

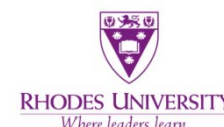
In-vivo Open Flow Microperfusion for evaluating topical bioavailability



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FDA project – bioequivalence

A big thank you!



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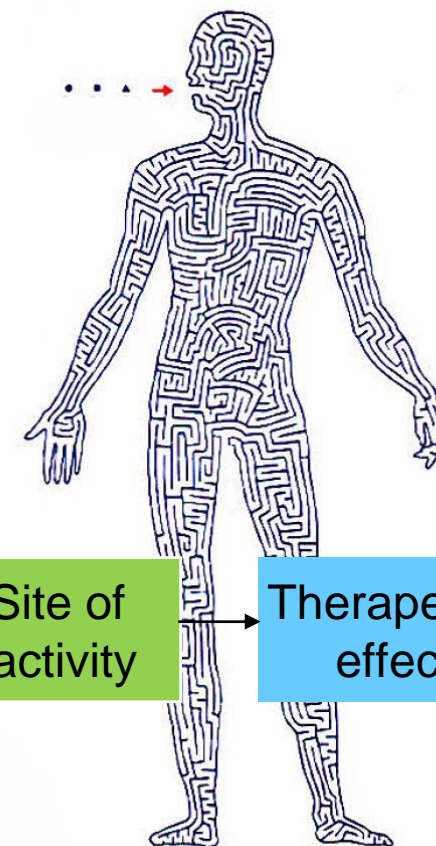
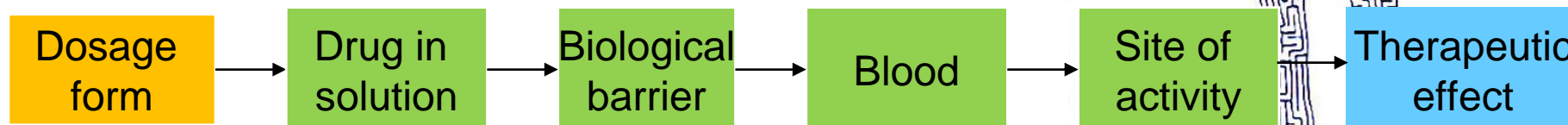
What is bioavailability?

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Bioavailability – part 1 (FDA)*

The rate and extent to which the active ingredient is absorbed from a drug product and becomes available at the site of action.

oral dosage

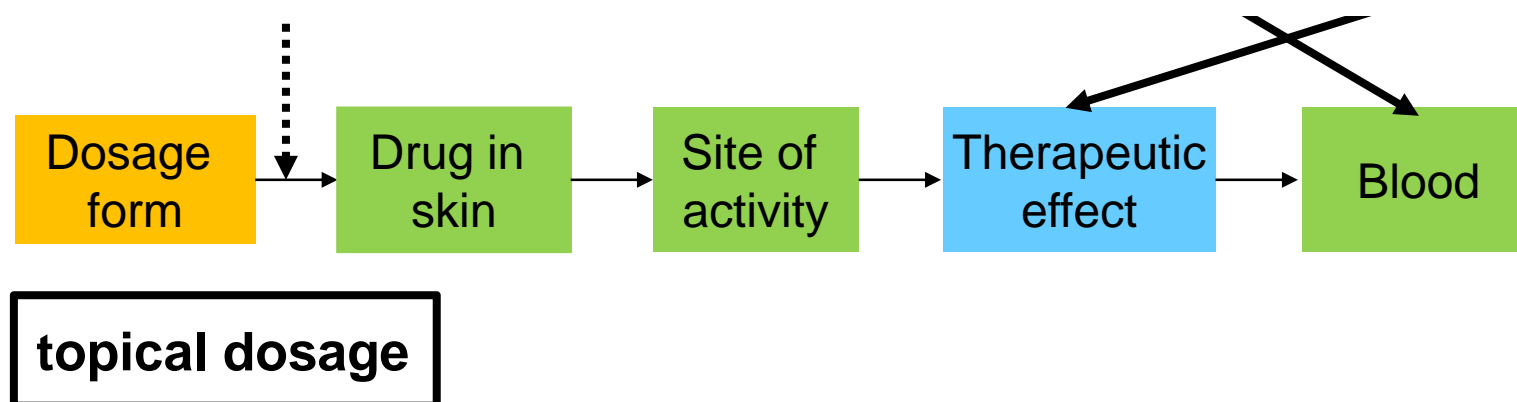


Bioavailability of topical drugs

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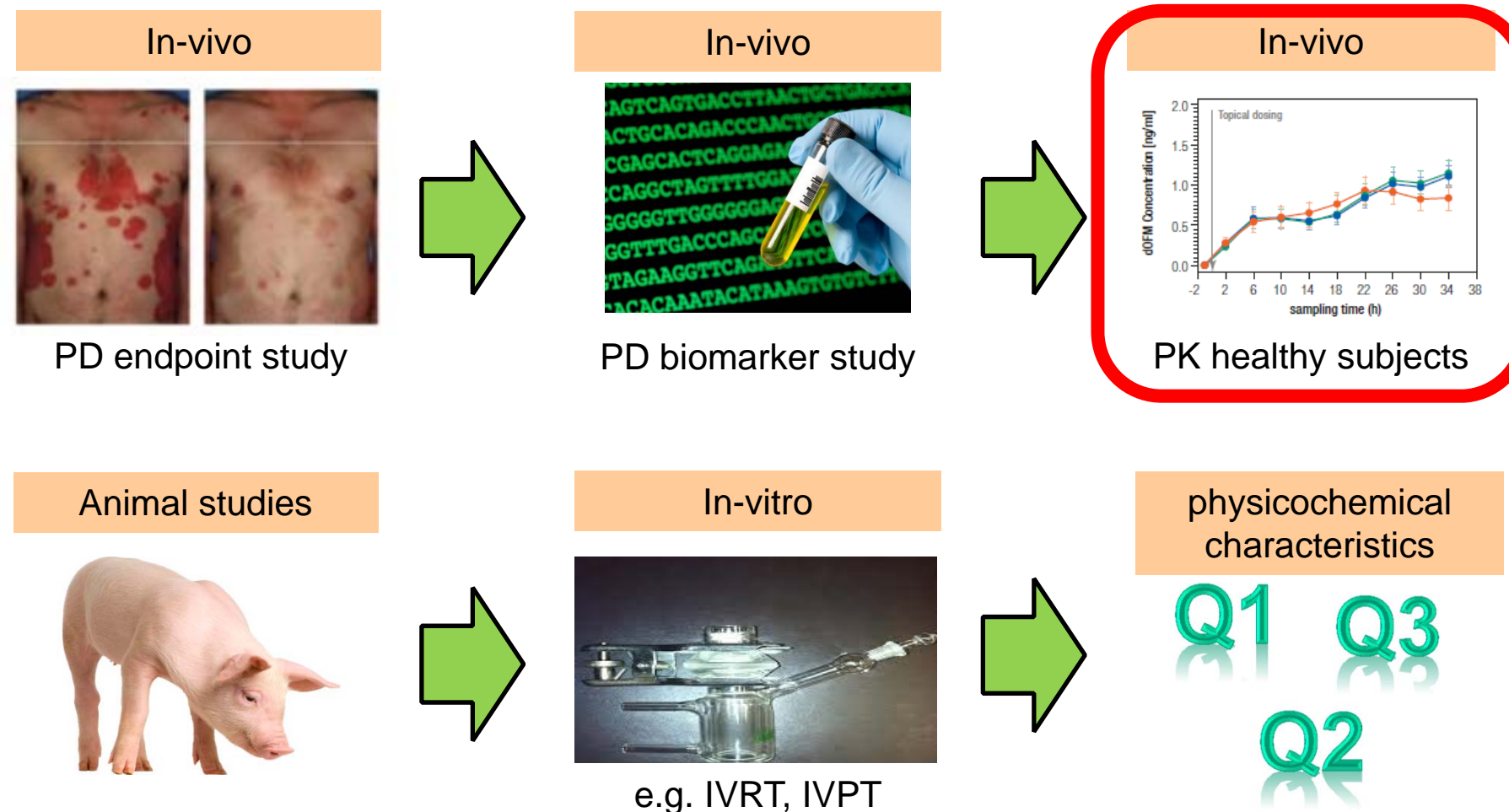
Bioavailability – part 2 (FDA)*

For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient becomes available at the site of action.



Testing of dermal generics

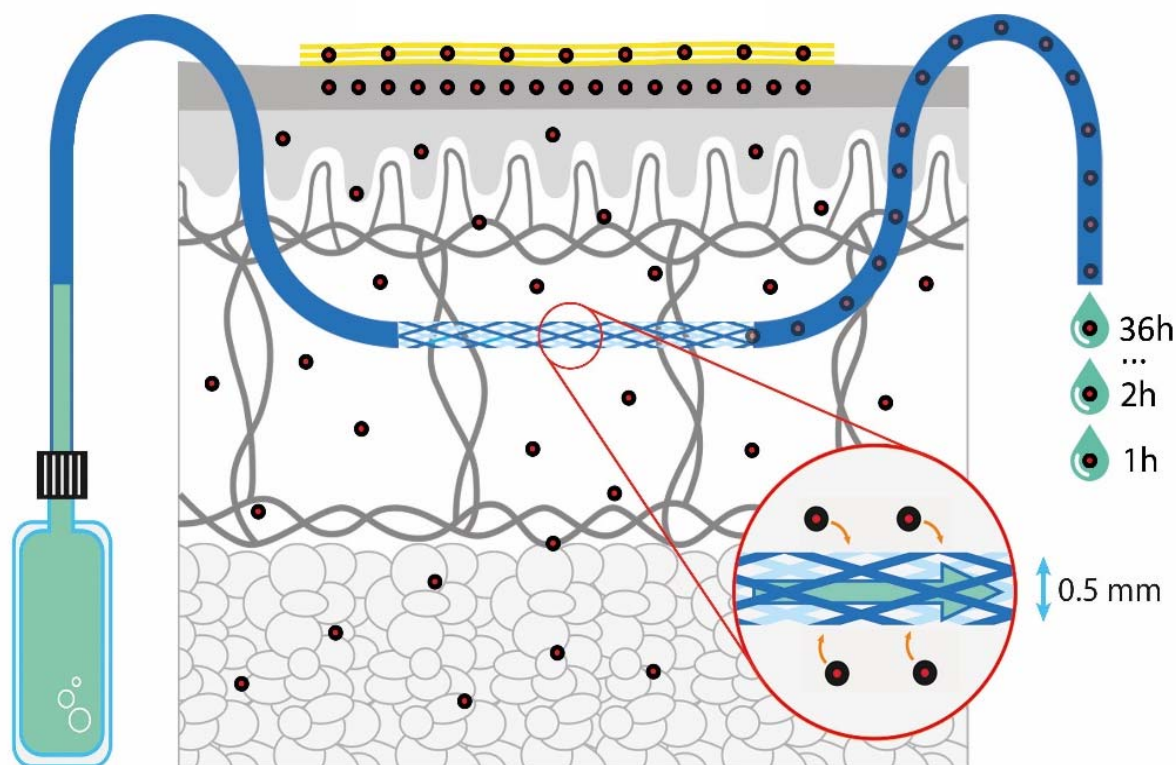
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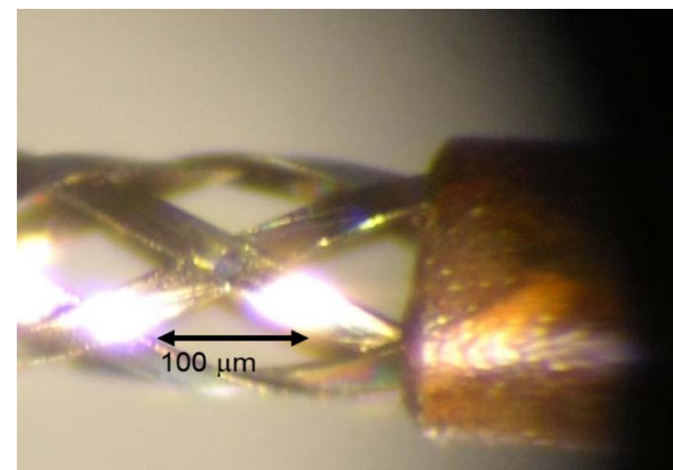
Sampling in the dermis

dermal Open Flow Microperfusion dOFM

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CE certified for clinical use



dOFM fact sheet

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- dOFM samples represent **diluted but unfiltered** interstitial fluid
 - Including **lipophilic** substances

Bodenlenz (under review) (CP-17 logP 3.5)
Holmgaard et al. 2011 (Fentanyl logP 4.5)
 - Including **high molecular weight** substances (up to cells)

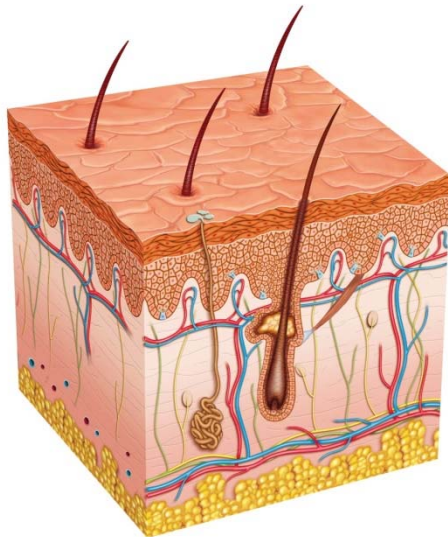
Dragatin et al. 2016 (Quantification of AB in skin)
- In-vivo sampling up to 48 hours
- Same dOFM setup in clinical, preclinical and ex-vivo studies
- JR Health performs highly standardized clinical studies

Standardization makes the difference

Screening of the sampling site

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- | | | |
|----------------------------------|---|--|
| • Hairiness | → | not controlled |
| • Hair shaving | → | subject is shaved 5 days before dOFM visit |
| • Sweat ducts | → | not controlled |
| • Skin permeation behaviour | → | monitored by TEWL and impedance |
| • Skin products use | → | not allowed 5 days before dOFM visit |
| • Skin condition (e.g. Solarium) | → | visual check at screening visit |

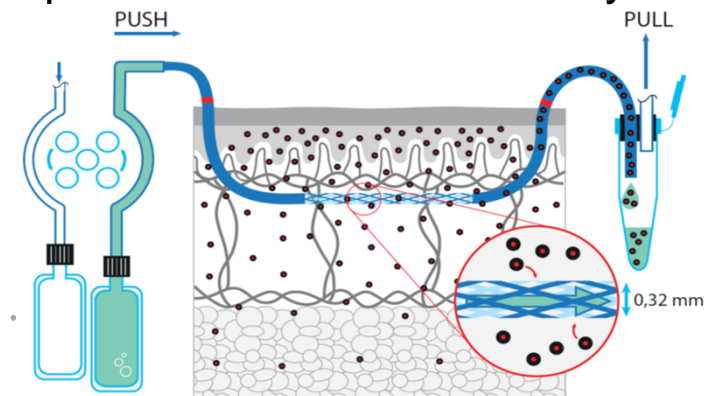


Controlled and monitored factors for sampling

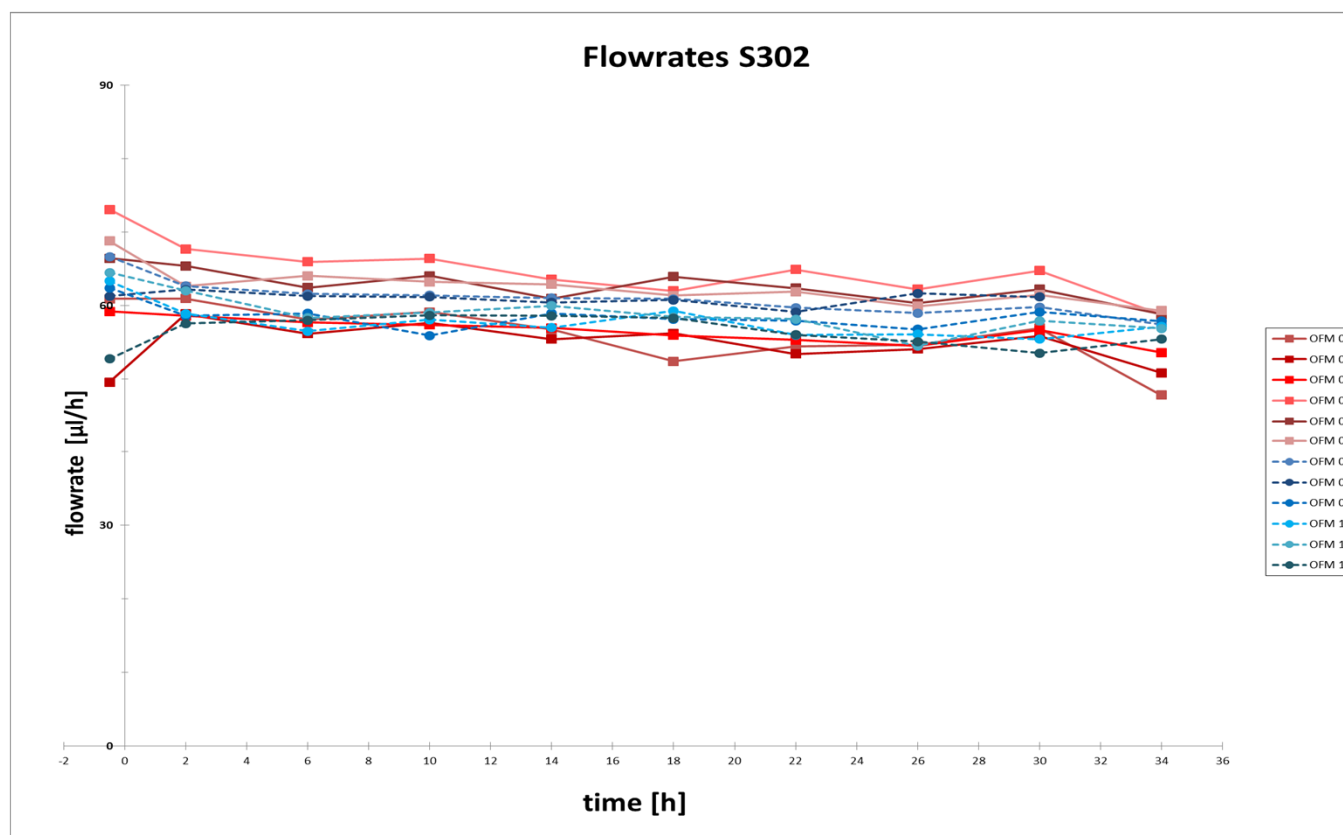
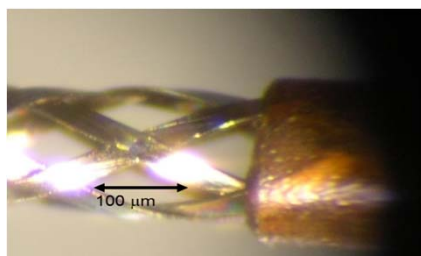
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Treated with cooling
Controlled by application template
Controlled by standardization
Monitored by ultrasound
Monitored by sample weight
Monitored by glucose marker
Negligible
No systemic exposure
Controlled $22 \pm 1^\circ\text{C}$ & 40-60% RH

← Trauma formation
← Application site
← Dosage application
← Probe depth
← Flow rate
← Local blood flow
← Lateral diffusion
← Systemic diffusion
← Room temperature & relative humidity

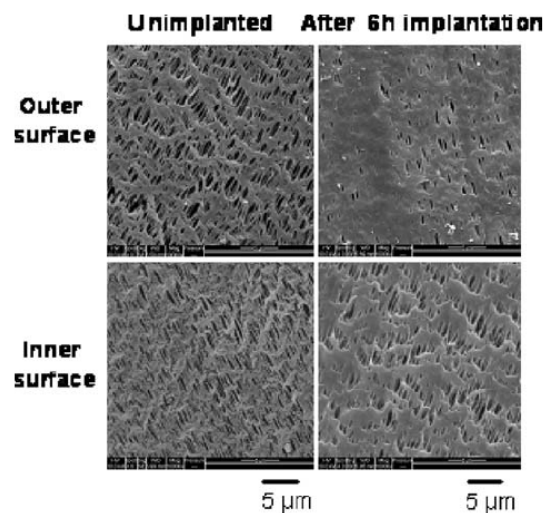


Influence of flow rate

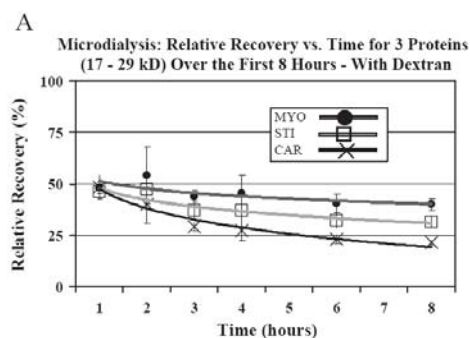


Influence of recovery

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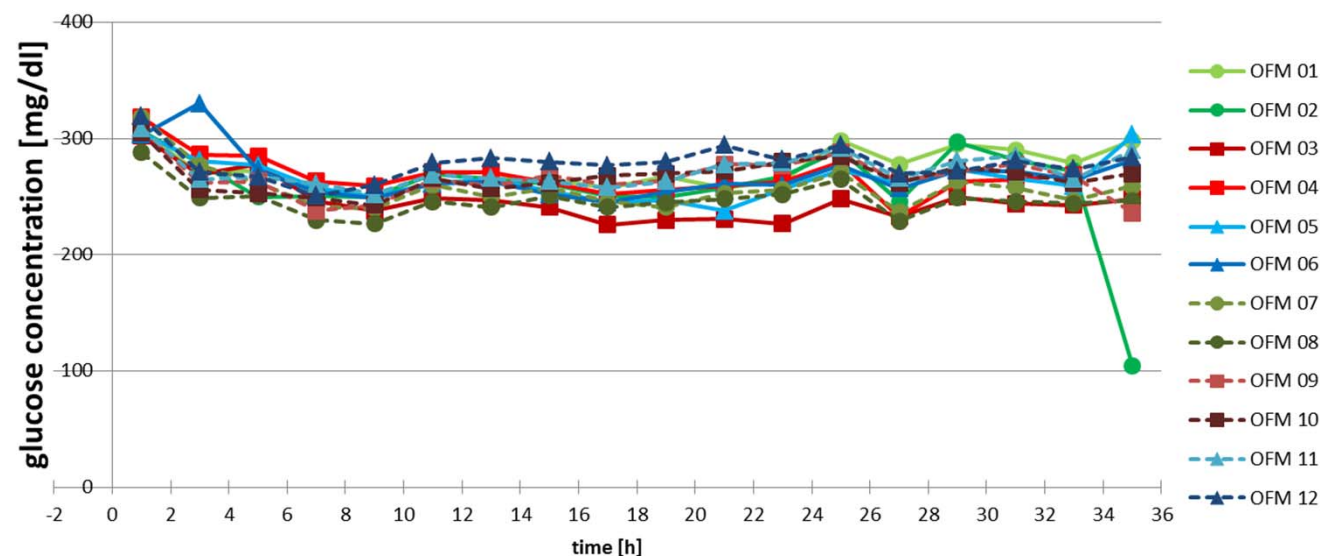


Stenken et al. 2010



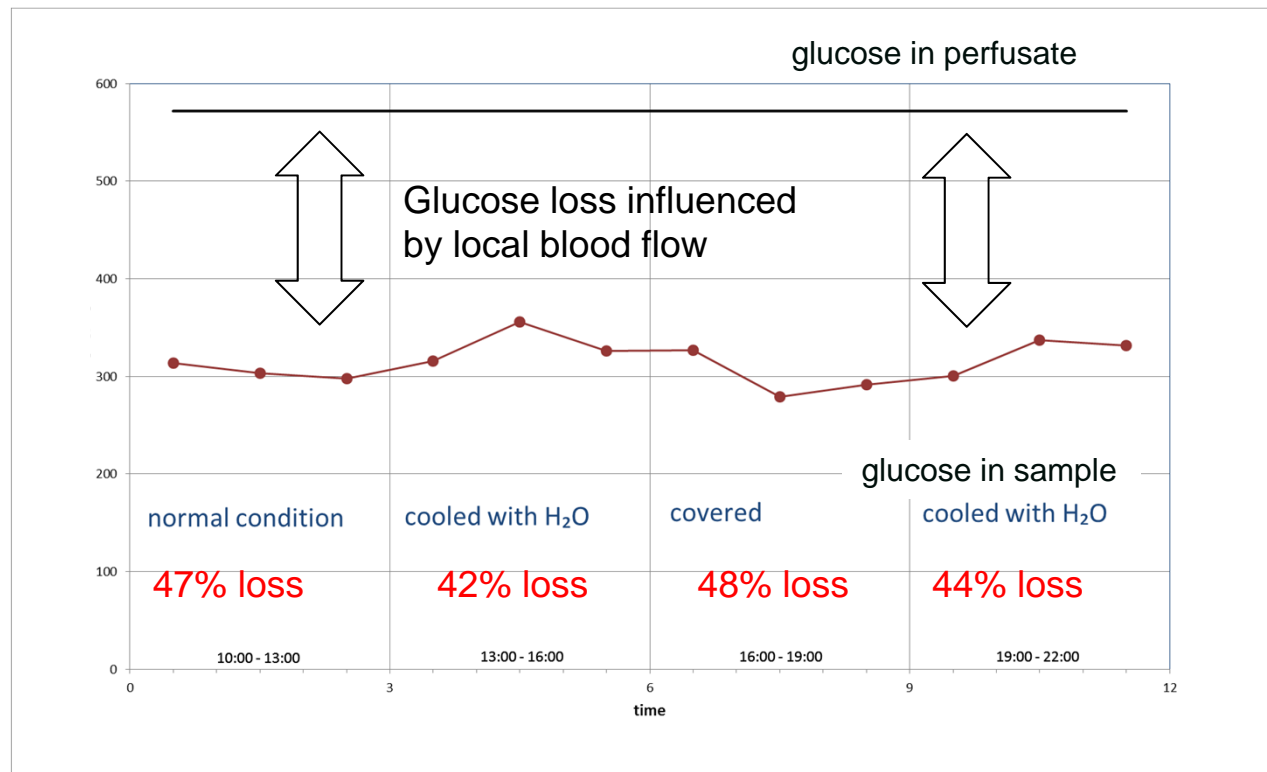
Rosenbloom et al. 2006

single probes glucose S206



Local blood flow

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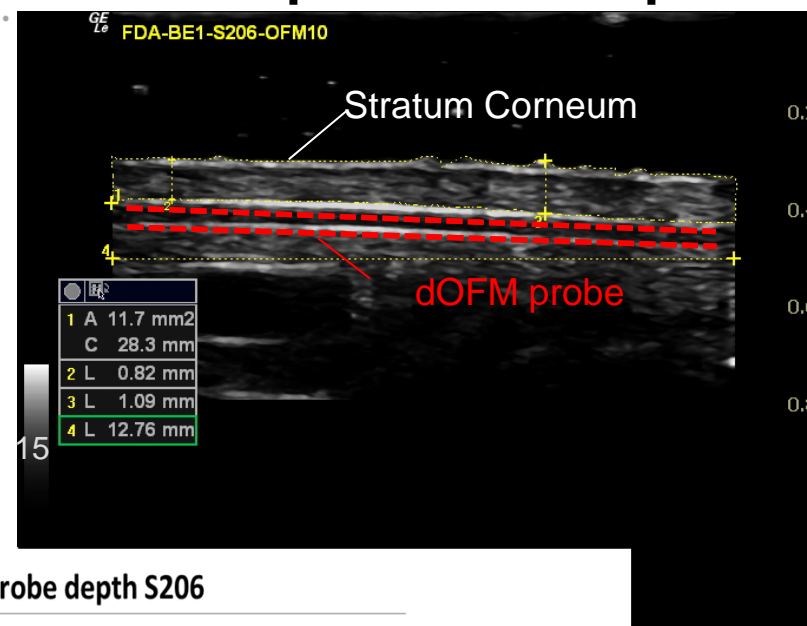
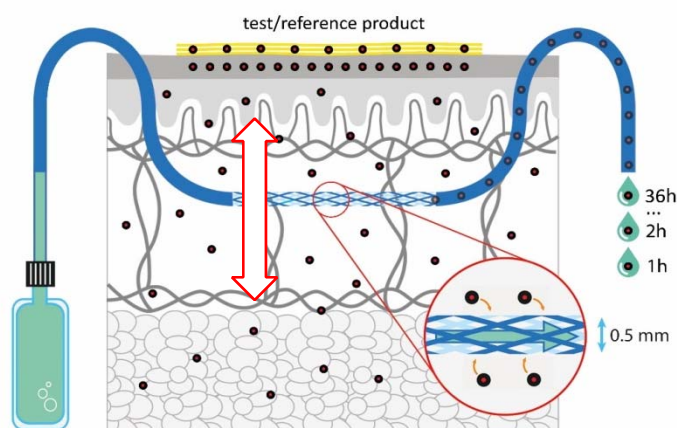
Glucose was used as an internal standard in OFM perfusate

Cooling was used to

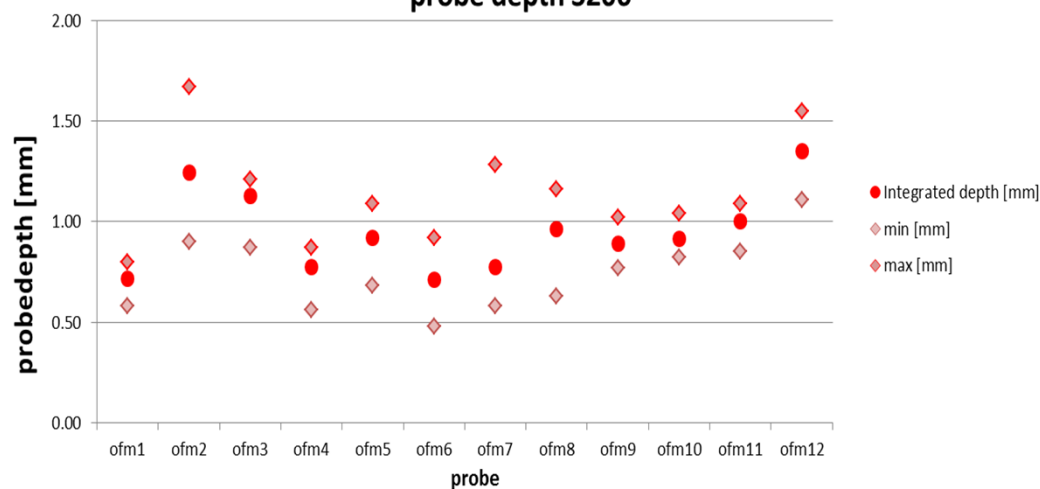
- reduce local blood flow
- lower glucose uptake into the blood

Influence of probe depth

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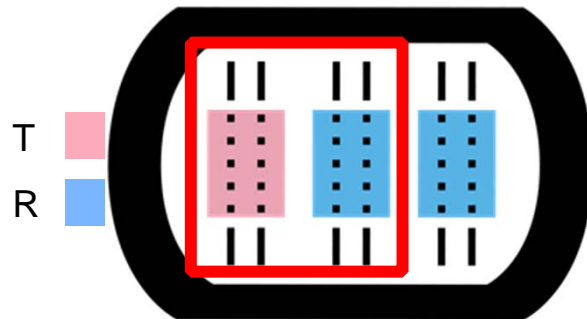
probe depth S206



Bioequivalence of topical drugs in a clinical study

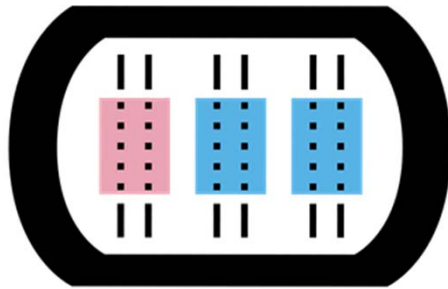
General study design

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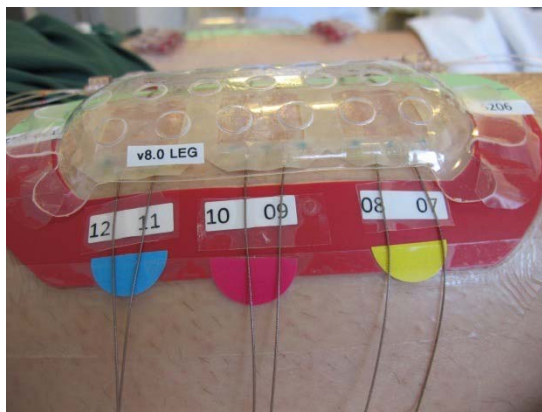
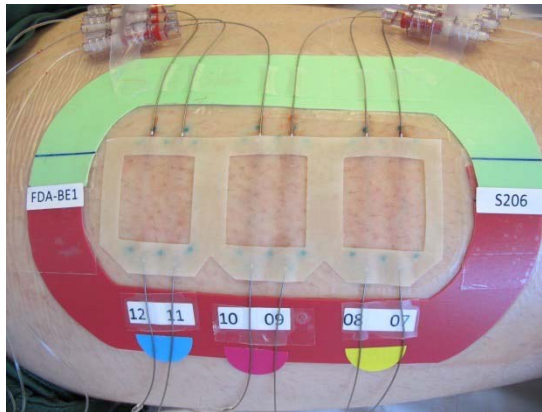
- Not-bioequivalence (R vs. T)
- Bioequivalence (R vs. R)
- API: Acyclovir
- Study drugs
 - R: Zovirax cream 5% US
 - T: Aciclovir cream 5% 1A Pharma





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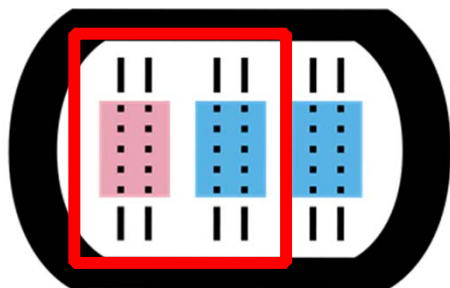
Clinical study design



- 20 healthy human subjects
 - 7 women, 13 men, age: 28 ± 5
- Application location
 - Thigh
- Analytical parameter
 - Acyclovir conc. in OFM sample

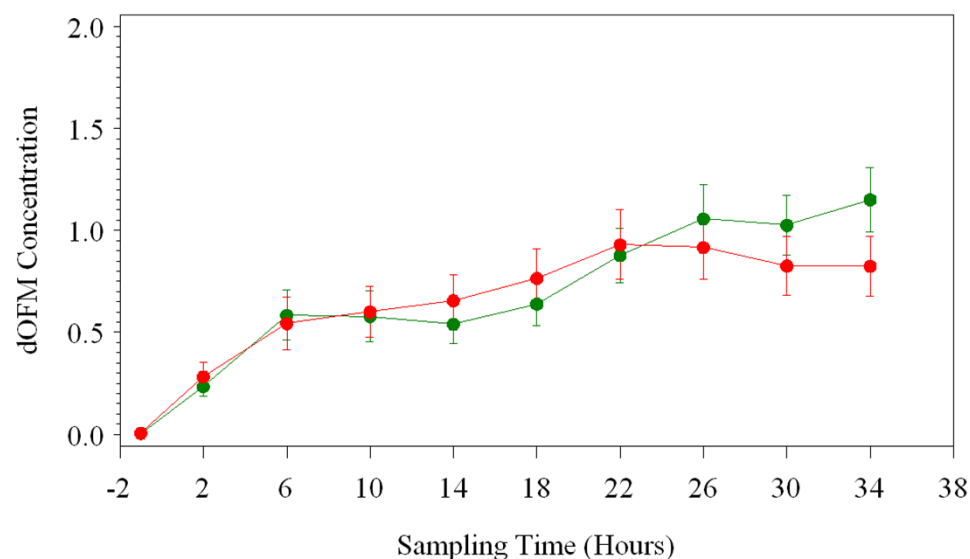
dOFM procedures are highly standardized and monitored

Results



Results R vs T

dOFM acyclovir concentrations as a function of time
Mean \pm SE (across all limbs)



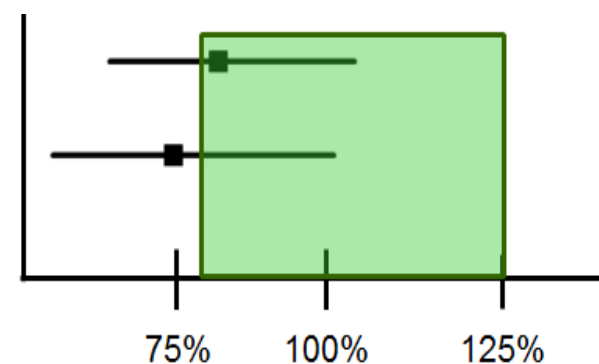
 non-BE

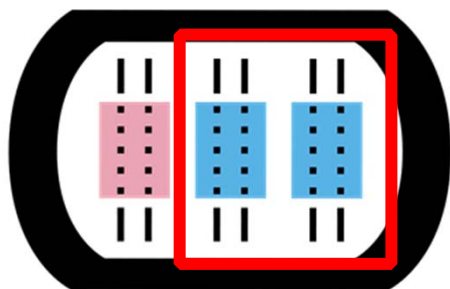
BE = 80 - 125%
AUC and C_{max}

Condition — Central reference condition — Test condition

AUC (T vs R₁)

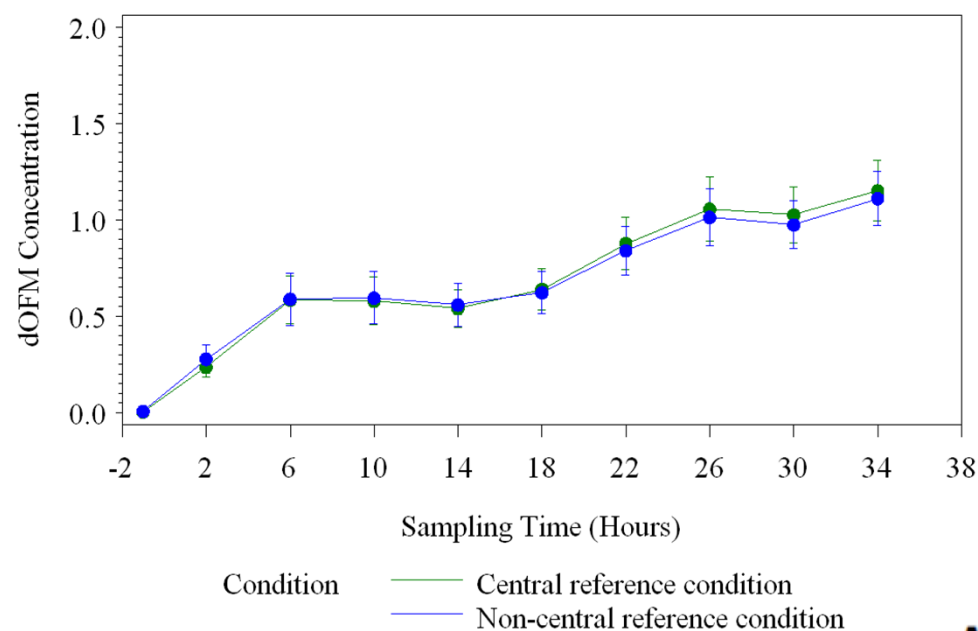
C_{max} (T vs R₁)





Results R vs R

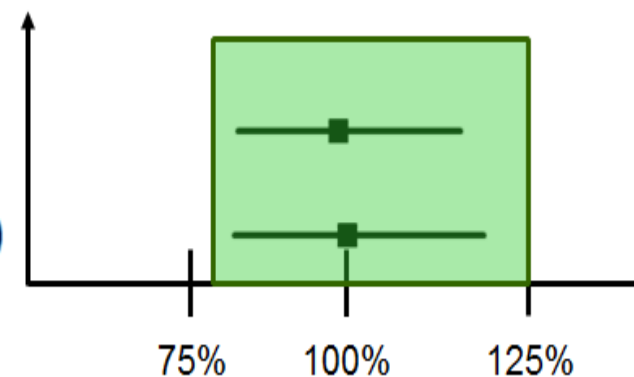
dOFM acyclovir concentrations as a function of time
Mean \pm SE (across all limbs)



BE

AUC (R_2 vs R_1)

C_{\max} (R_2 vs R_1)



Conclusion

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dOFM

- is highly standardized
- reflects the in-vivo skin PK profile
- is able to sample all substances (incl. lipophilic and large) for at least 36 hours

**dOFM allowed for the first
time to measure BE in skin
in a clinical study**