Meeting the Draft Guidance for Bioequivalence for Topical Products

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Introduction

A recent analysis by the US Government Accountability Office of drug pricing showed that topical generic drug prices had increased byanaverage of 276%, whereas for all otherroutes of delivery there had been no significant change. This was directly related to lack of generic competition and the height of barriers to entry for new topical generic products. Demonstrating bioequivalence (BE) *via* human clinical trials represents one the most significant barriers to generic competition in topical products. Clinical trials remain time consuming, expensive and risky. The variability in skin adds inherent risks to any clinical trial on top of the expense. As the skin also responds to most excipients there is no true placebo, just vehicle components that are accepted to have some effect. This makes primary endpoints more difficult to meet, further increasing the risk of failure. In turn this creates a challenge for governments wanting to promote theintroduction of topically applied generics as a wayof reducing their healthcare bills, whilst at the same time being clearly obligated to register generic products without any additional riskto patients.

To further facilitate generic product availability, the FDA published product-specific guidances describing the Agency's current thinking and expectations on how to develop and test generic drug products therapeutically equivalent to specific reference listed drugs (RLDs). With regards to testing, the guidances stipulate the use of *in vitro* performance models, i.e. *in vitro* skin permeation testing (IVPT) and *in vitro* drug release testing (IVRT), to demonstrate BE without the need for a clinical study.

The FDA's Draft Guidance on Acyclovir provides a detailed description of those *in vitro* assessment approaches for an acyclovir topical cream formulation. References to the same *in vitro* approaches are also included inmore recent FDA guidances covering multipletopical products.

Aim

The aim of this study was to investigate the applicability of IVRT and IVPT methods from the FDA's Draft Guidance on Acyclovir in demonstrating BE of TEST and RLD products. Gel formulations of threedifferentdrugs wereevaluated;Drugs A , B, and C.

Methods

IVPT:

Human skin was prepared and positioned between the two halves of the vertical diffusion cell with the *Stratum Corneum* facing the donor compartment allowing for application of the formulation. Formulation was applied to the top of the skin and the receptor solution sampled over the course of the experiment. Receptor solution drug concentrations were determined using validated LC-MS/MS methods.

IVRT:

A porous and non-rate limiting membrane was positioned between the two halves of the vertical diffusion cell, and an infinite dose of the formulation was applied to the top of the membrane. The receptor solution was sampled over the course of the experiment. Receptor solution drug concentrations were determined using validated LC-UV methods.

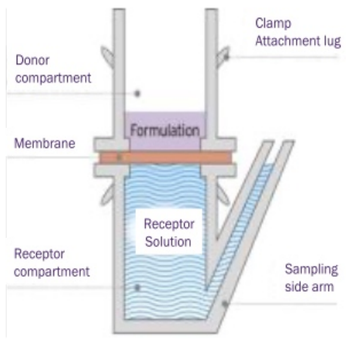

Fig 1. Schematic representation of a vertical diffusion cell.

Results

Sensitive, reproducible, and discriminatory IVRT methods, were developed and validated for the characterization of each drug's formulation(A, B and C). Similarly, IVPT methods were validated for formulationsof drugs A and B; however additional method development may be required for formulations of drug C. The *in vitro* methods were used (where possible) for bioequivalence assessment of generic formulationsvs RLDs.

Drug A –Based on statistical analysis of maximum flux, Jmax, and area under the curve, AUC (IVPT data; Figure 2a), the Test and RLD products were determined to be bioequivalent.

Bioequivalence was also demonstrated when comparing IVRT slopes (Fig. 2b).

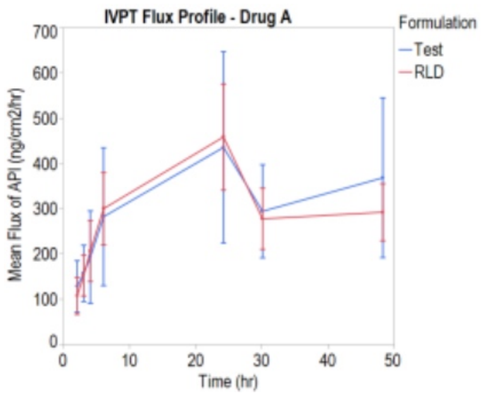

Fig 2a. Mean flux of Drug A (ng/cm²/h) calculated for each formulation. Data points represent the flux of Drug A from 4 replicates per donor, 3 donors (n=12). Error bars one standard error of the mean.

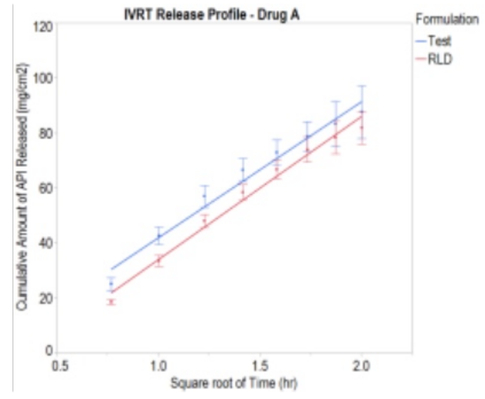

Fig 2b. Mean cumulative amount of Drug A (µg/cm2) released per unit area for each formulation. Data is represented as mean ± SD (n=6)

Drug B – A plateau in the flux for both formulations was observed at 32 h until the completion of the experiment at 48 h (Fig. 3a). Therefore, Jmax could not accurately bedetermined.

Statistical analysis was conducted using only AUC, as the cutaneous pharmacokinetic endpoint. The Test and RLD were determined to be bioequivalent.

Bioequivalence was also demonstrated when comparing IVRT slopes (Fig. 3b).

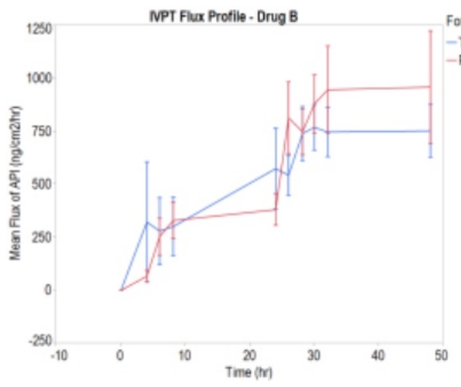

Fig 3a. Mean flux of Drug B (ng/cm2/h) calculated for each formulation. Data points represent the flux of Drug B from 4 replicates per donor, 3 donors (n=12). Error bars one standard error of the mean.

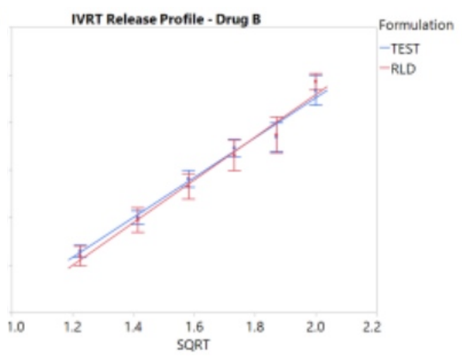

Fig 3b. Mean cumulative amount of Drug B (µg/cm2) released per unit area for each formulation. Data is represented as mean ± SD (n=6)

Drug C – Little to no drug was detected in the receptor solution over 48 hours and thus Jmax and AUC could not be determined.

Bioequivalence was demonstrated when comparing IVRT slopes(Fig.4).

Table 1. IVPT test parameters and

	Test Method Parameters
Thickness (µm)	500
No. skin donors	3
No. formulations	2
RS collection times	10 over 48 hours
Number of samples BLQ	> 50% at 48 hours
LLOQ	Lowest found in literature

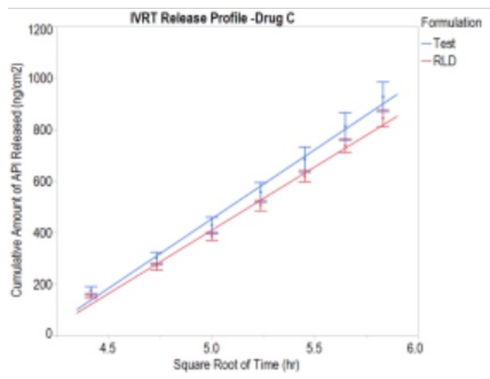

Fig 4. Mean cumulative amount of Drug C (µg/cm2) released per unit area for each formulation. Data is represented as mean ± SD (n=6)

Conclusion

Draft FDA guidances exist for Drug B and C, but not for Drug A. Of the three drugs tested, only Drug A fully met the *in vitro* requirements outlined in the FDA's Draft Guidance for Acyclovir. For Drug B and C, pharmacokinetic endpoints, Jmax and/or AUC, could not be achieved; therefore, not all statisticalIVPTcomparisonscouldbeperformedasper theFDAguidance.

To summarize, a one-size fits all approach for topical bioequivalence *in vitro* evaluation may not always be successful, therefore, modifications to the current IVRT/IVPT guidance should be considered.

Table 2. Summary detailing outcomes of the present study

Drug	Draft Guidance Available? (Y/N)	*In Vitro* Assessments in Guidance? (Y/N)	Meeting Acyclovir Guidance – IVRT? (Y/N)	Meeting Acyclovir Guidance – IVPT? (Y/N)
A	N	N	Y	Y
B	Y	Y	Y	N
C	Y	N	Y	N

References

- Brown M, Lenn J, Drummond J, "Cost-Effective Approaches for Successful Generic Dermal Drug Product Authorisations". ONdrugDelivery Magazine, Issue 84 (Mar 2018), pp 4-7
- FDA 2018. Guidance for Industry. Bioanalytical Method Validation issued by the U.S Department of Health and Human Services Fo od and Drug Administration FDA. May 2018
- FDA 2016. Draft Guidance on Acyclovir issued by the U.S Department of Health and Human Services Food and Drug Administration FDA. Dec 2014 (revised Dec 2016).

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