VICH draft GL57 (VICH-step 4*)

*VICH Step 4 is consultation stage before finalization.

JAPAN

24th CCRVDF

What is the purpose of VICH GLs?

- VICH is a trilateral (EU-Japan-USA) programme aimed at harmonising technical requirements for veterinary product registration.
- The role of VICH is to harmonise technical requirements for data necessary for the marketing authorisation (also called "registration") of a veterinary medicinal product. This is achieved by developing harmonised guidelines (GLs) on the studies to be submitted in a marketing authorisation application.

Title and Status of VICH GL57

- VICH GL 57 (MRK) –RESIDUES IN FISH
- December 2017
- For consultation at Step 4

- **Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-producing Species: Marker Residue Depletion Studies to Establish Product Withdrawal Periods in Aquatic Species**

GL57 is attached to CRD27 submitted by Japan.

VICH GLs: Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-producing Species

4 final GLs

- **GL46** :Metabolism study to determine the quantity and identify the nature of residues
- **GL47** :Comparative metabolism studies in laboratory animals
- **GL48 :Marker residue depletion studies to establish product withdrawal periods**
- **GL49**:Validation of analytical methods used in residue depletion studies

(http://www.vichsec.org/guidelines/pharmaceuticals/pharma-safety/metabolism-and-residue-kinetics.html)

GL48 is the parent GL of GL56 & GL57

VICH GLs:
Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-producing Species

2 draft GLs

- GL56:study design recommendations for residue studies in honey for establishing MRLs and withdrawal periods
- GL57:Marker Residue Depletion Studies to Establish Product Withdrawal Periods in Aquatic Species

(http://www.vichsec.org/consultations/active-draft-guidelines.html)

GL56 & GL57 are extensions to the GL48, and used with GL46, GL47, GL48 and GL49.

Contents of VICH GL57

TABLE OF CONTENTS

1. INTRODUCTION

- This guidance is one of a series developed to facilitate the mutual acceptance of residue chemistry data for veterinary drugs used in food-producing animals by national/regional regulators. This guidance was prepared after consideration of the current national/regional requirements and recommendations for evaluating veterinary drug residues in the VICH regions.
- The objective of this guidance is to provide study design recommendations which will facilitate the universal acceptance of the generated residue depletion data to fulfill the national/regional requirements.

2. GUIDANCE-2.1 Purpose

- Marker residue depletion studies for registration or approval, as applicable, of a new veterinary medicinal product in the intended species are recommended to:
  - demonstrate the depletion of the marker residue upon cessation of drug treatment to the regulatory safe level (e.g. maximum residue limit or tolerance).
  - generate data suitable for elaboration of appropriate withdrawal periods/withholding times to address consumer safety concerns.

2. GUIDANCE-2.2 Scope

- The intent is that a residue depletion study conducted according to the recommendations described in this guidance would satisfy the data requirements or recommendations for establishment of appropriate withdrawal periods in all VICH regions. Conducting a depletion study under worst-case conditions provides data for calculating the withdrawal period.
- The guidance encompasses food-producing aquatic species. The principles of this guidance are also applicable to eggs from aquatic species for human consumption. Studies should be conducted in conformity with the applicable principles of Good Laboratory Practice (GLP).

2. GUIDANCE-2.3 Test Article

- The test article used for the study should be representative of the commercial formulation.

2. GUIDANCE-2.4 Study Design
2.4.1 Animals

- Animals should be healthy and, preferably, should not have been previously medicated.
- Study animals should be representative of the commercial species and representative of the target animal population that will be treated.

2. GUIDANCE–2.4 Study Design
2.4.2 Critical Study Design parameters

- Critical residue depletion design parameters to address include water temperature, housing, and salinity. The body temperature and hence absorption, metabolism, and excretion of aquatic species is driven by the surrounding water temperature. Generally, the lower the water temperature the slower the depletion, but higher temperatures may result in higher absorption of drug. Table 1 shows examples of critical design parameters.

Table 1. Critical Study Design Parameters

Critical Parameter	Options	Choice
Water Temperature	High or Low within the test animal's recommended water temperature range	Choose the temperature that results in the worst case for residues
Salinity	Salt or Fresh Water	If applicable choose the one that results in the worst case for residues
Housing	Recirculation or flow-through or net pens	If applicable choose the one that results in the worst case for residues

2. GUIDANCE-2.4 Study Design
2.4.3 Animal husbandry

- Adequate environmental conditions should be ensured to be consistent with animal welfare, in accordance with applicable national and regional regulations.
- 2.4.3.1 Housing
- 2.4.3.2 Feeding
- 2.4.3.3 Water Temperature
- 2.4.3.4 Water Quality Parameter
- 2.4.3.5 Animal Anesthesia

2. GUIDANCE-2.4 Study Design
2.4.4 Single Species Claim

- Selection for the worst case scenario of the final design parameters should be justified.
- **2.4.4.1 In Feed Treatment**

  A claim for a single species can be supported by conducting a study in that species. Acceptance of the study in VICH regions is dependent on the study being conducted within the lowest range of temperatures in which in feed treatment is administered under commercial settings.

2. GUIDANCE–2.4 Study Design
2.4.4 Single Species Claim

- **2.4.4.2 Injectable Treatment**

  A claim for a single species can be supported by conducting a study in that species. Acceptance of the study in VICH regions is dependent on the study being conducted within the lowest range of temperatures.

- **2.4.4.3 Immersion**

  A claim for a single species can be supported by conducting a study in that species in consideration of worst case scenario parameters. Immersion treatments may result in differential drug absorption at different water temperatures. Selection of the appropriate water temperature should be investigated and subsequently justified.

2. GUIDANCE-2.4 Study Design 2.4.5 Single Order Claim

- A claim for an order can be supported by conducting a study in a representative species. A claim for an order can be supported by conducting a study in a representative species. The resulting withdrawal period can then be applied to other species of the same order. However, residue data in a second species to confirm the withdrawal period are recommended.

2. GUIDANCE-2.4 Study Design 2.4.5 Single Order Claim.

- Table 2 shows recommended target water temperature ranges for the residue depletion studies using representative species for different orders of finfish and shrimp.
- Representative species are chosen based on:

  1) the species being either widely cultured in a certain region (or a country) or closely related to such a species,

  2) residue depletion studies being able to be carried out at recommended water temperature range at which the species are cultured, and

  3) the assumption that the representative species have similar metabolism to other species in the same order. For immersion treatments the effect of temperature on residues should be considered.

Table 2. Representative Species and Recommended Water Temperature Range for Residue Depletion Study

Order	Representative Species	Recommended Water Temperature Range (°C)
Salmoniformes[1]	Atlantic salmon (*Salmo salar*) Coho salmon (*Oncorhynchus kisutch*) Rainbow trout (*Oncorhynchus mykiss*)	5-10
Cypriniformes	Carp (*Cyprinus carpio*) Common bream (*Abramis brama*)	15-20
Perciformes[1]	European seabass (*Dicentrarchus labrax*) Hybrid striped bass (*Morone saxaltilis X Morone chrysops*) Red sea bream (*Pagrus major*) Yellowtail (*Seriola quinqueradiata*) Walleye (*Sander vitreus*)	15-20
Scorpaeniformes	Mebaru (*Sebastes inermis/Sebastes cheni/Sebastes ventricosus*)	10-15
Silurformes	Channel catfish (*Ictalurus punctatus*) Mudfish (*Clarias anguillaris*)	16-21
Osmeriformes	Ayu (*Plecoglossus altivelis*)	13-18
Anguilliformes	Eel (*Anguilla japonica*) European eel (*Anguilla anguilla*)	20-25
Pleuronectiformes	Bastard halibut (*Paralichthus olivarceus*) Summer flounder (*Paralichthys dentatus*)	15-20
Tetraodontiformes	Japanese pufferfish (*Takifugu rubripes*)	13-18
Acipenseriformes	Siberian sturgeon (*Acipenser baerii*)	14-19
Gadiformes	Atlantic cod (*Gadus mohrua*)	5-10
Shrimp or prawns in the order of *Decapoda*	Japanese tiger prawn (*Penaeus japonicus*) Whiteleg shrimp *(Penaeus vannamei)*	18-23

[1] Order contains fresh and salt water representative species

2. GUIDANCE-2.5 Number of animals for the study

- The number of animals used should be large enough to allow a meaningful assessment of the data. Residue data from a minimum of 10 animals per time point are recommended. For small finfish or shrimp a composite sample of multiple animals can be used.
- Control (non-treated) animals are not necessarily called for as part of the actual marker residue depletion study; however, sufficient amounts of control matrices should be available to provide material for related analytical method testing.

2. GUIDANCE-2.6 Dosing and Route of Administration

- 2.6.1. General guidance

  Animal treatment should be consistent with the intended product label. At least the highest intended treatment dose should be administered for the maximum intended duration.

- 2.6.2. Immersion Treatment
- 2.6.3. In-feed Treatment
- 2.6.4. Injectable Treatment

2. GUIDANCE-2.7 Animal Euthanasia

- Animals should be euthanized using commercially applicable procedures, observing appropriate exsanguination times. Chemical euthanasia can be used unless it will interfere with the analysis of the marker residue.

2. GUIDANCE–2.8 Sampling

- 2.8.1. General considerations

  Following euthanasia, edible tissue samples in sufficient amounts should be collected, trimmed of extraneous material, weighed, and divided into aliquots (if appropriate). If the analysis cannot be completed immediately, the samples should be stored under frozen conditions pending analysis. If samples are stored after collection, the Sponsor generally bears the responsibility for demonstrating residue stability through to the time of assay.

- 2.8.2. Tissue Sampling

  -Table 3 indicates the recommended samples for collection for all VICH regions.

  -Table 4 indicates the additional tissues that should be sampled to address specific national/regional consumption habits and/or legal concerns.

Table 3. Sample Collection from Animals in the Marker Residue Depletion Study (All VICH Regions)

Aquaculture Species	Edible Tissue Samples
Finfish with edible skin	Muscle including skin in natural proportions, which is the entire fillet with the overlying skin from one or both sides of the fish (scales can be included or excluded based on consumption and practicality of removal)
Finfish with inedible skin (Example: Channel catfish, threadsail filefish)	Muscle, which is the entire fillet from one or both sides of the fish
Mollusks	Soft tissue excluding shell.
Shrimp or prawns with hard (inedible) shell	Soft tissue including mid-intestinal gland, excluding shell.
Shrimp or prawns (during molting) with soft (edible) shell	The entire animal including the shell is considered as the edible tissue. The edible tissue for shrimp includes the mid-intestinal gland and shell.

Table 4. Additional Tissues that can be Collected to Address Specific National/Regional Consumption and/or Legal Concerns in the Marker Residue Depletion Study

Order	Edible Tissue Type
Any orders of finfish	Either one additional tissue that has been shown to have the highest concentration or slowest depletion of residue among the tissues of visceral organs by previous residue studies, or the offal mixture of available liver, kidney, spleen, stomach, intestine, heart, ovary and testis.

2. GUIDANCE-2.9
Recommendations for products for 0 day Withdrawal Periods (Single Time-Point Studies)

- For products administered as one treatment or as several treatments (for example daily for 3-5 days), or for continuous use products in which residues have reached steady state, a single time point study can qualify for 0-day withdrawal, provided that the absorption and depletion characteristics of the drug have been described, for example, as indicated in VICH GL46. If such data are available, then a single time point study conducted with the specified minimum number of animals is recommended to demonstrate 0-day withdrawal.
- Number of animals: a minimum of 15 individuals or 15 composites
- The sampling time chosen for this study should be consistent with the peak concentrations.

2. GUIDANCE-2.10 Analytical Methods for Assay of Marker Residue

- The Sponsor should submit a validated analytical method for the determination of the marker residue in samples generated from the residue depletion studies. The method(s) should be capable of reliably determining concentrations of marker residue which encompass the appropriate reference point (i.e., MRL / Tolerance) for the respective tissues or products.
- The parameters to be included in the method validation are fully discussed in VICH GL49, "Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food Producing Animals: Validation of Analytical Methods Used in Residue Depletion Studies."

3 Glossary

- The following definitions are applied for purposes of this document.
- **Aquatic species** include finfish, crustaceans, and mollusks.
- **Degree days** means an expression of the withdrawal period where it is assumed that time multiplied by water temperature is constant.
- **Marker residue** is that residue whose concentration is in a known relationship to the concentration of total residue in an edible tissue.
- **Maximum residue limit (MRL)** is the maximum concentration of a veterinary drug residue that is legally permitted or recognized as acceptable in or on a food as set by a national or regional regulatory authority. The term 'tolerance,' used in some countries, can be, in many instances, synonymous with MRL.
- **Residue** means the veterinary drug (parent) and/or its metabolites.
- **Shrimps** and **prawns** belong to the family of *Penaeidae*. This includes most of the shrimps or prawns cultured worldwide but exclude crabs, *machrobrachium*, lobsters, and crayfishes. Some regions use the term shrimp and some use the term prawns and these terms can be used interchangeably.

Thank you very much for your attention.