Draft guideline on quality and equivalence of topical products – case study

Industry perspective

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Company introduction

WARSZAWA

Main competencies: ophthalmic and parenteral forms
New competencies: highly advanced sterile injectables

SIERADZ

Main competencies: soft gelatine capsules, non-sterile liquids
New competencies: DPI respiratory

STAROGARD GDAŃSKI and GDAŃSK

Main competences: solids dosage forms, parenteral forms SVP/LVP

- 3 R&D centers
- 6 production facilities in Poland

Product background

- Dimetindene maleate 1 mg/g gel
- ATC: D04AA13 – Antihistamines for topical use
- Gel for topical application (colorless, non-scented)
- Indications: Relief from itching in dermatoses, urticaria, bites of insects and marine animals, sunburn and superficial burns for adults and children from 1 month
- Reference medicinal product: Fenistil 1 mg/g gel
- Drug product developer/manufacturer: Medana Pharma SA
- Development completed in 2014
- Registered in 11 EU Member States
- Art. 10(3) – Hybrid application

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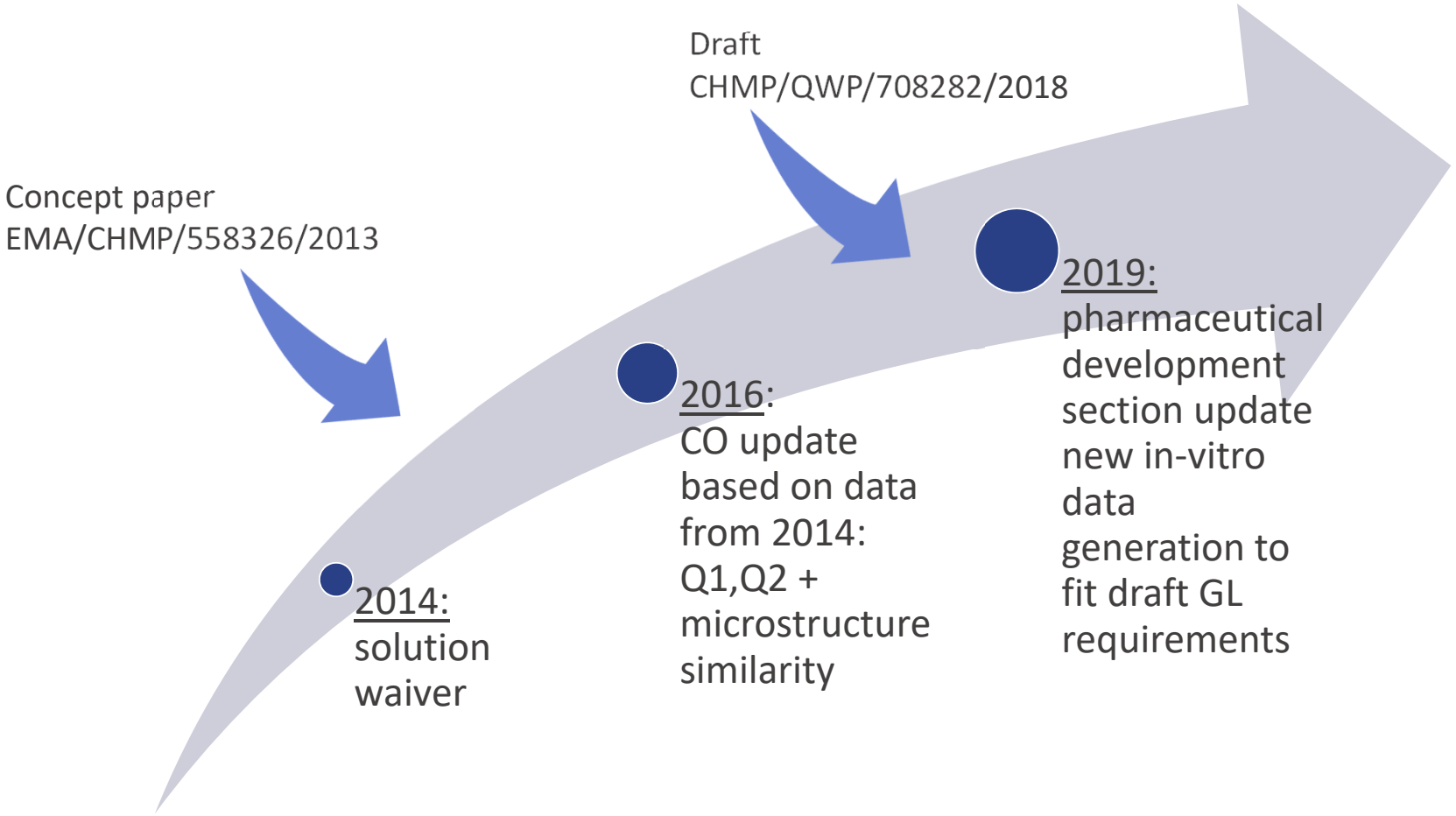
Same product, new data!



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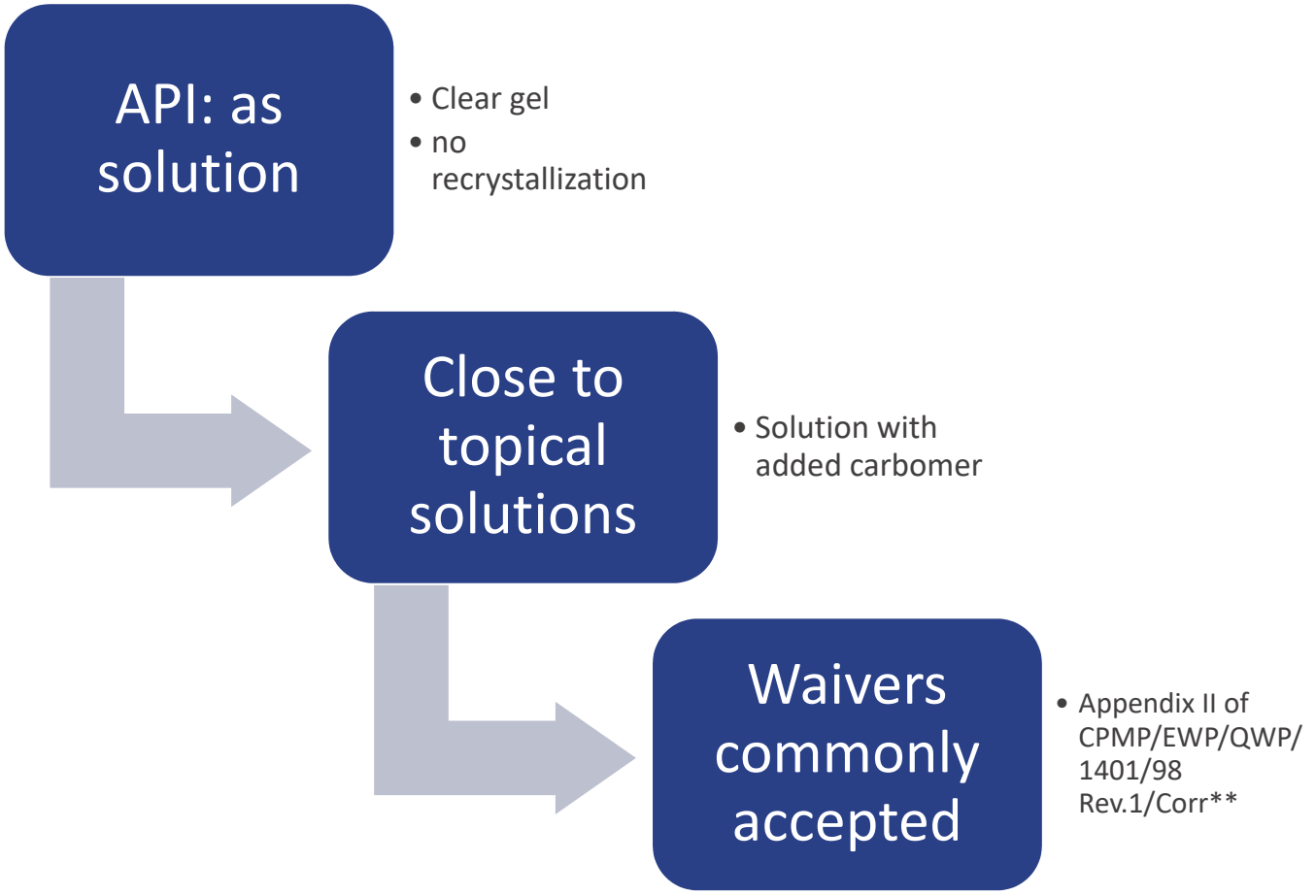
Initial justification background



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Composition

Composition of Test formulation is identical to EU Brand

Component name:	REFERENCE PRODUCT Fenistil 1 mg/g, gel	TEST PRODUCT Dimetindene maleate 1 mg/g, gel
	[mg/g]	[mg/g]
Dimetindene maleate	1.00	1.00
Carbomer (type 974 P)	9.00	9.00
Disodium edetate	0.50	0.50
Propylene glycol	150.00	150.00
Benzalkonium chloride	0.050	0.050
Sodium hydroxide*	3.00	3.00
Water, purified	up to 1 g	up to1 g

- as sodium hydroxide solution 30%

Differences in composition of the Reference product DE vs. rest of EU:

FENISTIL 1mg/g gel (ES)	FENISTIL 1mg/g gel (DE)
Dimetindene maleate	Dimetindene maleate
Carbomer (type 974 P)	Carbomer 980
Disodium edetate	--
Sodium hydroxide	Sodium hydroxide
Propylene glycol	Propylene glycol
Benzalkonium chloride	Methyl-4-hydroxybenzoate (E 218)(parabene)
Water, purified	Water, purified

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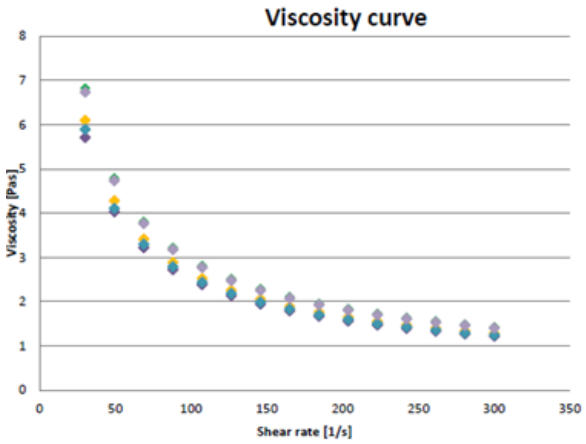
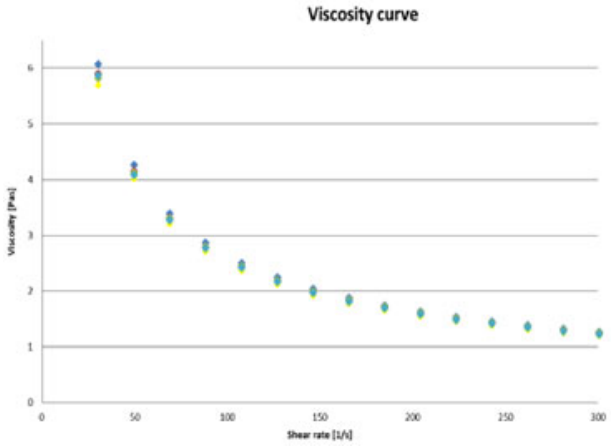
Similar physical and chemical parameters

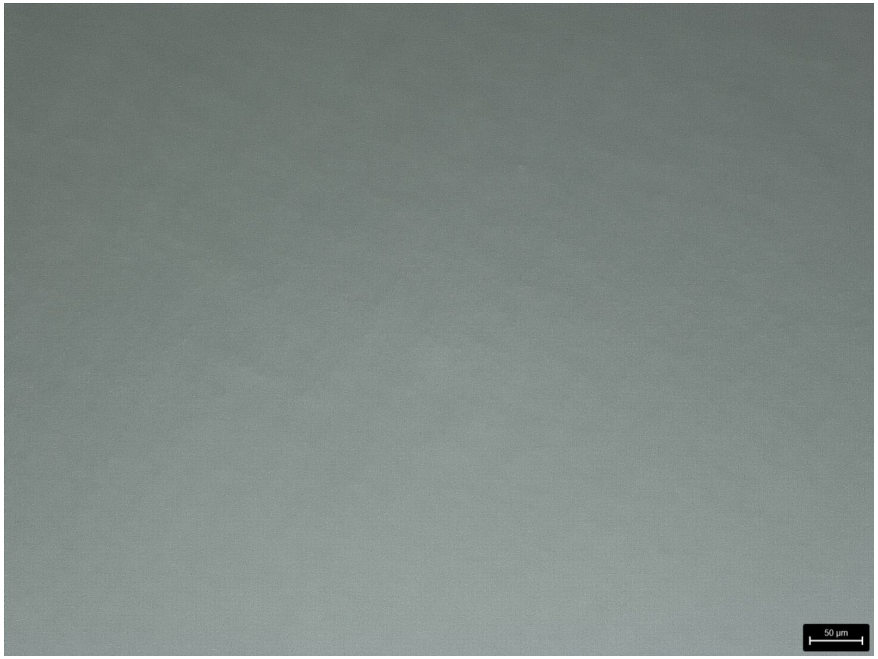
Refenece/Test product (batch)	pH	Viscosity (mPas)	Penetration [mm]
Fenistil® (Batch A)	7.2	4829	-
Fenistil® (Batch B)	-	4766	-
Fenistil® (Batch C)	-	-	40.18
Fenistil® (Batch D)	7.1	4820	38.37
Fenistil® (Batch E)	7.1	4940	38.52
Test lab batches (Batch L1)	7.2	-	-
Test lab batches (Batch L2)	7.2	-	-
Test R&D batches (Batch R1)	7.1	4776	40.03
Test R&D batches (Batch R2)	7.1	4823	40.53



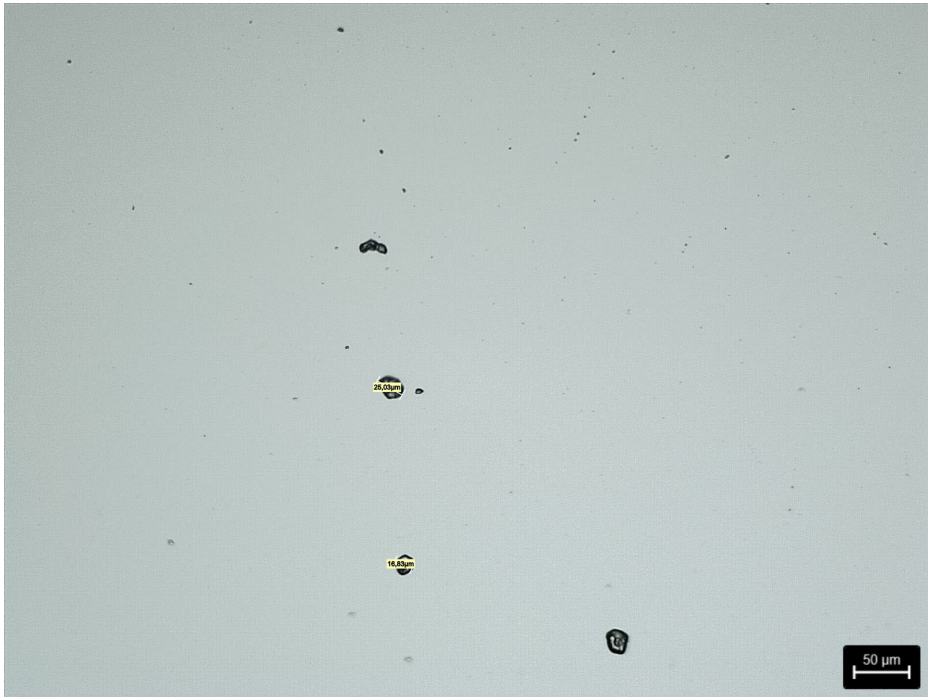


Optical microscopy

Microstructure?



Only artefacts of sample preparation



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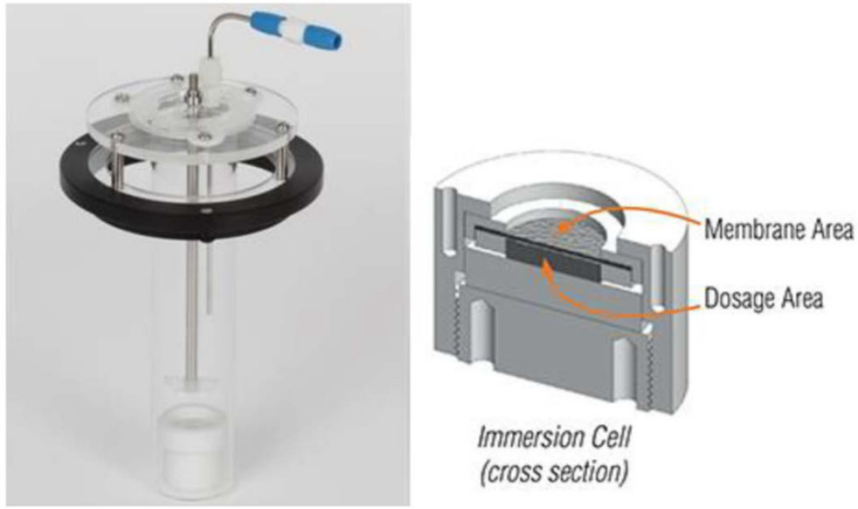
In-vitro release: surrogate of in-vivo skin permeability

Enchancer cell with artificial membrane



- Physical properties and microstructure similarity:
  - Appearance – both Test & Reference are clear, colorless, homogeneous gels
  - Same pH (10% of aqueous gel solution)
  - Similar viscosity curve
  - API solubilised in gel formulation (molecularly dispersed)
- Product performance similarity by in vitro test:
  - No standard method recommended by Ph Eur
  - Enhancer cell – selected method
  - Well known method used for semi-solid formulations for nearly 20 years now
  - Performance test for semi-solid dosage forms in the First Supplement to USP 36-NF 31 (“Immersion Cell Apparatus, Model A”)
  - Contact of the dissolution media with dosage form only via semi-permeable membrane (similar results for similarly permeable drugs)

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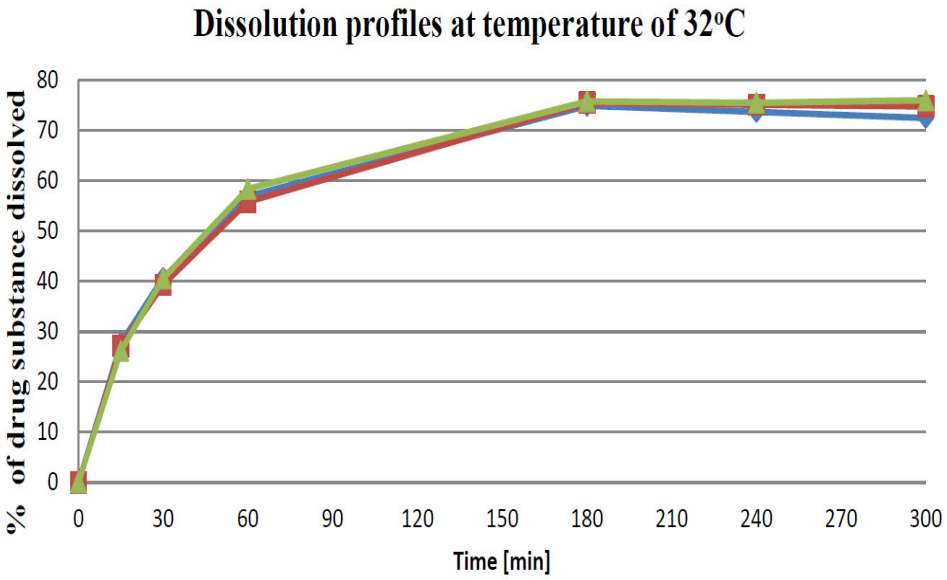
2014 development includes enhancer cell in-vitro release studies results

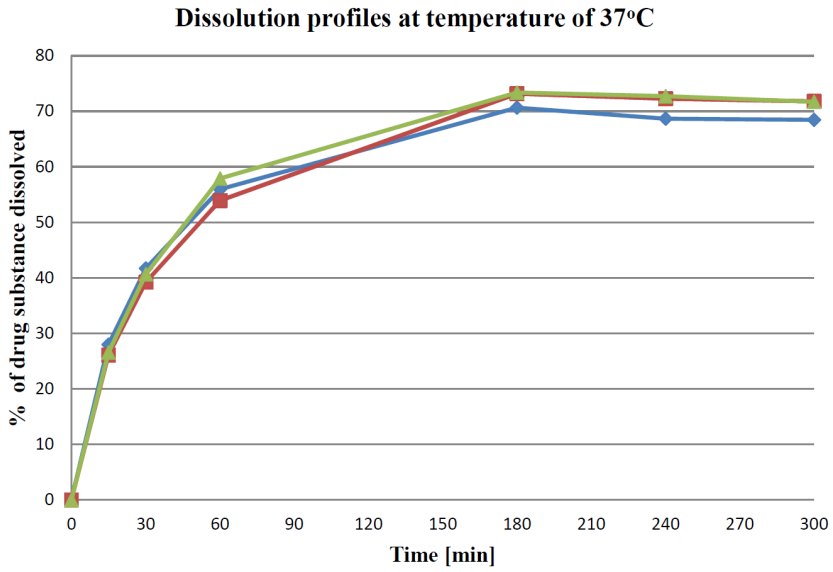
Assessed as dissolution at 32˚C

- Good old f2 comparison:
  - T1 vs. R = 88.6%
  - T2 vs. R = 83.5%
  - Similar! Or even identical!



Assessed as dissolution at 37˚C

- Good old f2 comparison:
  - T1 vs. R = 77.5%
  - T2 vs. R = 78.8%
  - Similar!



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Justification of clinical study waiver

- In line with the provisions of the guidelines:
  - CPMP/EWP/239/95 final,
  - CPMP/EWP/QWP/1401/98Rev.1/Corr**
  - FDA SUPAC GL for semisolids
  - and Concept Paper EMA/CHMP/QWP/ 558185/2014
    - (draft was not published)
- and based on demonstrated :
  - identical qualitative and quantitative composition,
  - essential microstructure similarity
  - similar physical properties,
  - similar product performance
  - identical way of administration between Test and Reference products
- a waiver of further comparative animal or clinical studies is considered justified with no critical uncertainty on therapeutic equivalence

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Major Objections (2019)

1. The microstructure has to be investigated by means of the necessary physicochemical parameters. See for example the list of parameters included in the draft guideline draft guideline on quality and equivalence of topical products.
2. The comparison of the physicochemical parameters that define the equivalence in the microstructure of the product should be conducted with appropriate statistical methods, i.e. the confidence interval of the test / reference ratio after log-transformation of the data should be within the predefined acceptance range.

- Appearance
- Microstructure
- pH
- Viscosity curve vs shear rate
- Penetrability
- Density
- Product behavior classification
- Thixotropic relative area
- Storage modulus
- Loss modulus
- Loss tangent
- Yield stress
- Viscosity at a specified shear rate
- Other parameters?

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Major Objections (2019)

3. A new IVRT should be performed in at least three production batches of test, reference and negative control products with a minimum of 12 samples per batch to demonstrate equivalence. The Applicant should take into account the requirements defined in the draft guideline on quality and equivalence of topical products, because although it is only a draft, it includes the present state of the art. At least 6 time points should be obtained in the linear portion of the drug release profile when represented versus the square root of the time, including the first sample immediately after drug diffusion has reached a steady state. Therefore, the selection of the membrane and the receptor medium should be justified because the present data does not seem to comply with that requirement.

    1. In addition, the drug release rate (R; the slope of the cumulative amount of active substance released versus the square root of time), the cumulative amount (A) of active substance released (usually expressed in mass units per surface area, at the last sampling time of the linear portion) and lag time (if present) should be calculated and submitted.
    2. The 90%CI for (R) and (A) parameters should be calculated and contained within the acceptance interval of 90 – 111%. In addition, a 90% confidence interval for the ratio of the median in vitro release rate (in the population) for the test product over the median in vitro release rate (in the population) for the reference product should be computed, expressed in percentage terms within the acceptance interval of 75%-133.33% as defined in the US-FDA SUPAC guideline for semisolids.

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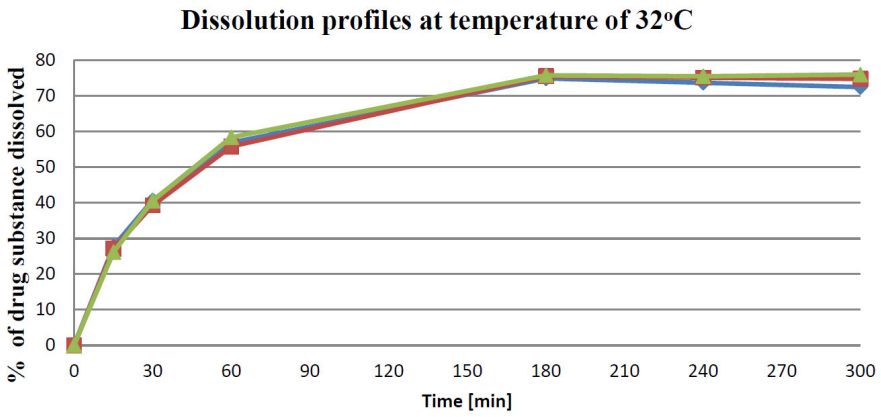
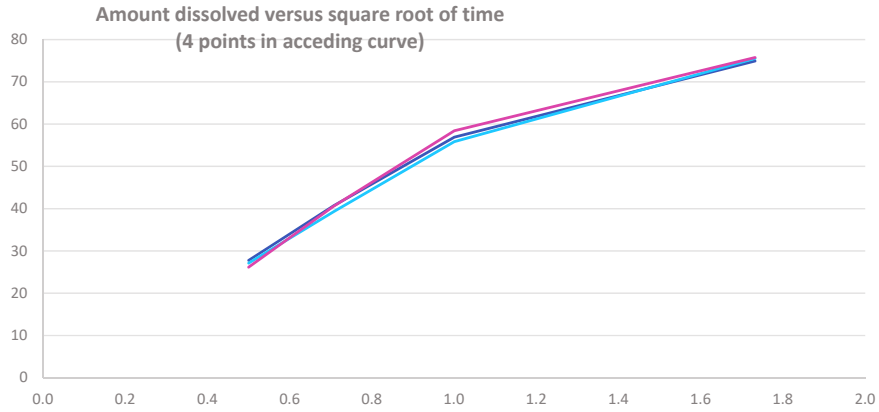
What if we assess available data via methods suggested? RTDG!

Assessed as dissolution

- F2 > 80%!





Assessed via Higuchi model of release

- Good old f2 comparison:
  - T1 vs. R = 88.6%
  - T2 vs. R = 83.5%
  - Identical!? Happy to see such results for biowaiver of tablets
- Slope analysis:
  - FDA SUPAC – pass!
    - 75-133% acceptance range for slopes and amount released
  - EMA draft GL 90% CI for rate
  - Slope for means:
    - R: 37.23; T1: 36.67; T2: 39.71
    - Fails based on individual slopes analysis for both Tests vs. R: exceeding upper acceptance limit of 90-111% limits

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R code example

```
alpha            <- 0.05
anovadata        <- lm(log(Slope) ~ DRUG, data=data, na.action=na.exclude)
Nr               <- sum(!is.na(data[data$DRUG=="Reference","Slope"]))
Nt               <- sum(!is.na(data[data$DRUG=="Test1","Slope"]))
GMean_R          <- exp(mean(log(data[data$DRUG=="Reference", "Slope"]), na.rm=TRUE))
GMean_T1         <- exp(mean(log(data[data$DRUG=="Test1","Slope"]), na.rm=TRUE))
PE               <- coef(anovadata)["DRUGTest1"]
CI               <- confint(anovadata, c("DRUGTest1"), level=1-2*alpha)
Point_Estimate   <- round(100*exp(PE), digits = 2)
Lower_CI         <- round(100*exp(CI[1]), digits = 2)
Upper_CI         <- round(100*exp(CI[2]), digits = 2)
data.frame(Nr, GMean_R, Nt, GMean_T1, Point_Estimate, Lower_CI, Upper_CI, CV, row.names="T1/R:",
stringsAsFactors = FALSE)
```

```
##        Nr  GMean_R Nt GMean_T1 Point_Estimate Lower_CI Upper_CI
## T1/R: 12 36.68743 12 37.92399         103.37    93.86   113.84
## T2/R: 12 36.68743 12 37.93643         103.40    93.90   113.88
```

List of additional studies

- New in-vitro release method developed and validated
- 12 units tested for
  - 3 batches of Reference
  - 3 batches of Test
  - Negative control
  - 50% assay & 150% assay
- Amount released and drug release rate compared using BE methodology and FDA SUPAC non-parametric method
  - T1 vs. R1
  - T1 vs. R2
  - T1 vs. R3
  - T2 vs. R1
  - T2 vs. R2
  - T2 vs. R3
  - T3 vs. R1
  - T3 vs. R2
  - T3 vs. R3
  - All T vs. negative control
  - All T vs. 50% assay batch
  - All T vs. 150% assay batch

Decrease of power?!

- Simple example pooled power decreases with multiple comparison if even 1 failure means failure of the program
  - Standard power for bioequivalence is 80%
  - Frequently used power 90%
  - We had 9 comparisons between different batches of Test and Reference
  - 0.9 x 0.9 x 0.9 x 0.9 x 0.9 x 0.9 x 0.9 x 0.9 x 0.9
  - = 0.3874 (or 38.74%)
  - 0.99 x 0.99 x 0.99 x 0.99 x 0.99 x 0.99 x 0.99 x 0.99 x 0.99
  - =0.9135 (or 91.35%)

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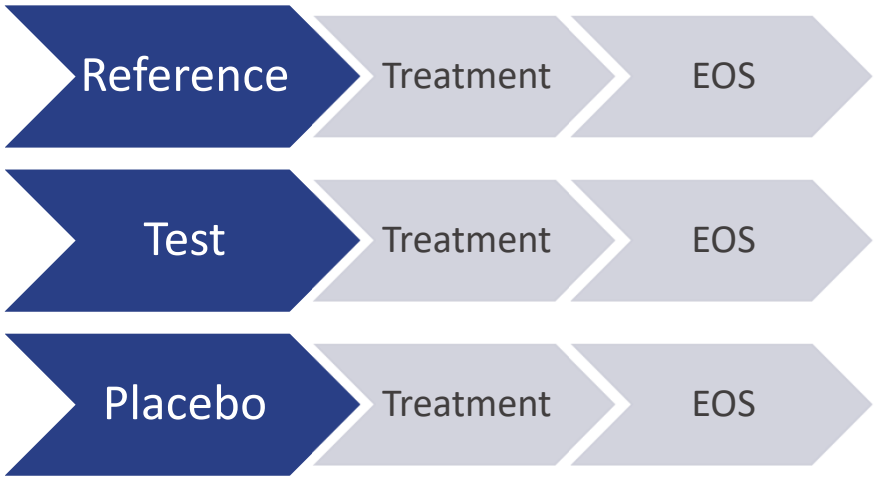
Alternatives?: phase III study!

Phase III, randomized, non-inferiority, double-blinded?

placebo-controlled



Challenges

- Assay sensitivity (dry eye products)
  - Clinical assessment is based on arbitrary scale system
  - Significant placebo or vehicle effect
  - What if superiority over placebo demonstrated for Reference was very slim?
- More complicated design of the study compared to pivotal study(-ies) of Reference product
- Narrow non-inferiority margin
  - How can we set a non-inferiority margin which should be clinically significant and still above placebo or vehicle effect?
- Huge sample size
- Practical and Ethical issues?
- Scientific advice (EMA advice for each case?)
  - Follow-up advices
  - Time of development increases

- Thank you very much for your attention!
- Let’s discuss!