International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

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Concept Paper for the Revision of GL47 "Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-producing Animals: Comparative Metabolism Studies in Laboratory Animals"

Introduction

This guidance is one of a series of residue chemistry guidances that provides recommendations to address the metabolism and depletion of veterinary drugs used in food-producing animals.

GL47 provides recommendations for internationally harmonized procedures to identify the metabolites of veterinary drugs produced by laboratory animals. The purpose of the comparative metabolism studies is to compare the metabolites of the species (laboratory animals and/or humans) used for toxicological testing to the residues of the veterinary drugs in the edible tissues of food-producing animals (as demonstrated in an *in vivo* study), in order to determine if the laboratory animals used for toxicological testing have been exposed to the metabolites that humans can be exposed to as residues in products of food-producing animal origin.

Problem statement, including references to existing technical and legislative requirements in the different regions

GL47 was finalized in 2011, implemented in 2012 and has not been revised since implementation. Because science has evolved since the guidance implementation date, it is generally a good idea for members of the EWG to consider whether the guidance recommendations need to be revised.

Along with other information, the guidance provides recommendations about generating comparative metabolism data using *in vitro* test systems (Section 2.3.2) and this section should be the focus of the re-evaluation. FDA has seen an increase in the use of *in vitro* test systems to generate comparative metabolism data and an increased interest in using this option. This increase in using *in vitro* test systems may be due to a preference in conducting fewer animal studies. Choosing an *in vitro* test system over an *in vivo* test system is consistent with the "3 Rs", which refers to the replacement, reduction, and refinement of animals used in research, teaching, testing, and exhibition. The 3Rs approach is included in many legislations worldwide. Also, sponsors may be choosing *in vitro* test systems because there will most likely be a cost saving for an *in vitro* test system compared to the cost of a study that uses live animals. Industry and regulatory authorities now have over 10 years of experience conducting and evaluating studies using *in vitro* test systems. That experience should be reflected in revisions to the guidance.

The guidance currently contains language implying that recommendations for *in vitro* test systems are in development: "Protocols for these *in vitro* systems have not yet been standardized.". Since the implementation of GL47, significant progress has been made in the field, including the publication of the OECD guideline on Good In Vitro Method Practices (GIVIMP, OECD Guidance No. 286), and an updated Guidance Document on Good Cell and Tissue Culture Practice 2.0 (GCCP 2.0). It is recommended that the EWG update the guidance to incorporate these recent advancements.

Based on FDA's evaluation of comparative metabolism studies submitted for review, there have been significant problems with the conduct of studies that use *in vitro* test systems, in particular those using primary hepatocytes. A recurring issue is the lack of optimization of the parameters selected to conduct the *in vitro* assay. The guidance could provide recommendations for conducting a pilot study to determine the optimum parameters for the cell culture assay such as cell number/density, drug concentration and duration of treatment. In addition, the guidance could describe how to characterize the cells regarding appropriateness and functionality.

The guidance could benefit from inclusion of recommendations on the use of cell viability assays to evaluate overall physiological condition of the cells prior to and after treatment. Cell viability assays (for those *in vitro* studies using primary hepatocytes) would provide information on the toxicity of the new drug under the parameters chosen to perform the treatment of the cells. Conditions under which the new drug is toxic to the cells may promote changes (pH, activation of stress pathways, cell death pathways) that may affect the metabolism of the new drug.

Impact for public health, animal health and animal welfare

Providing clear guidance for *in vitro* studies will help reduce the number of animals needed for laboratory studies, which is line with the 3Rs.

Anticipated benefit to:

- Industry and Other Interested Parties

Industry would benefit from additional guidance regarding *in vitro* comparative metabolism studies to increase the chances of useful data being generated, which would reduce the number of review cycles and time for addressing human food safety information for veterinary drugs.

- Regulatory Authorities

Regulatory authorities would benefit because industry could follow the global recommendations instead of each individual sponsor seeking guidance. Standardized studies provide a path for more consistent review and evaluation of the conduct and results.

Timetable

The concept paper was adopted at the 44th VICH Steering Committee (SC) meeting in November 2025. The revision of GL47 aims to be completed by the end of 2027.

Milestones

Milestones for this project would be as follows:

1. December 2025 to April 2026 – FDA and JMAFF (Ryoji Koike) will virtually solicitate the MRK EWG members for initial suggestions about revising the guidance.
2. April 2026 to August 2026 – FDA in conjunction with AHI and JMAFF will prepare an initial revised guidance.
3. August 2026 to November 2026 – MRK EWG members will provide feedback on the initial revised guidance. If the revisions are extensive, the EWG may need to meet in person at the November 2026 meeting to discuss the revisions.
4. November 2026 to February 2027 - FDA and JMAFF in conjunction with AHI will prepare a second revision of the guidance.
5. February 2027 to May 2027 – Final comments will be received from the EWG.
6. May 2027 to June 2027 - The revised guidance will be prepared for publication as a draft guidance for public comment.

Impact assessment for Industry

1. Provide clarity and global consistency for comparative metabolism studies.
2. Improve compliance with the principles of the 3Rs.
3. Save resources and money by conducting studies with design parameters that have global agreement.

Impact assessment for Regulatory Authorities

1. Bring consistency to the assessment of comparative metabolism studies for veterinary drugs.
2. Improve availability of veterinary drugs by decreasing the number of review cycles and potentially shortening the development timeline.

References to literature, existing relevant international guidelines or standards (e.g. ICH, OECD, CODEX, JECFA…)

The OECD guidance (No. 286), Guidance Document on Good Cell and Tissue Culture Practice 2.0 (GCCP 2.0) and the FDA draft guidance (https://www.regulations.gov/docket/FDA-2017-D-5961/document) may contain relevant recommendations about *in vitro* test systems that could be incorporated into GL47. The title of the FDA draft guidance is, “In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies”.