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**Summary**

To address concerns around human consumption of edible tissues, registration of veterinary pharmaceuticals in food-producing animals requires data to demonstrate both depletion of the marker residue to regulatory-determined safe levels and an adequate post-dose withdrawal period.

SAFETY ASSESSMENT

# Considerations in the Design of Non-radiolabeled Residue Studies

The regulations for the registration of veterinary medicinal products in food-producing animals includes the requirement for data from marker residue depletion studies to establish appropriate withdrawal periods in edible tissues including meat, milk, and eggs. Consideration must be given to appropriately designing a study in order to enable universal acceptance of the residue depletion data that is generated and fulfil the relevant national or regional requirements.

The aims of the study are twofold:

- Demonstrate the depletion of the marker residue to the regulatory-determined safe level following completion of the dosing phase of the study.
- Generate data to establish an adequate withdrawal period in order to address any concerns around human consumption of edible tissues following drug administration.

A typical non-radiolabeled residue study design will comprise of a minimum of 16 animals of a species that represents both the commercial breed and intended target population of the clinical formulation. Some study designs require additional considerations, however. For example, in the case of tissue residue studies in birds, at least 6 samples are required per slaughter time point and therefore an adequate number of birds should be used to obtain this number. In the case of egg residue studies, 10 or more eggs are required at each interval time point and again, sufficient numbers of laying hens are required to achieve this. Other factors in species selection reflect the tissue endpoints to be included in the study design. For instance, where it is anticipated that marker residues will be measured in milk, the difference between ruminant and pre-ruminant animals must be taken into consideration. Furthermore, all stages of lactation should be appropriately represented in the study groups and the guidelines recommend a higher number of study animals to accommodate this.

While it is preferable that the test article is formulated to GMP it is not essential; a GLP standard test article is adequate as long as it is representative of the commercial formulation. Doses should be administered in accordance with the intended clinical regimen and at the highest dose level for the maximum length of administration, unless long term clinical administration is anticipated in which case dosing to a steady state in target tissues is acceptable. At the completion of the dosing phase, samples of all the edible tissues recommended for product registration in the intended VICH region are collected, as well as any additional tissues required to address either specific national or regional consumption habits or other safety concerns. Milk and egg samples, where appropriate, are also collected based on a predetermined protocol.

## Sample Anaylysis

A validated analytical method is required for the determination of the marker residue in the various tissue samples collected, as well as in milk and eggs where appropriate. The method(s) should be capable of reliably determining concentrations of marker residue that encompass the maximum residue limits (MRL)/tolerance for the respective tissues and products.

In determining the acceptability of a method, the validation studies must be able to adequately demonstrate standard performance characteristics, i.e., linearity, accuracy, precision, limit of detection, limit of quantitation, selectivity, stability in matrix, process sample stability, and robustness.

Included in the sample analysis regime can be the dose formulation analysis and injection site analysis. Again, validated methods that encompass the expected concentration range of the test item or marker residue are required.

## Study Management

Much of the expertise in reporting these studies lies in the interpretation of the analytical data, and our recommendation would be that the study director be from the analytical, rather than the in-life phase of the study. Residue depletion times can result in protracted time points and samples are often taken well after actual dosing has been completed. Further roadblocks to timely completion of the final report can be minimized by having the sample analysis and live phase conducted on the same site. This reduces the potential for delays resulting from sample shipment, scheduling, troubleshooting, dealing with stability issues, and communication.