Notes on the Design of Bioequivalence Study: Ribavirin

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Unit – Medicines Assessment Team (PQT/MED) are issued to aid manufacturers with the development of their product dossier. Deviations from the approach suggested below can be considered acceptable if justified by sound scientific evidence.

The current notes should be read and followed in line with the general guidelines of submission of documentation for WHO prequalification. For guidance on issues related to bioequivalence (BE) studies for immediate-release, solid oral dosage forms, see the ICH Harmonised Guideline M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (2024). For BE issues outside the scope of the ICH M13A guideline, e.g., for additional strength biowaivers, please consult the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability" in: *Fifty-seventh Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2024. WHO Technical Report Series, No. 1052, Annex 8.

Below, additional specific guidance is provided on the invited immediate release products containing ribavirin.

Pharmacokinetics of ribavirin

There is a linear relationship between dose and AUC following single doses of 200-1,200 mg ribavirin. Ribavirin is absorbed rapidly following oral administration of a single dose with a mean T_{max} = 1.5 hours. Single dose elimination half-life is 80 hours. The bioavailability of a single oral dose of ribavirin was increased by co-administration of a high fat meal (AUC and C_{max} both increased by 70 %). Ribavirin should be administered orally with food.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of ribavirin, the following guidance with regard to the study design should be taken into account:

Design: A single-dose cross-over design is recommended.

Dose: As the EoI includes 200, 400 and 600 mg capsules, the highest strength of 600 mg should be employed in the bioequivalence study. However, if ribavirin is shown to be a highly soluble drug according to the BCS classification system, the bioequivalence study could be conducted with any strength. Further, if the Applicant generates the solubility data and stability data in the physiological pH range and classifies the drug according to the BCS criteria as highly soluble, ribavirin could be classified as BCS class III drug and a BCS biowaiver could be applicable.

For the 40 mg/ml syrup, the dose of 600 mg should be administered but, if as it seems, ribavirin can be classified as a BCS class III API, any therapeutic dose could be administered. The bioequivalence study could be waived if the test product contains the same excipients (i.e. glycerol, sucrose, sorbitol liquid (crystallising), propylene glycol) in similar concentrations as the comparator. Buffers, preservatives and flavours could be changed (i.e. sodium citrate, citric acid anhydrous, sodium benzoate, bubble gum flavouring).

Fasted/fed: As ribavirin the comparator product should be taken with food, bioequivalence should be investigated in the fed state.

Subjects: Healthy adult subjects should be recruited. It is not necessary to include patients in the bioequivalence study.

Parent or metabolite data for assessment of bioequivalence: The parent drug is considered to best reflect the biopharmaceutical quality of the product. Therefore, bioequivalence should be based on the determination of ribavirin.

Sample size: Information currently available to PQT/MED indicates that the intra-subject variability for ribavirin is around 15 - 20%. These data may facilitate the calculation of a sufficient sample size for the single-dose cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of ribavirin in the fed state of 80 hours, a washout period of 5 or 6 weeks is considered sufficient to prevent carry over.

Blood sampling: The blood sampling should be intensive for the first hours after administration to properly characterize the C_{max} of ribavirin. For example, blood samples might be taken at pre-dose and at 0.25, 0.5, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 6.00, 8.00, 10.00, 12.00, 24.00, 48.00 and 72.00 h after drug administration. It is not necessary to take samples after 72 hours.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure ribavirin in human plasma using LC-MS/MS analytical methodology. The bioanalytical method should be sufficiently sensitive to detect concentrations that are 5% of the C_{max} in most profiles of each formulation (test or comparator). See Guideline on bioanalytical method validation and study sample analysis. In: WHO Technical Report Series, No. 1060, Annex 6, or the ICH Harmonised Guideline M10 for more information on bioanalytical recommendations.

Statistical considerations: The data for ribavirin should meet the following bioequivalence standards in a single-dose crossover design study:

- The 90% confidence interval of the relative mean $AUC_{0\text{-}72h}$ of the test to reference product should be within 80.00–125.00%
- The 90% confidence interval of the relative mean C_{max} of the test to reference product should be within 80.00–125.00%.

Biowaiver: If the applicant can demonstrate high solubility of ribavirin according to the BCS based on the highest therapeutic single dose, a BCS biowaiver would be feasible provided the additional requirements for granting a BCS-based biowaiver are met as outlined in the WHO Guideline "*Biopharmaceutics Classification System-Based Biowaivers*" (TRS1052, Annex 7, 2024) and the PQT/MED guidance "*PQT/MED-specific Annotations for the WHO Guideline on Biopharmaceutics Classification System (BCS)-based Biowaivers*" (2024).