Metabolism and Residue Kinetics Expert Working Group

Chairperson: Stefan Scheid (E.U.)

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Introduction

The Expert Wproking Group (EWG) on "Metabolism and Residue Kinetics" was founded at the 16th VICH Steering Committee meeting in May 2005 (Washington DC, USA). Following expert nominations, the EWG took up work in autumn 2005 and the main topics were identified. The 1st EWG meeting was in Berlin/Europe (March 2006) to discuss an outline of guidelines (GLs) and to nominate topic/co-topic leaders. Four draft GLs were prepared for/discussed at the 2nd Meeting in Yokohama, Japan (October 2007) and remaining open issues settled via written procedure. The GLs were released for consultation by the VICH SC November 2009 at step 4 for a public consultation period which ended in May 2010.

EWG Composition

Stefan Scheid – Chair (EU, g) 	Johan Schefferlie (EU, g) 	David Gottschall (IFAH-Europe, i) 	Leo Van Leemput (IFAH-Europe, i) 
Ryoji Koike (JMAFF, g) 	Kazuo Fukumoto (JVPA, i) 	Bruce W. Martin (AHI, i) 	John L. Nappier (AHI, i) 
Javad Shabam (Canada, g) 	Phil Reeves (Australia/ New Zealand, g) 	Julia Oriani (US FDA, g) 	

Government (g), Industry (i)

Guidelines under Development

GL 46 Nature of Residues:

Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals and determine the quantity and identify the nature of residues

This information is relevant for the purpose of consumer exposure assessment, the choice of a marker residue for analytical methods intended for compliance purposes, the selection of the target tissue(s), and identification of any specific hazards associated with the metabolic pattern. These studies provide data for the determination of the marker residue to total residue ratio.

GL 47 Comparative Metabolism:

Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: comparative metabolism studies in laboratory animals

This information is relevant to determine whether the laboratory animals used for the toxicity testing have been auto-exposed to the range of metabolites that humans will consume from tissue of the treated food animals. These data are used to validate the ADI in the risk assessment. An important feature of this guideline is that it allows for conducting all investigations in vitro. As a consequence, studies with radiolabelled material in laboratory animals can be avoided and therefore this guideline contributes largely to the 3-R's objective of the VICH.

GL48 Marker Residue and Depletion:

Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: marker residue depletion studies to establish product withdrawal periods.

This information is needed to demonstrate the depletion of the marker residue to the regulatory safe level and to generate the data for establishing the withdrawal periods for the final VMP. The study is conducted using non-radio-labelled drug.

GL49 Method Used in Residue Depletion Studies

Guidance for the validation of analytical methods used in residue depletion studies

Uniform validation criteria are established for analytical methods used in residue studies.

Key scientific issues

Scientific issues are under discussion because the guidelines are still in the consultation phase. Key scientific issues include:

VICH GL46
- Sacrifice intervals and number of animals per timepoint
- Glossary of scientific keywords

VICH GL47
- An option to conduct an in-vitro study
- Collecting and analysis of excreta

VICH GL48
- Single timepoint studies for a zero withdrawal product
- Number of animals needed for a single timepoint study
- Definition of practical zero
- Collection of multiple injection sites per animal
- Necessity of collecting ring tissue around the injection site (2nd sample)
- Limitation on number of additional tissues collected for regional authorities

VICH GL49
- Acceptable range for accuracy
- Examples of procedures to set LOQ and LOD
- Example of a protocol for method validation

Key benefits of the harmonised guidelines

The key benefits of these guidelines are to harmonize the requirements needed for studies that provide data to demonstrate the safety for humans consuming the edible tissues of animals treated with veterinary drugs. Harmonized requirements will allow a uniform study design to be applicable for approval of veterinary drugs on a worldwide basis. Fewer residue studies will be needed which will result in lower costs for drug development, less animals sacrificed, more stream-lined drug approvals, and ultimately, greater human food safety to consumers.

New topics

Topics to be addressed in the future are:
- Harmonization of the withdrawal time calculation model;
- Applicability of the guidelines to minor species;
- Data requirements for combination products.