TACKLING FORMULATION COMPLEXITY IN BIOEQUIVALENCE ASSESSMENT OF TOPICAL GENERIC PRODUCTS

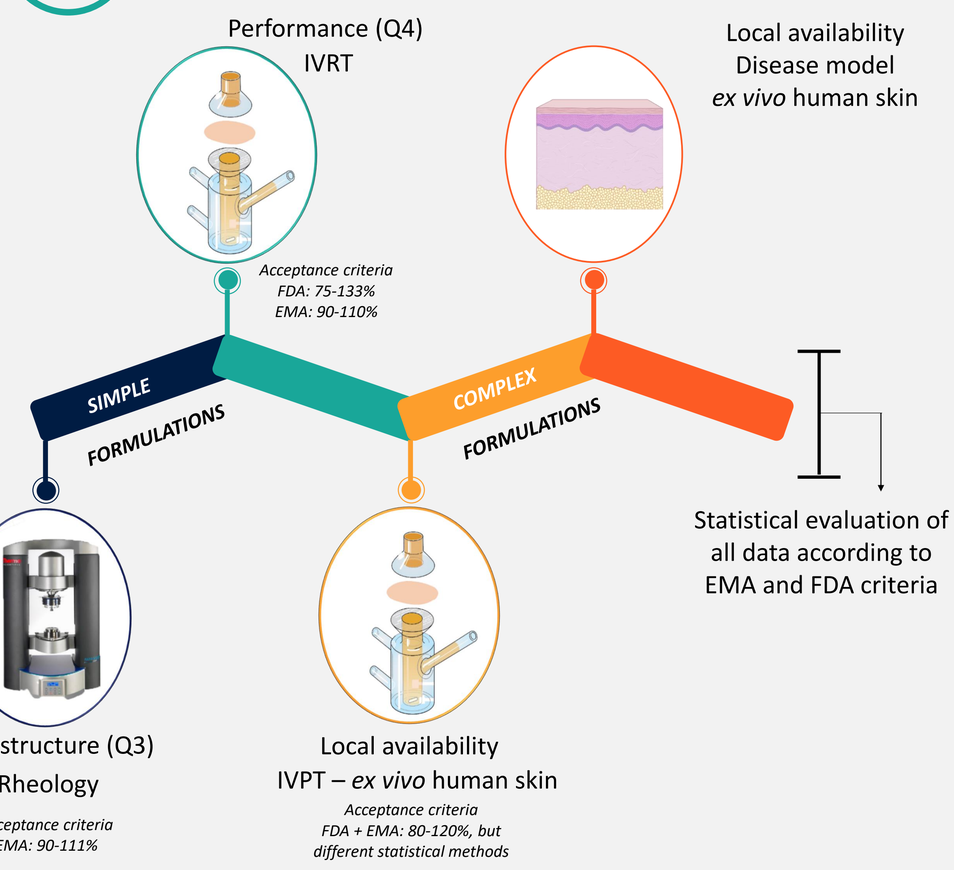
Margarida Miranda[1,2], Carla Vitorino[2,3]

[1]CiiEM – Centro de investigação interdisciplinar Egas Moniz, Egas Moniz School of Health and Science, Monte de Caparica, Portugal; [2]Coimbra Chemistry Centre, Institute of Molecular Sciences – IMS, Department of Chemistry, University of Coimbra, Coimbra 3000-535, Portugal; [3]Faculty of Pharmacy, University of Coimbra, Coimbra 3000-548, Portugal

1 INTRODUCTION

- A marketing authorization of a topical generic product (TGP) requires the demonstration of the pharmaceutical and therapeutic equivalence, as topically applied and locally acting products are not designed to be systemically available. Bioequivalence (BE) can thus be inferred by pharmacodynamic assays or by comparative clinical endpoint studies, which are extremely expensive. Ensuring the access to affordable and high quality generics is a public health priority, therefore this issue has sparked attention of regulators, and has resulted in new guidelines. FDA and EMA now advise on a modular strategy for BE documentation; nevertheless, there are significant differences between both agencies.
- This work aims to tackle bioequivalence (BE) assessment issues of TGP starting by statistical implications of the EMA/FDA approaches concerning the documentation qualitative (Q1), quantitative (Q2), microstructure (Q3), performance requirements (Q4) and local availability sameness.
- 3 case studies were considered – dimetindene maleate 1 mg/g gel, embodying a simple formulation, bifonazole 10 mg/g cream and diclofenac 20 mg/g emulgel, representing increasingly complex formulations.

2 METHODS

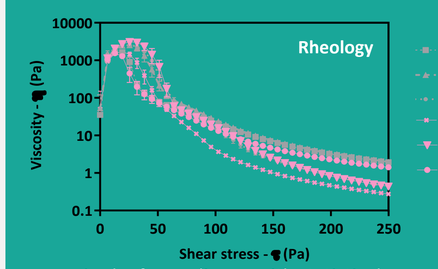


3 RESULTS AND DISCUSSION

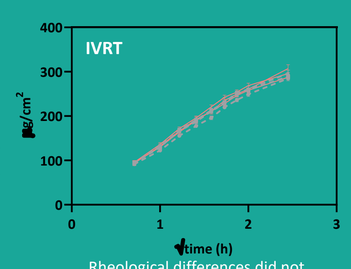
All methods were validated

Case study #1: Dimetindene maleate 1 mg/g gel

- Dosage form: Hydrogel → Monophasic formulation
- BE Strategy: Rheology + performance assessment
- Study design: 3 RP batches vs. 3 TP (Q1+Q2 equivalent)



Lack of compliance with statistical requirements (3/9)



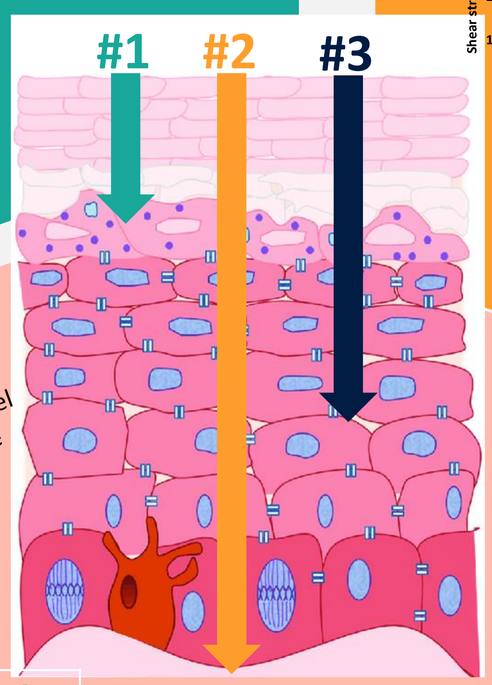
Rheological differences did not affect product performance

IVRR	Qf
97.75 – 105.8%	98.76 – 104.8%

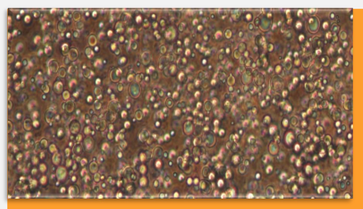
Q1 ✓ Q2 ✓ Q3 ✗ Q4 ✓

Variability drivers

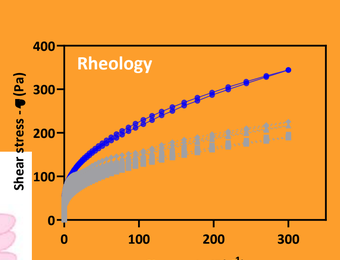
- TP and RP studies in ≠ stages of product lifecycle
- Source of raw materials
- Scale of manufacturing



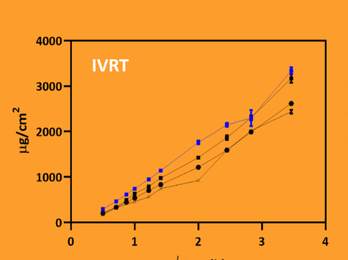
Case study #2: Diclofenac 20 mg/g emulgel



- Dosage form: o/w emulgel → Multiphasic formulation
- BE Strategy: Rheology + performance + local availability assessment
- Study design: 3 RP batches vs. 1 TP (PK equivalent, commercially available)



Rheology endpoints (1/9)



IVRT endpoints: did not comply with **EMA + FDA**

- Observed differences in Q3, Q4 and local availability parameters are not expected to translate into clinically significant differences

IVPT	J_{MAX} (μg/cm²/h)	A_{TOTAL} (μg/cm²)
EMA	68.42 – 141.22	69.60 – 143.89
FDA	SCI_{UB} = 0.8772 GMR = 0.9830	SCI_{UB} = 0.7710 GMR = 0.8584

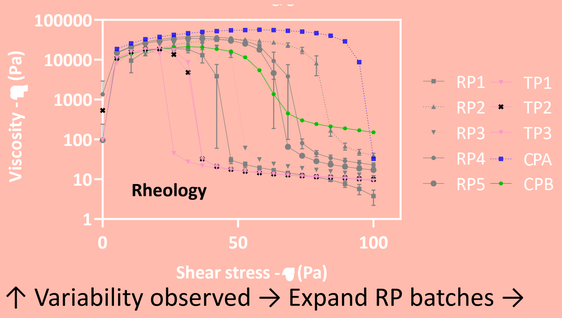
! Study limitation – n. of TP batches + n. of donors (n=9)

Q1 ✓ Q2 ✓ Q3 ✗ Q4 ✗ Local availability ✗

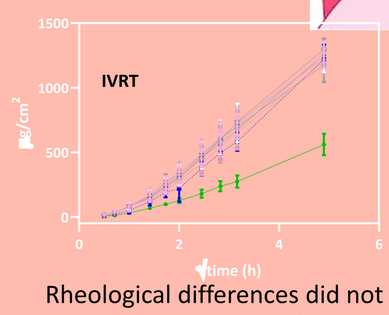
- IVPT with 2 RP batches with opposite viscosity behaviours. RP1 (↓ viscosity) + RP4 (↑ viscosity)
- In IVPT studies more skin donors than #2 (n=11)
- Disease model mimicking an antifungal skin infection

Case study #3: Bifonazole 10 mg/g cream

- Dosage form: o/w cream → Multiphasic formulation
- BE Strategy: Rheology + performance + local availability assessment + Disease model
- Study design: 5 RP batches vs. 3 TP (Q1/Q2 equivalent) vs. commercially available comparators CPA (Q1) + CPB (not Q1)



↑ Variability observed → Expand RP batches → Evaluate RP variability



Rheological differences did not affect IVRT, except CPB (Q1/Q2≠ formulation)

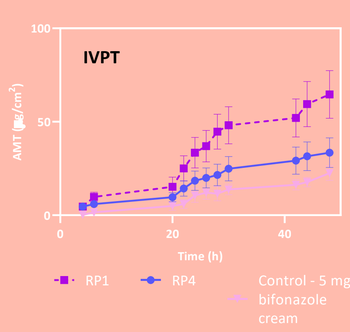
But:

RP vs. RP → EMA ✗

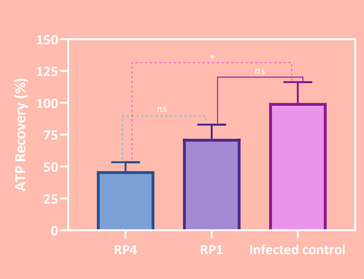
RP vs. RP → FDA ✓

All RP vs. TP → EMA & FDA ✓

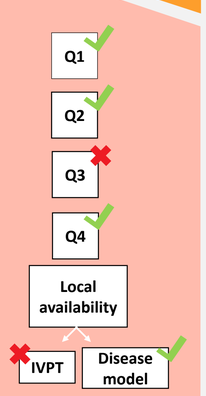
How do differences in rheology and IVRT affect local efficacy in RP batches?



NC results according to EMA and FDA



Disease model was unable to statistically differentiate between the formulation batches



4 CONCLUSIONS AND OUTLOOK

#1 Q3 failed to be documented for the **dimetindene gel formulation**. The RP rheological profile proved to be inequivalent towards the TP, however these differences did not condition its performance

#2 Q3 + Q4 + local availability studies failed to be documented for the **diclofenac emulgel formulation**. However, the TP displays equivalent PK profile, therefore, Q3, Q4 and local availability differences are not expected to translate into clinically significant differences.

#3 The **bifonazole cream** RP rheological variability impaired Q3 equivalence assessment, but these differences were nor reflected in IVRT. Nevertheless, in IVPT equivalence could not be supported between the different viscosity RP batches. In contrast, this statistical difference was not observed in the disease model, suggesting that this method could pose as a reliable strategy to infer on topical antifungal bioavailability, as it is not expected that different batches would yield a different therapeutic response.

REFERENCES

Miranda, M., et al, 2023. Eur. J. Pharm. Biopharm. 185, 94–106. https://doi.org/10.1016/j.ejpb.2023.02.006

Miranda, M., et al, 2022. Int. J. Pharm. 121705. https://doi.org/10.1016/j.ijpharm.2022.121705

Miranda, M., et al, 2024. Int. J. Pharm. 656, 124012. https://doi.org/10.1016/j.ijpharm.2024.124012

ACKNOWLEDGEMENTS

The authors would like to acknowledge Medpharm for the conduct of the infected skin disease studies and to Professor Marc Brown for all the assistance in this work. The Coimbra Chemistry Centre (CQC) is supported by the FCT through the projects UIDB/00313/2025 and UIDP/00313/2025.