Equivalence testing of rheological parameters of generic and branded cream, facing criteria of EMA Draft Guideline 2019

Philipp Böhm, Melanie Köllmer, Michael Herbig
RaDes GmbH
Schnackenburgallee 114
22525 Hamburg, Germany

Background & Introduction

- The EMA “Draft guideline on quality and equivalence of topical products” from 2019 provides specific guidance on equivalence testing for topical product in lieu of clinical equivalence trials. This includes a range of specific rheological tests and concrete criteria for equivalence.
- The comparison of viscosities at different shear rates (flow curve), thixotropy testing, and oscillatory parameters, such as yield and flow stress, viscoelastic storage and loss moduli as well as loss tangent are proposed from the guideline.
- The equivalence is defined by the following criteria of the Guideline:

  „For quantitative quality characteristics, the 90% confidence interval for the difference of means of the test and comparator products should be contained within the acceptance criteria of ±10% of the comparator product mean, assuming normal distribution of data.“[1]
- In order to enable statistical evaluation, the guideline recommends at least 12 samples per batch and at least 3 batches per product.
- To assess the appropriateness of the acceptance criteria and identify potential challenges, a generic and brand of a hydrocortisone-containing, semi-solid formulation were tested for rheological equivalence. The generic product was approved prior to the publication of the EMA guideline and was identical in qualitative composition and microscopic microstructure.

Methods

- Ten rheological parameters, including the ones mentioned by the Draft Guideline, were studied.
- Deviating from recommendation of the Guideline, we considered 12 samples per batch as excessive and investigated five samples per batch which we considered are sufficient.
- Rheometry was performed on an MCR 102 rheometer by Anton Paar, using CP25 at 25°C.
- Amplitude sweeps were performed in oscillation mode with 0.01 to 1000 % deformation and a constant angular of frequency of 10/s. Shear viscosity was determined from 0.00001 – 1000 1/s. Hysteresis curve was performed from 0.01 – 100 1/s, holding for 30 seconds at 100 1/s and decreasing again from 100 – 0.01 1/s.
- In addition, an ORO-test (oscillation-rotation-oscillation) was performed as an alternative, more precise way to describe the thixotropy. This method regards the structural recovery at a specific time after an applied shear stress.[4] After an initial oscillation (0.02 % at a constant angular frequency of 10 rad/s), a rotational shear rate of 1000 1/s is applied, and finally the recovery of the storage modulus (G’) within 480 s is observed under oscillation.
- For the statistical assessment of equivalence, a formula presented by Ocaña J. et al. was used for calculation. By applying the formula to the log-transformed data, values close to 1 were obtained for the two ends of the 90% confidence interval. When the confidence interval was within 0.9 and 1.1, the parameter are considered equivalent.[2,3]

Results

5 out of 10 parameters of branded (red shaded bars) and generic (green shaded bars) cream pass the equivalence criteria the EMA draft guideline demands.

Table 1. Confidence intervals of the observed rheological parameters.

Rheological parameter	Yield strain γ_L	Yield stress τ_y	Flow stress τ_f	Complex modulus |G*|	Flow transition index τ_f/τ_y	Phase angle δ	Zero shear viscosity η_0	Viscosity at 100 1/s η_{100}	Rel. thixotropy area S_R	Recovery after 480 s	***+/- 10 % range***
Confidence interval	0.923	0.778	0.810	0.826	0.923	0.974	0.821	0.981	1.100	0.950	***> 0.9***
	1.080	0.945	0.920	0.905	1.098	1.015	0.955	1.032	1.431	1.077	***< 1.1***
Passes the euqivalence criteria?	Yes	No	No	No	Yes	Yes	No	Yes	No	Yes	-

Amplitude sweep

Six oscillatory parameters were evaluated: yield strain, yield stress, flow stress, phase angle, flow transition index and complex modulus. Yield strain, phase angle and flow transition index pass the equivalence criteria.

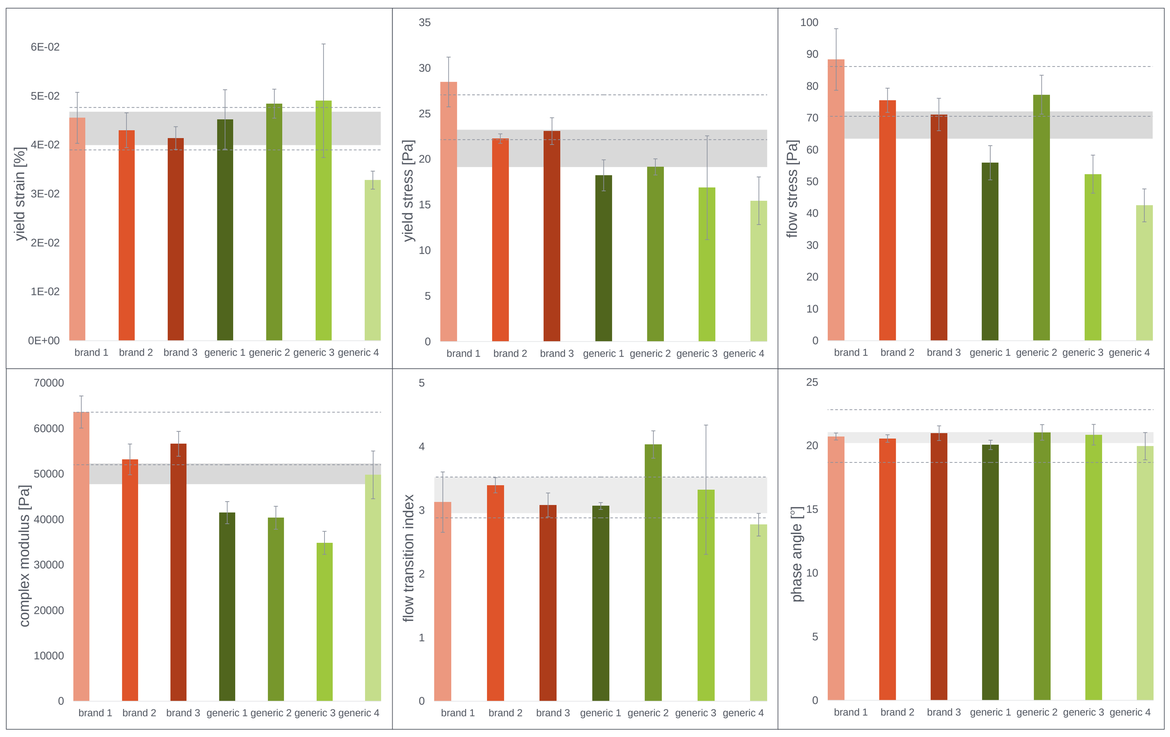

Figure 1. Oscillatory parameters
The dashed lines illustrate the +/- 10 % limits and the gray bar represents the 90% confidence interval.

Shear viscosity

As “viscosities at specific shear rates” we decided to compare the zero-shear viscosity, measured at the plateau of shear rates 0.00001 - 0.0001 1/s, and the viscosity at 100 1/s. Since at high shear rates structural formations are usually broken, the consideration was that the viscosity at 100 1/s must be more stable within the different batches. Conversely zero-shear viscosity is dependent on structural formations, which can vary even between component batches.

Just as predicted, the viscosity at 100 1/s is more stable and passes the equivalence criteria, whereby the zero-shear viscosity fails.

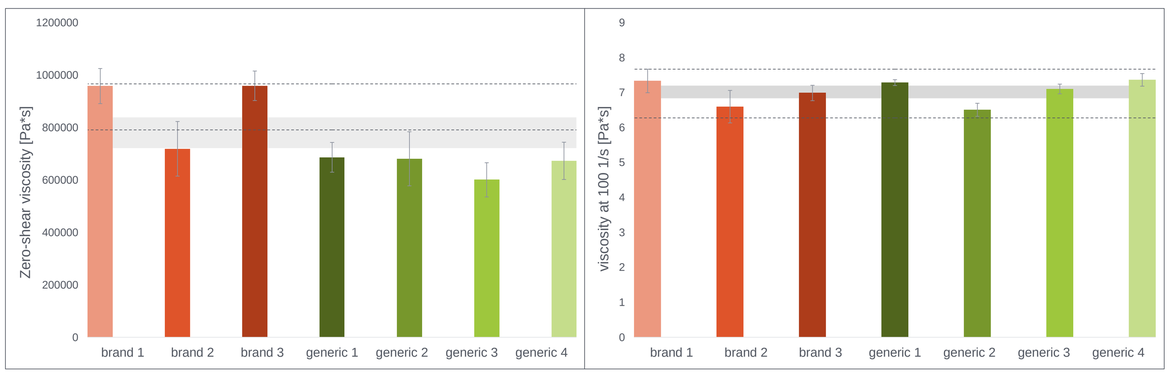

Figure 2. Viscosities at different shear rates
The dashed lines illustrate the +/- 10 % limits and the gray bar represents the 90% confidence interval.

Thixotropy

The relative thixotropic area fails the equivalence range. Recovery after 480 s instead meets the criteria well. Since the modern definition of thixotropy puts structural recovery in the foreground, the ORO-testing seems to be more appropriate to represent it.[4]

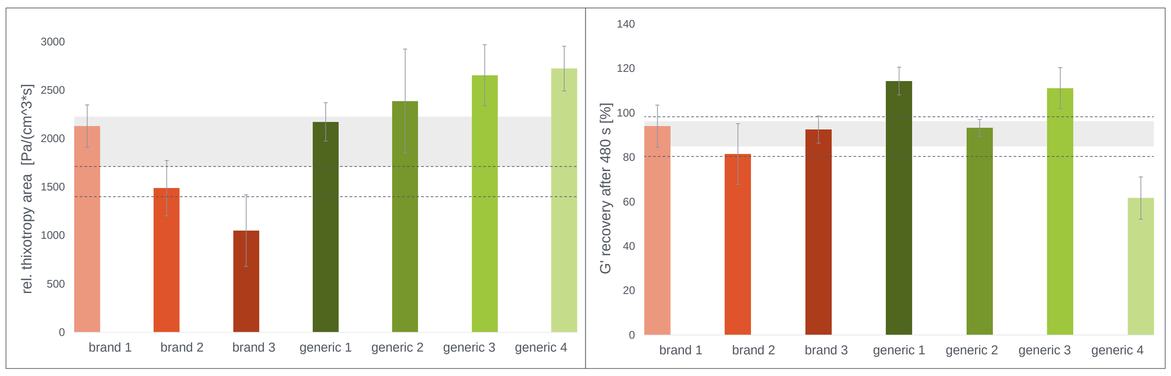

Figure 3. Hysteresis vs. recovery
The dashed lines illustrate the +/- 10 % limits and the gray bar represents the 90% confidence interval.

Conclusions

- The equivalence criteria of the EMA draft guideline appear to be strict for rheological parameters that highly depend on formations of inner structures which may be susceptible to batch-to-batch variability of excipients and manufacturing processes. Such differences can add up and cause irregularities, especially in parameters as yield/flow strain and zero-shear viscosity.
- A wider range of +/- 20 % or the frequently used interval of 80 – 125 % includes almost all parameters tested for equivalence in the present study.
- For thixotropy equivalence, the structural recovery (G’ recovery) is more stable and fits the modern definition of thixotropy as opposed to traditional relative thixotropy area. It should therefore be possible to prefer this parameter to the relative thixotropic area in equivalence study.
- As the EMA draft guidance puts emphasis on the concept of critical quality attributes (CQAs) in formulation development and control, a focus on CQA-related rheological attributes may also be worthwhile to discussing authorities. In general, amended requirements for rheological equivalence testing should be considered for a final version of the draft guideline.

References

[1] EMA Draft guideline on quality and equivalence of topical products (EMA/CHMP/QWP/708282/2018)
[3] W. Allen Wallis, Harry V. Roberts. Methoden der Statistik. Ein neuer Weg zu ihrem Verständnis. Rororo Taschenbuch Ausgabe August 1969.
[2] Ocaña J, Monleón-Getino T, Merino V, Peris D, Soler L. Statistical Methods for Quality Equivalence of Topical Products. 0.5 mg/g Betamethasone Ointment as a Case-Study. Pharmaceutics. 2020; 12(4):318.
[4] Thomas G. Mezger. Applied Rheology. Anton Paar GmbH 2014