**VETERINARY MEDICINES BIOWAIVER APPLICATION FORM FOR PARENTERALS**

1. ***PRODUCT INFORMATION***

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| *Date of submission* |  |
| *Application number* |  |
| *Product name* |  |
| *Active Pharmaceutical Ingredient API(s)* |  |
| *Dosage form and strength* |  |
| *Scheduling status* |  |
| *Applicant name and address* |  |
| *Manufacturer name and address* |  |
| *Manufacturer applied for name and address* |  |
| *API Manufacturer name and address (Reference)* |  |
| *API manufacturer applied for name and address* |  |
| *Indications* |  |
| *Pharmacological action* |  |
| *Foreign registration status* |  |

***INTRODUCTION***

The formulation and API characteristics, including the route of administration and species, are factors which may affect requirements to waive bioequivalence studies (i.e., to compare the rate and extent of absorption between two formulations containing same active substances).

Applicants must submit the following relevant information in support of a biowaiver for parenterals.

1. ***QUALITY REQUIREMENTS***

***2.1 SUMMARY OF REQUIREMENTS***

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| ***Requirements***  | ***Outcome*** |
| *Therapeutic range (and dose)* | Narrow / Non-narrow |
| *Aqeous solubility at different pH and temperature* |  |
| *Dosage form* | Solution/Suspension |
| *Route of administration* | IM/SC/IV |
| *Valid CoAs*  | API Assays within 5 % of label claim (limits greater than 5 % should be justified) |

* 1. ***COMPOSITION***

**2.2.1 In the table below include the following:** Qualitative and Quantitative composition,Critical Quality Attributes; Grade of excipients (as applicable).

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| ***Reference product composition*** | ***Test Product composition*** |
| **Active substance:****Comparison of Excipients:**  | **Active substance:****Comparison of Excipients:** |

***2.2.2 DISCUSSION AND JUSTIFICATION FOR APPLICATION OF A BIOWAIVER***

In your discussion, give the strength and dosage form of the test and reference products.

Discuss the composition and similarity.

Include the “Declaration of Sameness”, CoAs and API assays, as applicable.

Include the manufacturers and whether the two products are manufactured by the same company.

a) Aqueous intravenous solutions must contain the same active substance as the currently approved product. Comment on possibility of excipients interacting with the active substance (e.g., complex formation) and a different salt if used.

b) Both products should contain the same or similar excipients in sufficiently similar quantity. If not, justify any difference in the type and quantity of excipient to demonstrate that it does not affect the pharmacokinetics of the active substance. Unacceptable differences are not recommended.

c) Intramuscular or subcutaneous: Same type of solution should contain the same concentration of the API and excipients in similar quantitative and qualitative amounts as the reference product. Justify that any differences in the excipients or salts and/or their concentration will not have influence on the rate and extent of absorption of the active substance.

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| *Comments from review of Section 2 – For SAHPRA use only* |
| **Reviewer’s comments:**Assess and comment on the information presented in section 2: Comparisons of composition, CQAs, identicality etc. |

***3. SAFETY AND EFFICACY REQUIREMENTS***

***3.1 Status of the reference/ innovator product***

Refer to an innovator/reference product registered by a Regulator that SAHPRA aligns with.

***3.1.1 Basic pharmacokinetic information***

Pharmacology

***3.1.2 Therapeutic indications and dose***

***3.1.3 Pharmacovigilance data to support the safety of the product.***

Provide any available pharmacovigilance data.

***3.1.4 Injection site reactions***

Discuss any injection site reactions observed (if applicable). (Literature review may be used***)***

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| *Comments from review of Section 3 – For SAHPRA use only* |
| ***Reviewer’s comments:****Assess and comment on the information presented in section 3 – including relevant background information on the reference product* |

***4. FOOD SAFETY MATTERS FOR CONSIDERATION WITH RESPECT TO BIOWAIVERS***

***4.1 INTRODUCTION***

Food safety of veterinary medicines used in production animals for products intended for human consumption is of critical importance. Residue data should be provided or be available to justify withdrawal periods for e.g., milk, meat, eggs for each species for which the veterinary medicine is indicated.

For certain veterinary medicines, such as generic veterinary medicines for which biowaivers have been granted, residue data to confirm the withdrawal period assigned to the reference product might not be necessary.

There are situations where an abbreviated depletion study may be required even after the demonstration of pharmaceutical equivalence and/or bioequivalence of a generic product.

In accordance with the EMA (guideline on the conduct of bioequivalence studies for veterinary medicinal products) bioequivalence or waivers cannot be used for extrapolation of withdrawal periods between products with a potential to leave local residues e.g., IM & SC injectables.

Consideration of any waiver of residue depletion data for generic veterinary medicines, change in formulations or for different strengths will be on a case-by-case basis taking into consideration the quantitative and qualitative pharmaceutical equivalence of the API and all excipients. The Applicant will be required to provide a full scientific justification for the waiver of residue depletion data.

When a waiver cannot be granted, the residue depletion studies to confirm or establish that the withdrawal period of the generic product is the same as approved for the reference product will be required.

***4.2 SITUATIONS AND CONDITIONS WHERE RESIDUE DEPLETION DATA COULD BE WAIVED***

* For formulations (i.e., API plus all excipients) that are qualitatively and quantitatively the same or similar and where a waiver for the requirement of bioequivalence assessment had been granted. A justification by the Applicant still needs to be provided.
* If bioequivalence is granted on blood-level studies, the assay method needs to be sensitive enough to measure the terminal (elimination) phase of the medicine concentration versus time curve in blood for the entire withdrawal period established for the reference product, if correlation data between the depletion of the medicine from the blood and marker residue in the target tissue exists.
* In minor species where residue data in a major species has been generated.

***4.3 SITUATIONS AND CONDITIONS WHERE RESIDUE STUDIES CANNOT BE WAIVED***

* In all cases where no residue data are available on file for the reference product – the generic product must meet current standards of the guideline. A comprehensive residue depletion study would be required.
* In cases where a waiver for pharmaceutical equivalence or bioequivalence was not granted.
* An abbreviated residue depletion study is generally required for non-aqueous products for injection by IM and SC routes.
* For veterinary medicines where the formulation (e.g., pH, vehicle, excipients) differ from that of the reference product and concerns about residue depletion are evident – even though the generic product is pharmaceutically equivalent and a waiver for a bioequivalence study had been granted.
* For veterinary medicines where the terminal portion of the disposition curve between the test and reference products differ.
* Differences in the location of injection sites or evidence of significant injection site tissue reaction that may lead to an altered tissue residue depletion pattern.
* An Applicant seeking a shorter withdrawal period for the generic product. A comprehensive residue study will be required.
1. ***CONCLUSION (FOR SAHPRA USE ONLY)***

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| *Comments from review of Section 4 – For SAHPRA use only* |
| **Reviewer’s comments:**Discuss information submitted in section 4 – Reviewer to discuss the justification submitted by the applicant to demonstrate food safety. |

***RECOMMENDATIONS***

**Registration is recommended/not recommended.**

**State the basis for recommending registration or list the queries to the applicant.**

1. ***REFERENCES BY APPLICANT***

Relevant regulatory guidelines