 99^{th} percentile for milk.

        - Assessment of linearity of regression assumptions: The assessment of linear regression assumptions (homogeneity of variances, linearity and normally distributed errors) can differ by the method applied, e.g. the test used for the homogeneity of variances (EU, Australia and New Zealand use the Cochran test, the USA, and Canada use the Bartlett's test, Japan uses either), because expert

judgement is used in the analysis, and/or the conclusions drawn, e.g. to exclude a value as an outlier or not. Such analysis could also lead to the conclusion that the statistical analysis is not appropriate and that an alternative approach for determining the withdrawal period should be applied, and this would probably lead to more significant differences in the outcome between the authorities.

- Use of values below LOQ/LOD: For residue concentrations below the limit of quantification (LOQ) the values may be disregarded entirely (USA and Canada) or 1/2 LOQ is used in the analysis and calculations (EU, Japan in most cases and New Zealand), while in Australia based on expert judgement either 1/2 LOQ or the reported numerical value (if available) may be used, or the value may be disregarded. Values below the limit of detection (LOD) are disregarded in the calculations by the EU, Japan, USA, Australia and Canada, while New Zealand uses in these cases 1/2 LOD.

- Outliers: There is no defined set of criteria when a specific measured residue concentration or datum from an animal could or should be considered an outlier and disregarded. In general, this decision will be taken based on expert judgement considering whether the outlier(s) is/are linked to a documented error during testing/ or analysis. Where too many values would be identified as outliners this may lead to the rejection of a study.

- When a statistical analysis is not possible: If the results of a residue depletion study do not allow carrying out a statistical analysis, e.g. most of the residue concentrations are below the LOQ, inappropriate slaughter timepoints or other issues, alternative methods may be explored to still allow setting a withdrawal period based on the data. This could be to establish the withdrawal period at the time point where the concentrations of residues in all tissues for all animals are at or below the respective MRLs (Canada), with addition of a safety span (EU, Japan and Australia) or some additional conservatism, e.g. a safety span, (New Zealand). The approach to be applied in the USA is considered on a case-by-case basis. As the exact approach to set a withdrawal period based on a specific dataset or the safety span applied may vary between authorities and this will lead to differences in the resulting withdrawal period.

- Milk withdrawal periods: Establishing withdrawal periods for milk follows basically the same principles as for tissues with adjustments to the calculations applied. In particular the regression analysis for milk is much more complicated because milk residues are not ‘independent from each other’ (in statistical terms), therefore alternative, more appropriate methods have been developed for calculating milk withdrawal periods, e.g. the Time To Safe Concentration (TTSC), the Safe Concentration Per Milking (SCPM) and the Safe Concentration from Linear Regression (SCLR). Again differences in the withdrawal periods can arise due to differences in the calculation approach chosen by the authorities.

- In the EU guidance the TTSC method is recommended, as this method has been shown to be applicable in the largest number of realistic cases and leads to similar withdrawal periods as the other methods, but all three methods are included in the software provided. As for tissues a 95/95 tolerance limit is used. The USA and Canada utilise a linear regression approach to estimate the milking interval (USA) or milk withholding time (Canada), at which the upper tolerance limit for the 99th percentile with 95% confidence is less than the established tolerance value/MRL. The FDA statistical calculation program can be made available on request.

- Also differences in the local situation regarding milk and dairy product consumption and residue control may lead to differences in the withdrawal period calculation. For example, in the EU, Japan and Canada milk from individual or a few animals is used for consumption or for small-scale dairy products at farm level, and therefore milk withdrawal periods are established for milk from individual animals. In the USA, residue values from individual animals are used to calculate the milk withdrawal period for bulk tank milk pooled from an entire dairy herd to reflect milk that would be sampled as part of the residue monitoring program. Therefore, the statistical procedure for calculating the milk withdrawal period contains a term for the number of animals contributing milk to the bulk tank. To approximate the size of a small dairy operation, the FDA uses a value of 10 for this term.

- Considerations in relation to the establishment of MRLs/safe limit:

  - MRLs (or tolerance values) are established by responsible authorities in VICH countries and regions and at international level (JECFA/Codex Alimentarius). The data requirements are largely harmonised and VICH guidelines have been developed for most parts of the safety file and residue file. The assessment of data and decision on the permitted values lies with the responsible authority for their jurisdiction. While all countries/region review existing MRLs/safe concentrations set on international level and often also by other countries, the scientific approaches in interpretation and use of data as well as regulatory principles, and possibly the data provided themselves differ to some extent and may lead to different MRLs/other permitted safe concentrations. This document does not attempt to analyse the entire process of establishing MRLs/tolerances to identify the potential sources for differences but addresses only a few relevant elements that were raised in VOF discussions.

  - Injection site residues: As residues at the injection site may persist much longer than in other tissues, specific considerations for establishing withdrawal periods may be required in relation to the safe concentration they correspond to.

    In the EU withdrawal periods are in general based on the normal (non-injection site) muscle MRL; however, in cases for very slow depleting residues, e.g. for long acting formulations, which would lead to prohibitive extended withdrawal periods, an Injection Site Residue Reference Value (ISRRV), which is a concentration set at a level that ensures that, at the likely withdrawal period, a standard food basket including 300g of injection site muscle would contain residues below the ADI, is derived to use as reference for establishing the withdrawal period. In Japan withdrawal periods are in general as well based on the MRL established for normal muscle tissue, provided that even if an injection site at the WP is ingested, it will not represent a consumer safety concern. In the USA and Canada, safety of injection site residues may be addressed by lowering the target tissue tolerance with a resultant extension of the withdrawal period to ensure that injection site residues are less than 10 times the muscle safe concentration where there are no concerns regarding acute effects; for the latter cases the Acute Reference Dose (ARfD) is calculated and serves as additional legal safe concentration. The ARfD is also established in Australia, New Zealand and Canada when concerns regarding acute effects from potential injection site residues have arisen. The calculation of the withdrawal period is in Australia based on residues in normal muscle provided the acute dietary exposure level of the injection site does not

exceed the ARfD, In New Zealand it is based on 10X the normal muscle MRL, in case of identified acute effects on the ARfD.

- Dual use substances: In the EU in the case of substances used both as plant protection products as well as veterinary medicines, when establishing MRLs a portion of the ADI (guidance 45%) may be reserved for veterinary use. Where appropriate Australia and New Zealand may consider the transfer of veterinary chemicals from their use as agriculture chemicals in their MRL calculations.

- Partitioning of the ADI: When establishing new MRLs for new active substances consideration is made for reserving a portion of the ADI for possible future extensions of the product to other uses or species so that, for example, it will be possible to establish later a milk MRL for an active substance first only used in meat production (EU, USA). This approach is considered necessary as in the calculation of MRLs / permitted concentrations the exposure of the consumer to residues is taken into account based on the assumption of a daily diet containing all edible tissues, milk, eggs and honey, the so-called ´standard food basket, which is used in many jurisdictions for the establishment of MRLs/tolerances.

Withdrawal periods for generics

While the exact definitions of a generic differ between the different jurisdictions, the general concept is that a generic is considered (bio)equivalent to an authorized reference product based on specific criteria defined by the different jurisdictions and on specific documentation and/or studies to the provided by the authorities as required according to the legislation in the jurisdictions.

In most cases an *in vivo* bio-equivalence study measuring blood levels of the active substance(s) to study its/their rate and extent of absorption is required to prove essential similarity of the generic with the reference product within the margins allowed. Where bioequivalence is accepted, as per assessment/requirements of the country/region, the withdrawal period of the generic product would normally be the same as the reference product. However, for products expected to leave local residues at the site of application, e.g. for injectable products via intramuscular (IM), subcutaneous (SC) or transdermal (TM) administration routes, additional specific residue data may be required to demonstrate that the residue level at the withdrawal period does not exceed the MRL (EU, Japan, Canada) even if bio-equivalence can be proven in general.

Depending of the outcome of these studies the resulting withdrawal period can be the same as the one for the reference product, or can be shorter or longer if the residue data provided give reason for a different withdrawal period. In the USA, several approaches are available for generic products. Depending on the approach and information provided, a generic product can be assigned the same withdrawal period as the reference product or a withdrawal period that is longer or shorter. In Canada, generics can only get the same WP as the reference product, not shorter or longer.

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Annex

Summary table of elements contributing to a withdrawal period calculation

	EU	USA	Japan	Australia	Canada	New Zealand
MRLs / Tolerances	Own MRL	Own tolerance	Own MRL	Own MRL	Own MRL	Own MRL
- Considering internat. MRL	- Yes	- Yes	- Yes	- Yes, also MRLs set by other countries: consideration given to MRLs set in major export markets for Australian animal product.	- Yes	- Yes, also MRLs set by other countries
- Partitioning of ADI	- Yes	- Yes	- No	- No. MRLs and WP considered together based on partitioning of compound at the withdrawal period and the associated dietary exposure, including for agricultural uses for dual use compounds	- No	- No
WP Calculations						
Analysis of linearity of regression:						
- Homogeneity of variances	- Cochran test	- Bartlett's test	- Cochran or Bartlett's test	- Cochran test	- Bartlett's test	- Cochran test
- Linearity	- F-test	- F-test	- F-test	- F-test	- F-test	- F-test

	EU	USA	Japan	Australia	Canada	New Zealand
Confidence limit/percentile population	95/95	95/99	95/99	95/95	95/99	Stratified by species and commodity: 95/90 for ruminants, horses and honey; 95/95 for poultry, pigs, emus, farmed fish, and eggs 95/99 for milk.
Use of residue conc. below LOQ/LOD	< LOQ: 1/2 LOQ < LOD: disregarded	< LOQ: disregarded < LOD: disregarded	< LOQ 1/2 LOQ (in most cases) < LOD: disregarded	<LOQ: based on expert judgement, may use 1/2 LOQ, the reported numerical value (if available) or be disregarded. < LOD: disregarded	< LOQ: disregarded < LOD: disregarded	< LOQ: 1/2 LOD < LOD: 1/2 LOD
Tool/software used	EMA software	CVM Application	not designated	EMA software	Health Canada software/JECFA tool	EMA software
WP when statistical method is not possible	Timepoint where residue concentration below MRLs for all animals + safety span	Considered on a case by case basis.	Timepoint where residue concentration below MRLs for all animals + safety span	Timepoint where residue concentration below MRLs for all animals + safety span	Timepoint where residue concentration below MRLs for all animals	Timepoint where residue concentration is below the MRLs for all commodities plus some additional conservatism (e.g. “safety span”)

	EU	USA	Japan	Australia	Canada	New Zealand
Injectable products/injection site residues	In general WP based on normal muscle MRLs. For very slow depleting residues: at ISRRV	Injection site residues considered in target tissue WP assignment	In general, WP is established based on normal muscle MRLs, provided that even if an injection site at the WP is ingested, it will not represent a consumer safety concern.	WP based on residues in normal muscle (not injection site residues) provided the acute dietary exposure level of the injection site does not exceed the ARfD.	WP set at 10X muscle safe concentration; if acute effects: at ARfD. N.B. Safe concentration refers to Total Residue Level (TRL)	WP set at 10X muscle MRL; if acute effects: at ARfD
Generics approach	Proof of essential similarity (normally by BE study): WP normally same as reference product. For IM, SC and TD products: residue data demonstrating that residues at WP do not exceed MRL; resulting WP can be same, shorter or longer than WP of reference product.	Depending on the approach and information provided, a generic product can be assigned the same withdrawal period as the reference product or a withdrawal period that is longer or shorter.	Proof of essential similarity (normally by BE study): WP normally same as reference product For IM, SC and TD products: residue data demonstrating that residues at WP do not exceed MRL; resulting WP can be same, shorter or longer than WP of reference product.	Consideration is given to formulation differences between the proposed product and a registered reference product as well as the results of the BE study. Residue data demonstrating that residues at WP do not exceed MRL may be required if the formulation is different and BE cannot be demonstrated.	Proof of essential similarity (normally by BE study): WP normally same as reference product. For IM, SC and TD products: residue data demonstrating that residues at WP do not exceed MRL; resulting WP is the same as the reference product.	Proof of pharmaceutical and therapeutic equivalence by BE study): WP normally same as reference product. Additional data requirements determined on a case by case basis; resulting WP can be same, shorter or longer than WP for reference product.