Dermal Open Flow Microperfusion for the **bioequivalence** assessment of topical products **based on skin PK**

Funding for this project was made possible, in part, by the Food and Drug Administration through grant U01FD004946-01. The views expressed in this abstract do not necessarily reflect the official policies of the Food and Drug Administration, the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

Generic Drugs

Generic Product*

"A generic drug product is considered to be ''essentially similar'' or bioequivalent to an innovator (brand name) product. Bioequivalence implies that a generic drug product is essentially identical to the brand name (reference) drug product in terms of active ingredient(s), strength, dosage form, route of administration, quality, safety, efficacy, performance characteristics, and therapeutic indication."

Reference Listed Drug

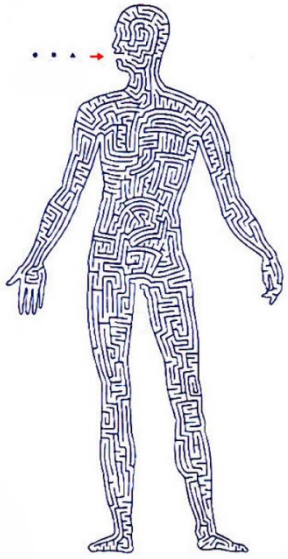
(NDA) Requirements

- Labeling
- Pharm/Tox
- Chemistry
- Manufacturing
- Controls
- Microbiology
- Inspection
- Testing
- **Animal Studies**
- **Clinical Studies**
- **Bioavailability**

Generic Drug

(ANDA) Requirements

- Labeling
- Pharm/Tox
- Chemistry
- Manufacturing
- Controls
- Microbiology
- Inspection
- Testing
- **Bioequivalence**



* https://pharmachitchat.files.wordpress.com/2015/05/generic-drug-product-development-solid-oral-dosage-forms.pdf

BA/BE of generic drugs

oral route

Dosage form → Drug in solution → Biological barrier → Blood → Site of activity → Therapeutic effect

BA/BE

end point study

Dosage form → Drug in skin → Site of action → Therapeutic effect → ~~Blood~~

topical route

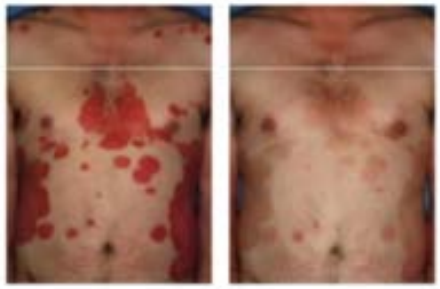
BA/BE

end point study

Clearence

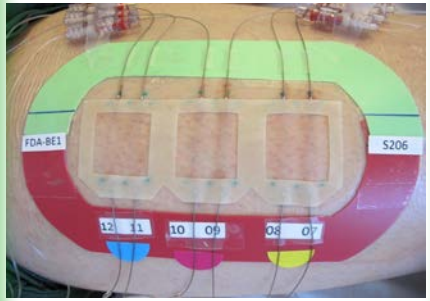
BE of topical generic drugs

In-vivo



end point study
patients

In-vivo



skin PK
healthy subjects

Use continuous dermal interstitial fluid (ISF) sampling to assess dermal BA and to prove BE of topical locally acting drugs

Why is dermal in vivo ISF sampling not accepted by FDA today?

Strengths

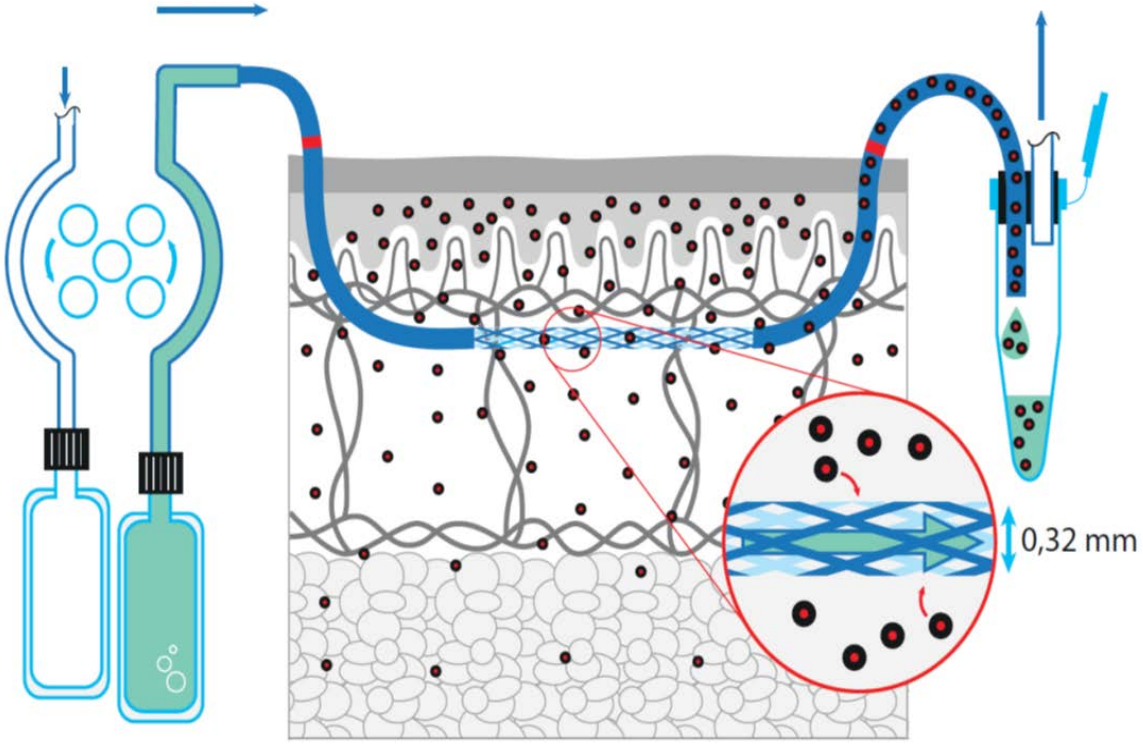
1. Provides a direct in-vivo measurement of the rate and extent of the active moiety at or near the site of action in the skin.
2. Evidence indicates that dermal sampling has the potential to differentiate pharmacokinetic profiles by their magnitude.

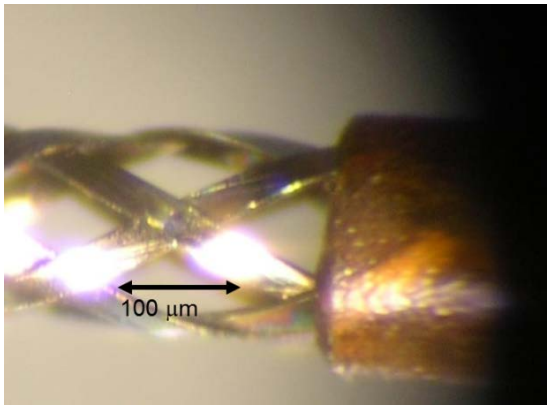
Limitations

1. Limitations of existing sampling methods
2. Limited sampling time, often < 8 hours
3. Various factors contribute to data variability

Open Flow Microperfusion

✓ **OFM samples represent <u>diluted but unfiltered</u> interstitial fluid**

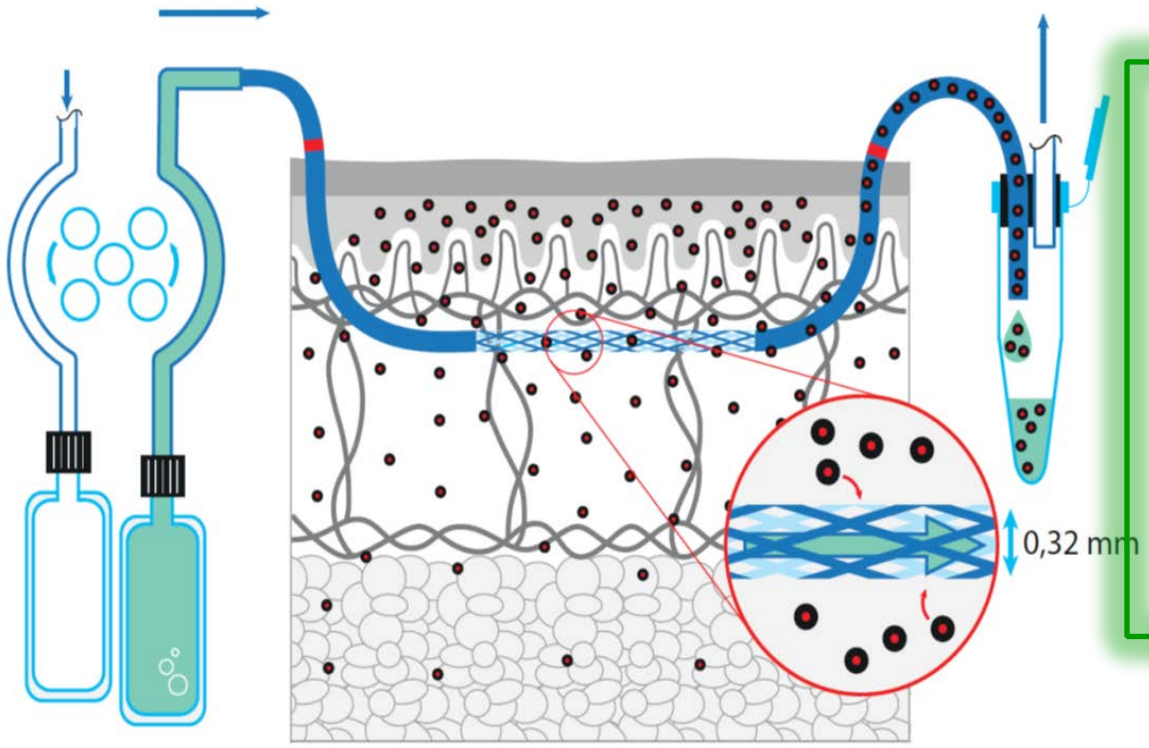




CE-certified for clinical use

Open Flow Microperfusion

✓ **All drugs are accessible in-vivo in the dermis**



lipophilic substances

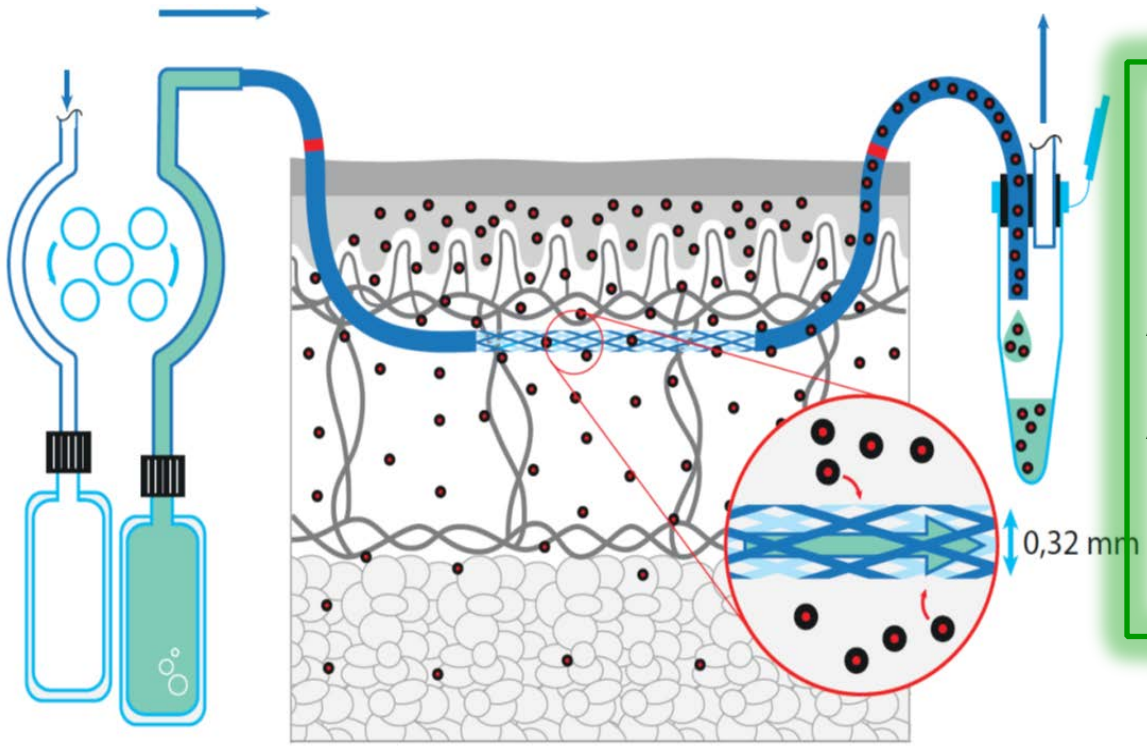
Bodenlenz et al. 2016 (CP-17; logP 3.5)
Holmgaard et al. 2011 (Fentanyl; logP 4.5)

high molecular weight substances (up to cells)

Dragatin et al. 2016
(Quantification of antibodies in skin)

Open Flow Microperfusion

✓ **In-vivo sampling in the dermis up to 48 hours**

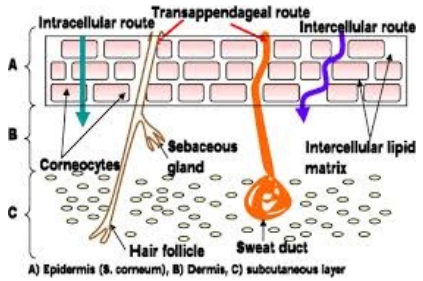


Clinical dOFM studies in skin:

Acyclovir (topical) – 36 h clinical
Corticoid (topical) – 26 h clinical
Antibody (SC) – 17 h clinical

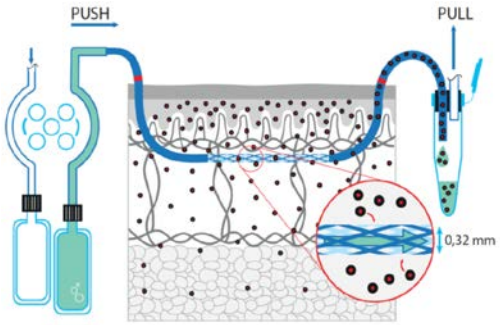
Continuous dermal ISF sampling
Sources of Variability

variability due to sampling site



- Differences in skin structure
  - Between subjects
  - Parts of the body
- Hairiness
- Sweat ducts
- Day/night rhythm of local blood flow
- Hair shaving
- Skin care products use
- Skin condition (e.g. solarium)

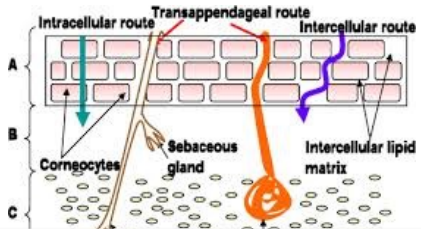
variability due to methods



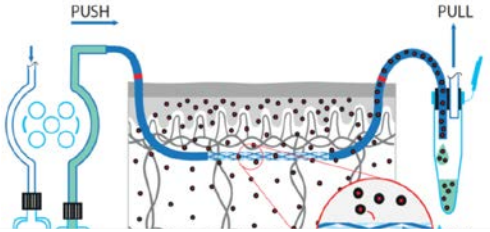
- Trauma formation
- Dosage application
- Probe depth
- Flow rate
- Local blood flow
- Lateral diffusion
- Systemic diffusion
- Room temperature and humidity

Continuous dermal ISF sampling
Sources of Data Variability

variability due to sampling site



variability due to methods



➔ **control all significantly contributing factors that add to data variability**

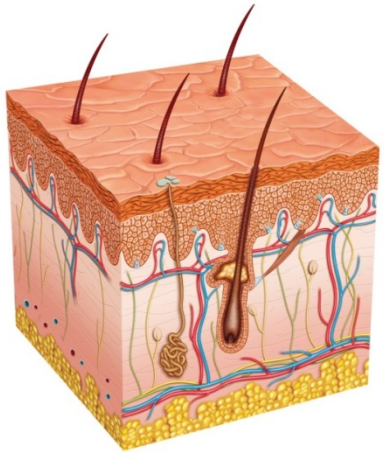
➔ **factors that cannot be controlled are monitored**

- Between subjects
  - Parts of the body
- Hairiness
- Sweat duct
- Day/night rhythm of local blood flow
- Hair shaving
- Skin care products use
- Skin condition (e.g. solarium)

- Dosage application
- Probe depth (dOFM)
- Flow rate (dOFM)
- Local blood flow
- Lateral diffusion
- Systemic diffusion
- Room temperature and humidity

Continuous dermal ISF sampling
Reduce skin PK variability

- 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



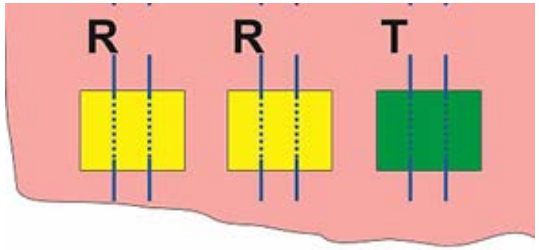
dOFM
Controlled and Monitored Factors

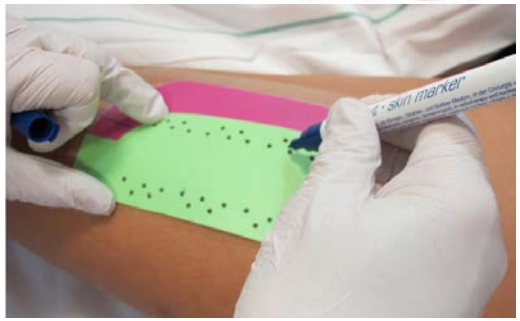
✓ **In-vivo variation significantly reduced**

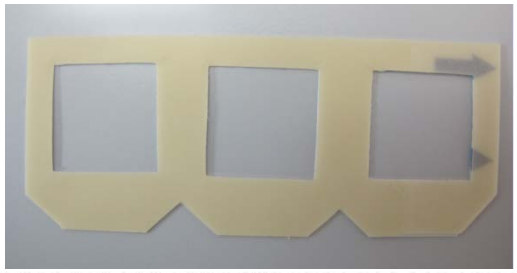
	variability due to methods
Controlled by cooling	← Trauma formation
Controlled by application template	← Application site
Controlled by standardization	← Dosage application
Monitored by ultrasound	← Probe depth
Monitored by sample weight	← Flow rate
Monitored by glucose marker	← Local blood flow
Negligible	← Lateral diffusion
No systemic exposure	← Systemic diffusion
Controlled 22 ± 1° C & 40 - 60% RH	← Room temperature & relative humidity

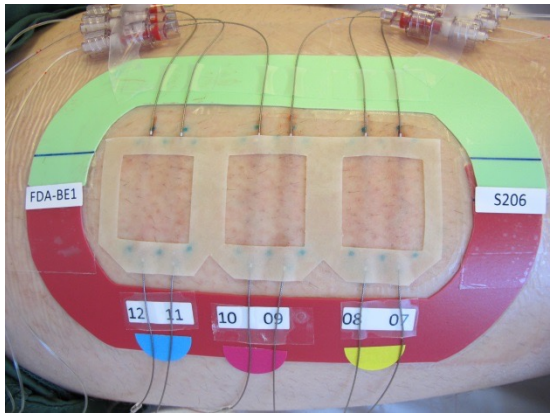
Dermal Open Flow Microperfusion
Standardization

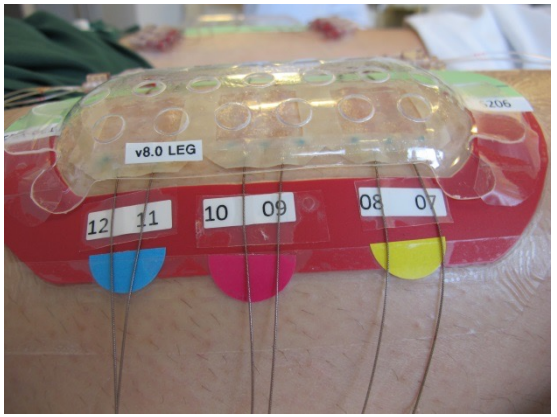
✓ **All dOFM procedures are highly standardized**

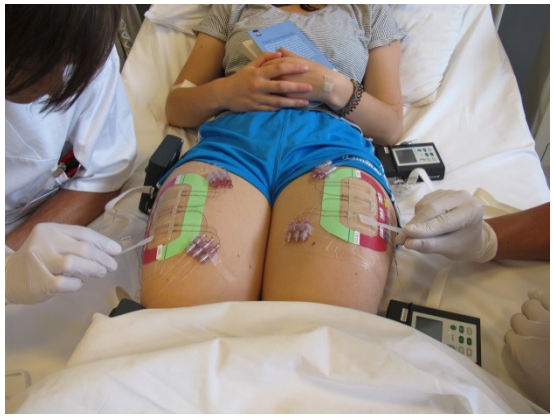


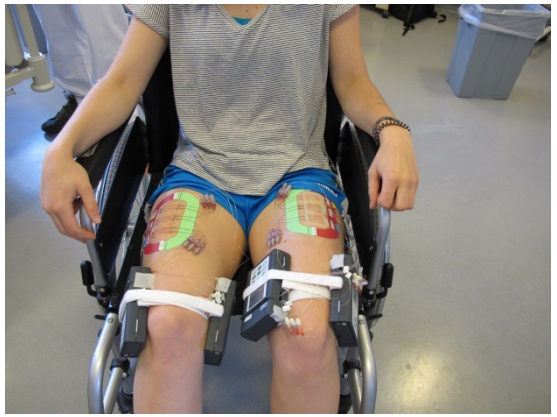






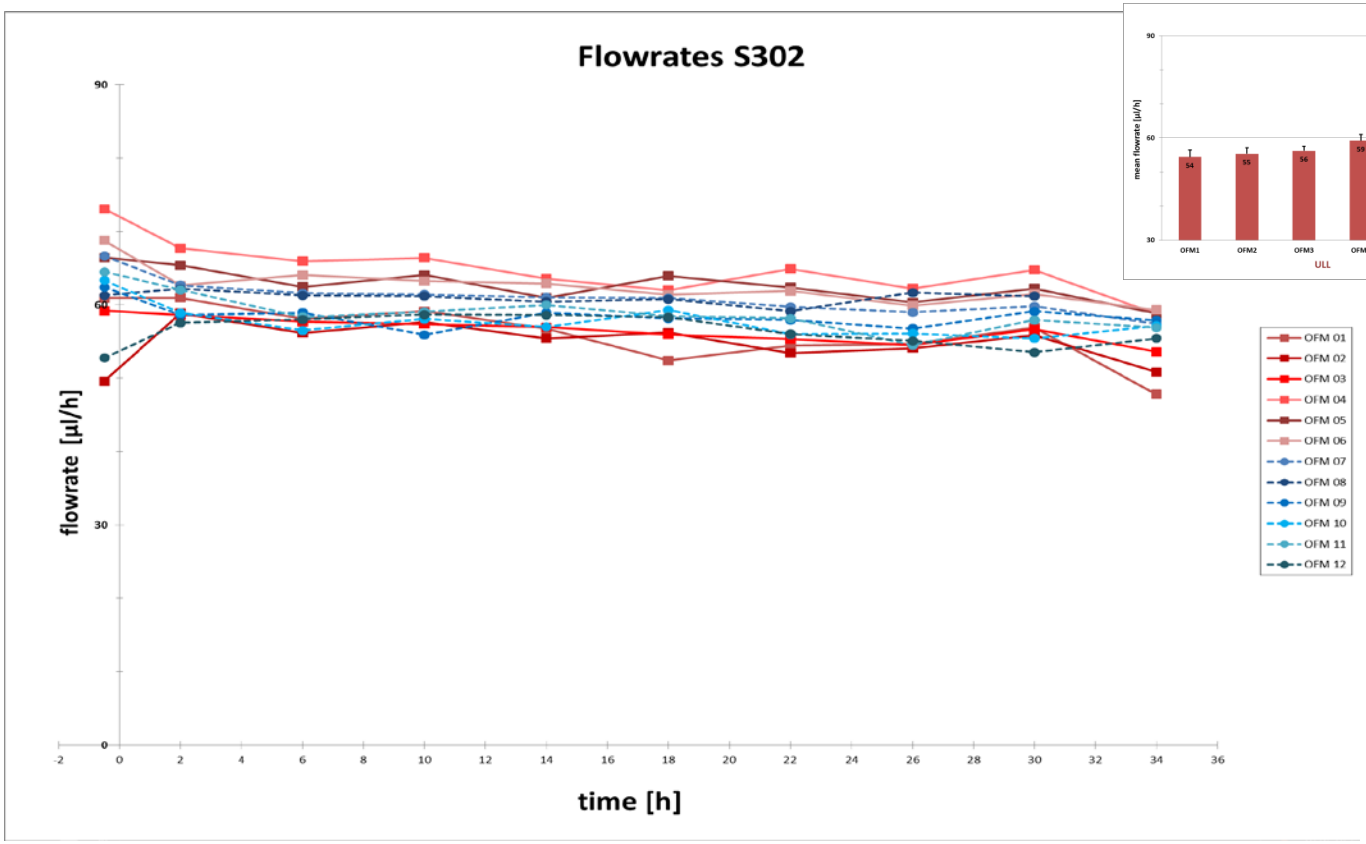


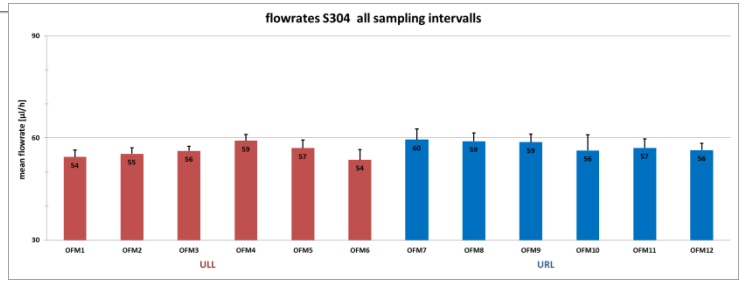


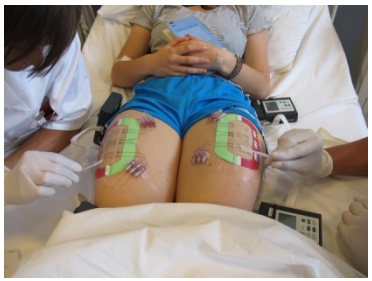


Dermal Open Flow Microperfusion
Performance Verification

✓ **dOFM provides a stable flow rate for 36 hours**

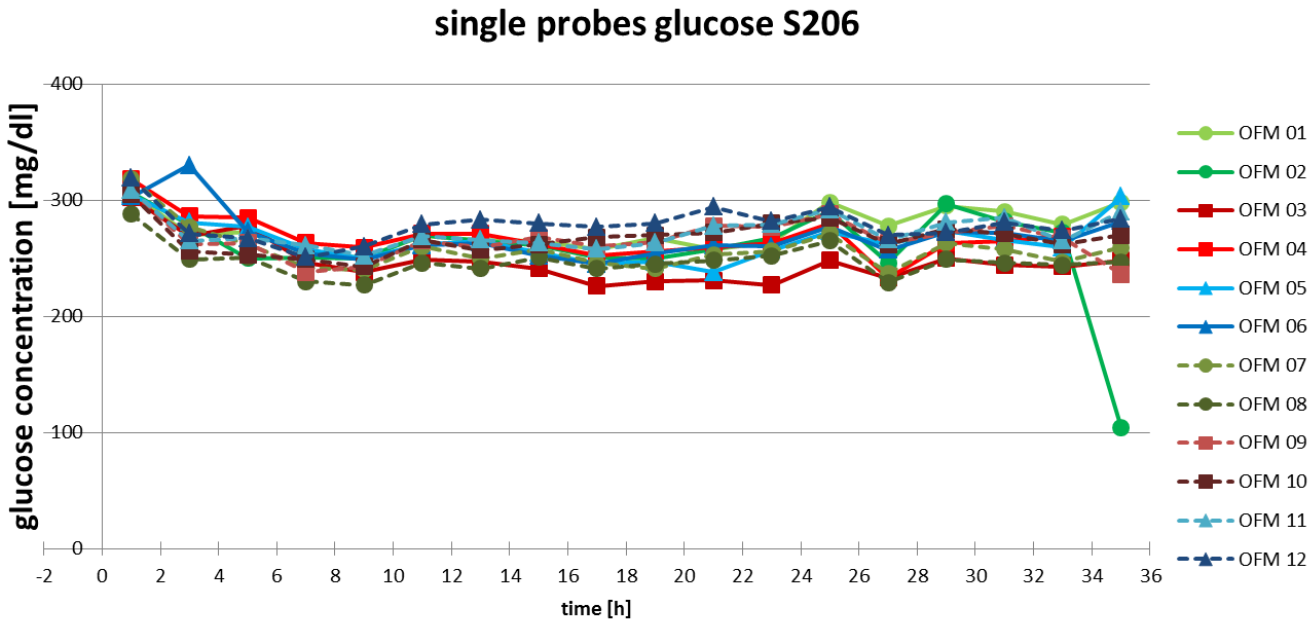


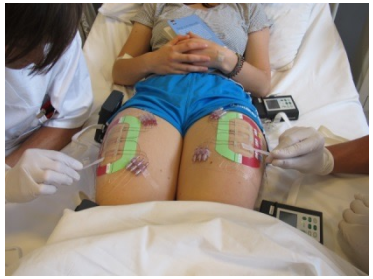




dOFM
Performance Verification

✓ **dOFM shows stable recovery for 36 hours**

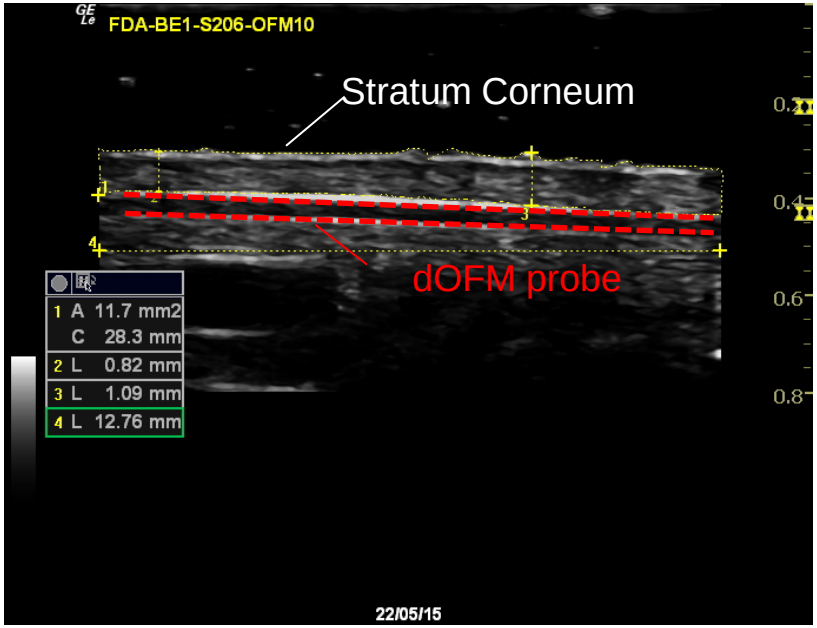


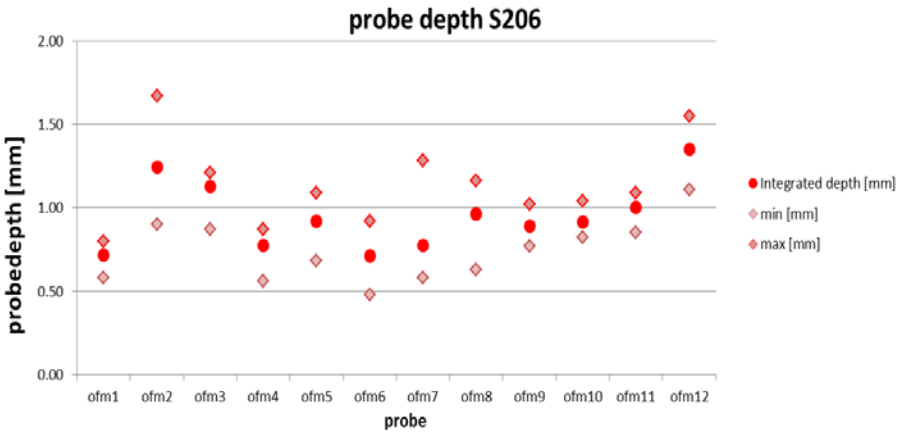


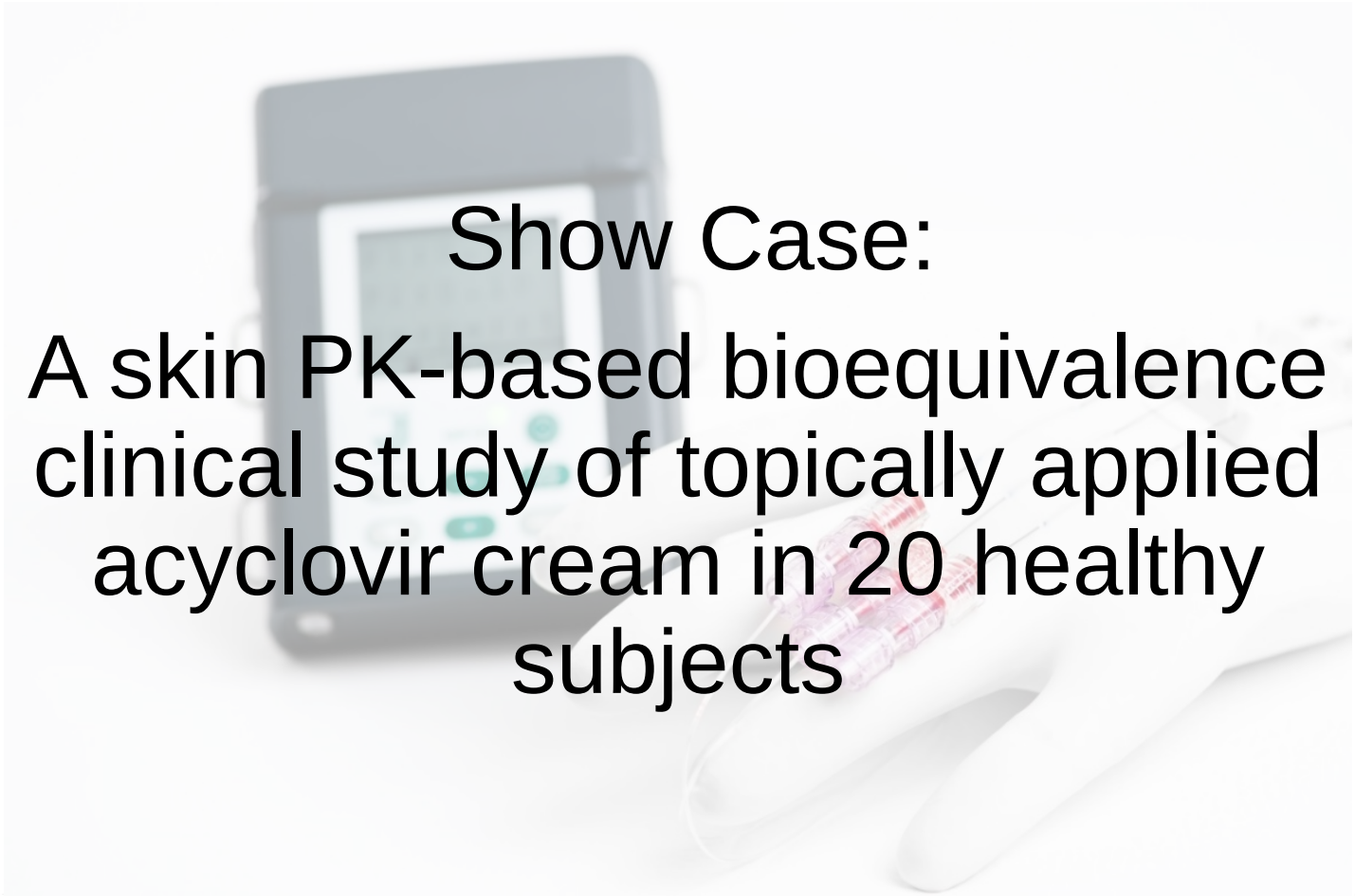
dOFM
Probe Depth

✓ **Uniform probe depth**

Monitoring of probe depth along the whole exchange area



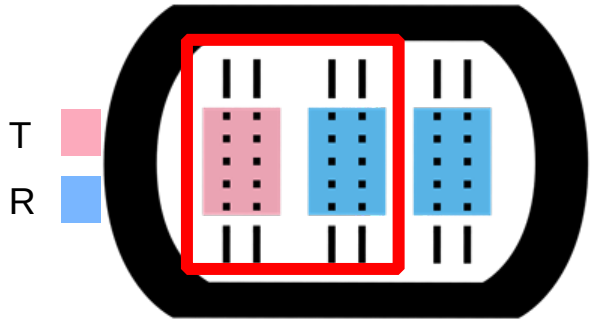




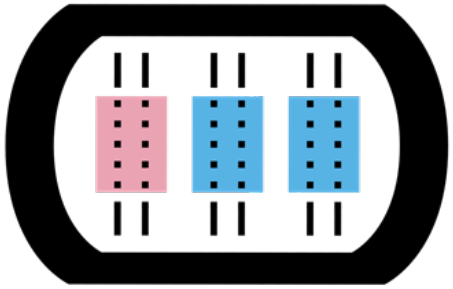
Show Case:

A skin PK-based bioequivalence clinical study of topically applied acyclovir cream in 20 healthy subjects

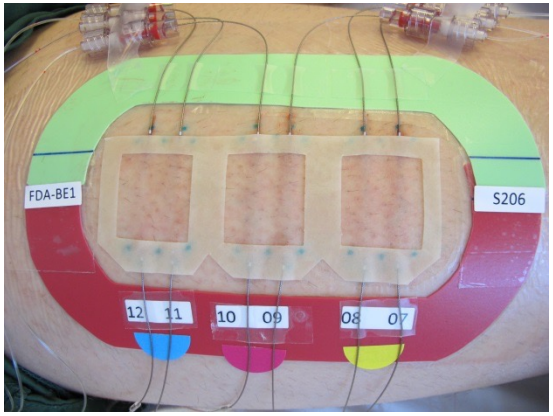
dOFM for BE
General Study Design

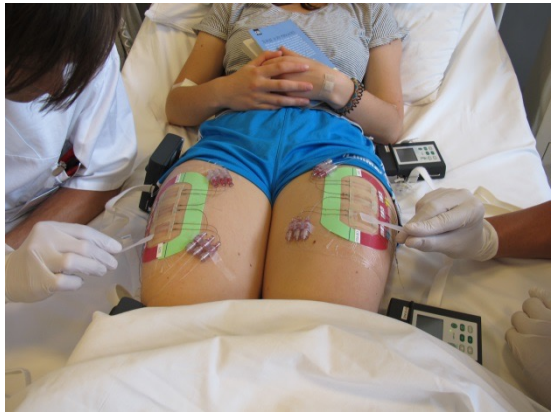


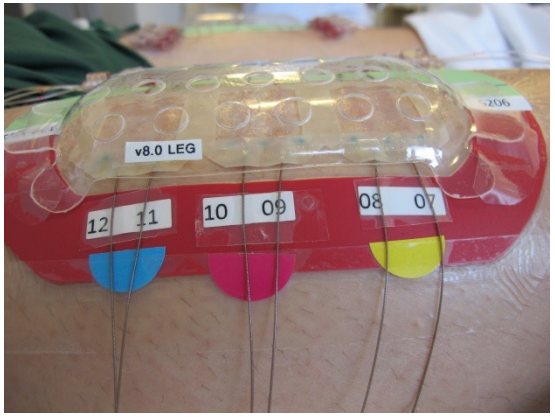
- Not-bioequivelence (R vs. T)
- Bioequivalence (R vs. R)
- API: Acyclovir
- OFM sampling for 36 hours
- Two “Triplets” (R-R-T) per subject
- Study drugs
  - R: Zovirax cream 5% US
  - T: Aciclovir cream 5% 1A Pharma
  - R and T non-Q1!

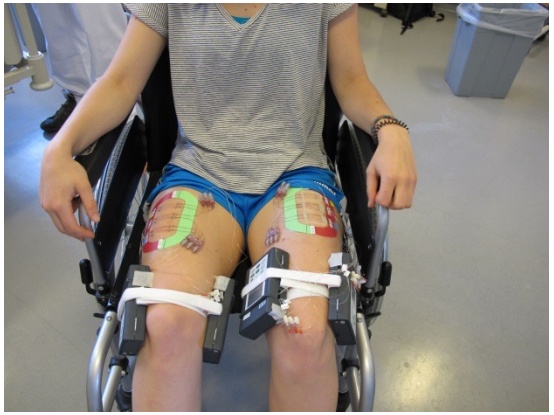


dOFM for BE
General Study Design



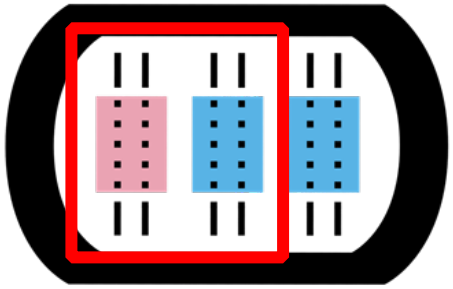






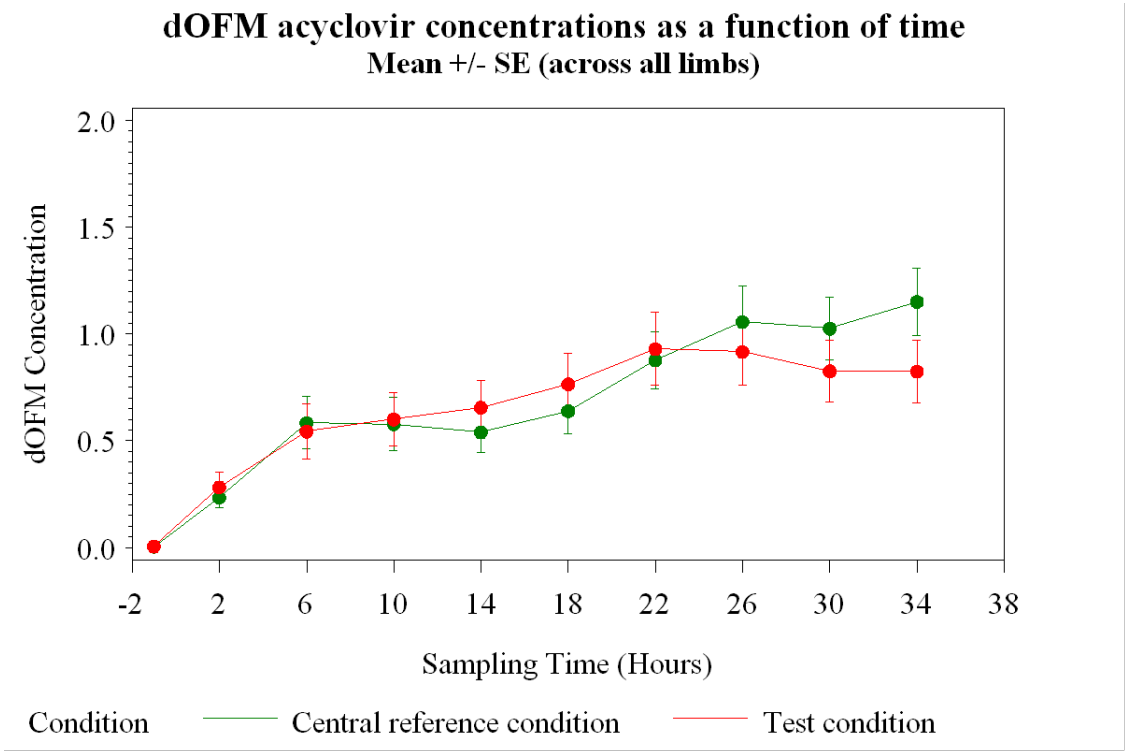
- 20 healthy subjects
  - 7 women, 13 men, age: 28 ± 5
- Application location
  - Thigh
- Analytical parameter
  - Acyclovir conc. in OFM sample

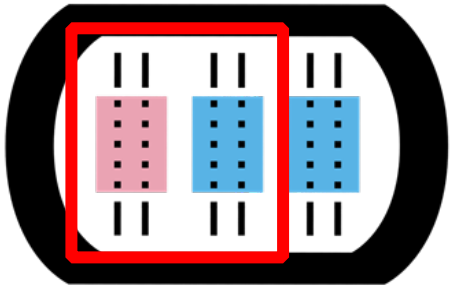
dOFM procedures are highly standardized and monitored



Clinical Bioavailability
Test versus Reference

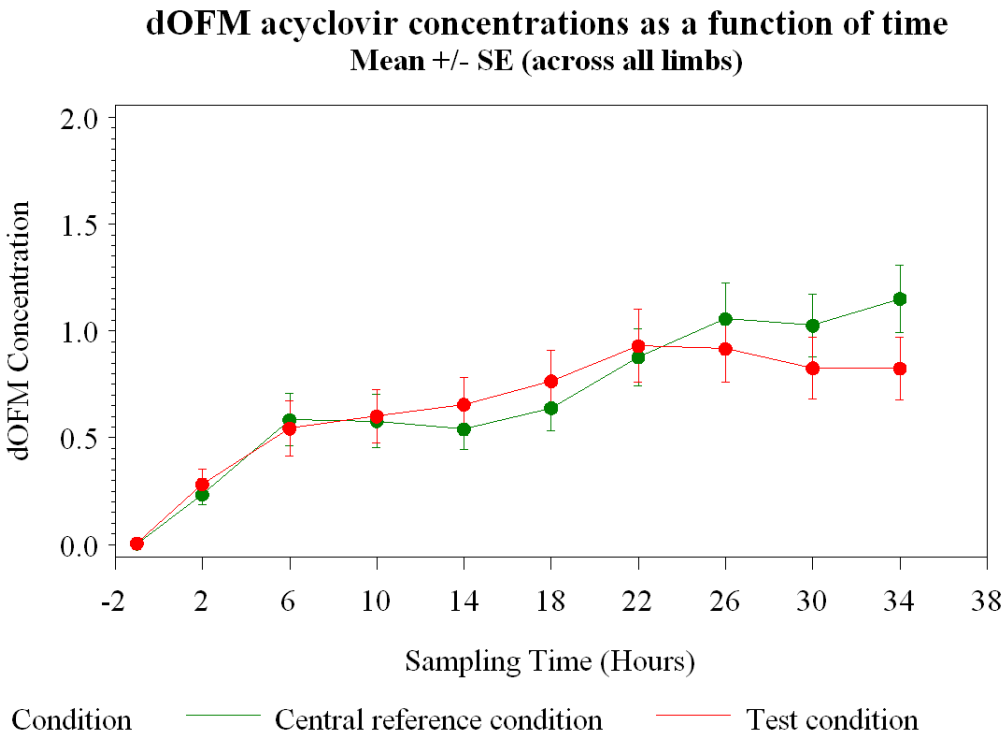
✓ **Bioavailability: AUC and T_{max} of Aciclovir A1 are highly reproducible**
AUC and T_{max} of Zovirax US are highly reproducible

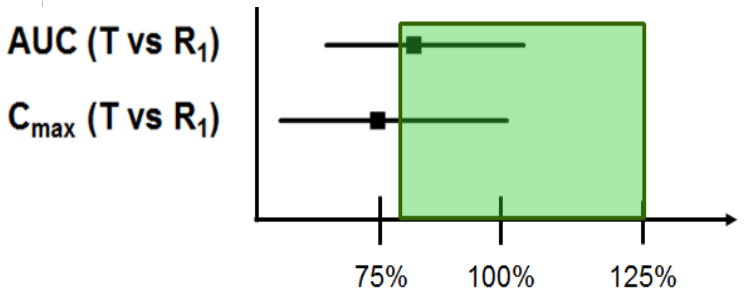




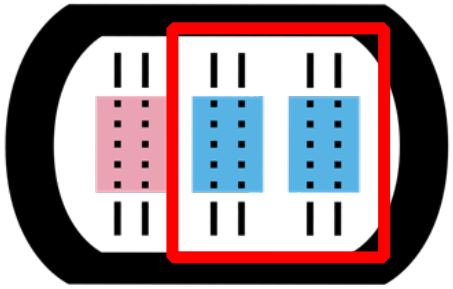
Clinical Bioavailability
Test versus Reference

✓ **Bioavailability: AUC and T_{max} of Aciclovir A1 are highly reproducible**
AUC and T_{max} of Zovirax US are highly reproducible



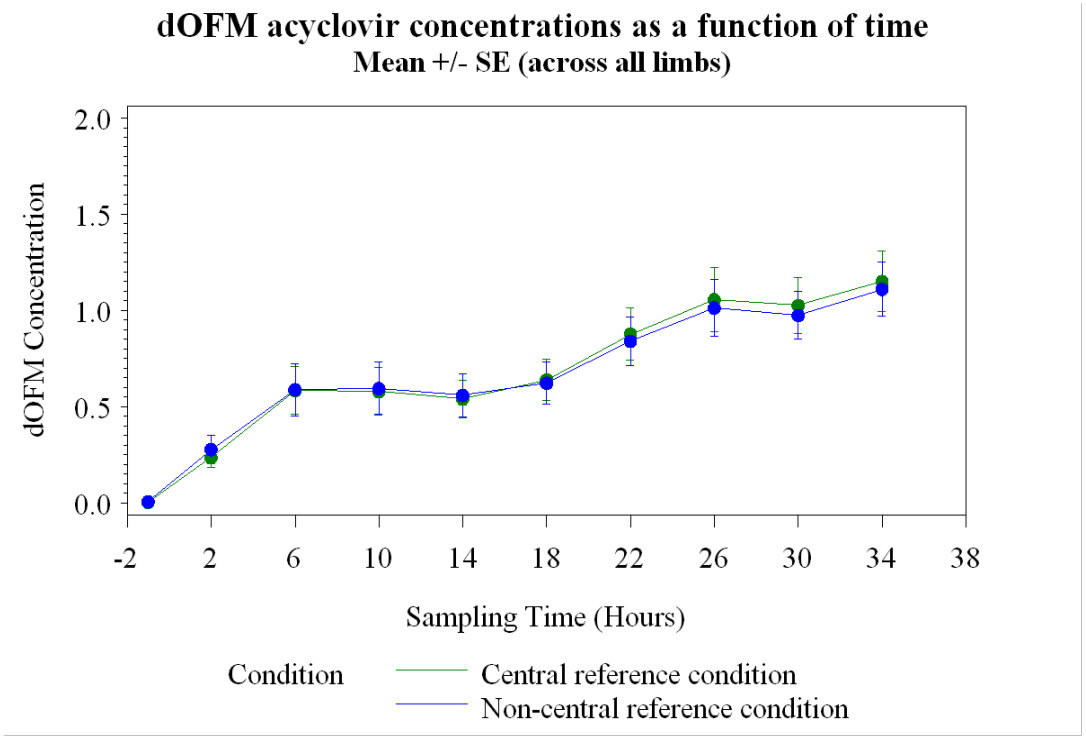


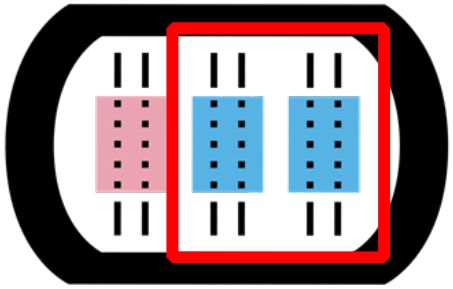
☒ BE



Clinical Bioavailability
Reference versus Reference

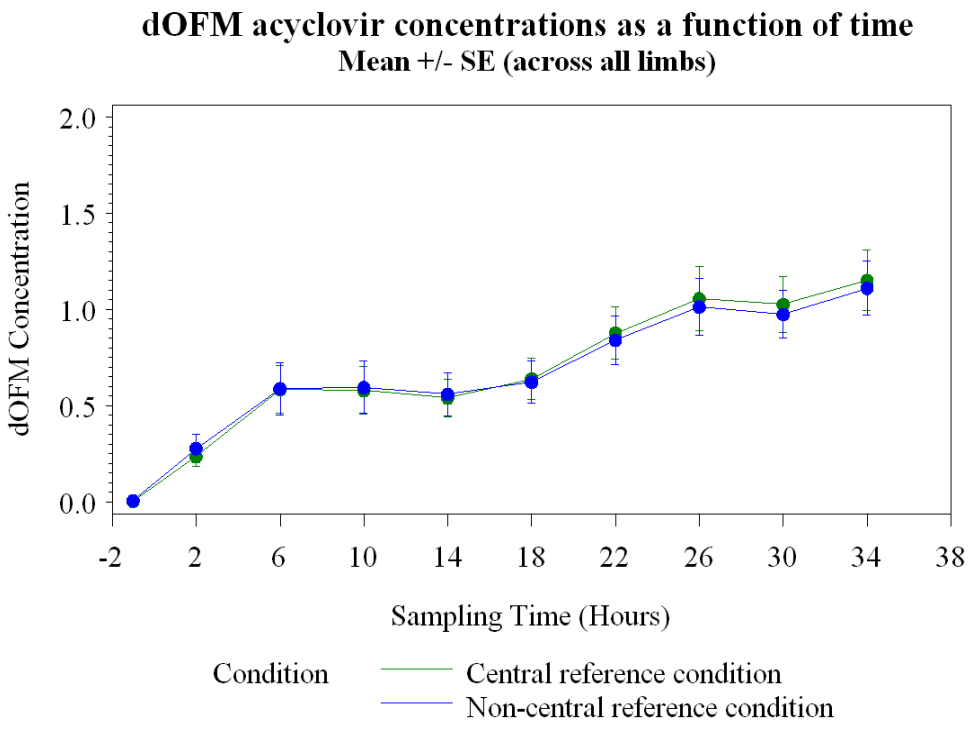
✓ **Bioavailability: AUC and C_{max} of Zoriax US are highly reproducible**

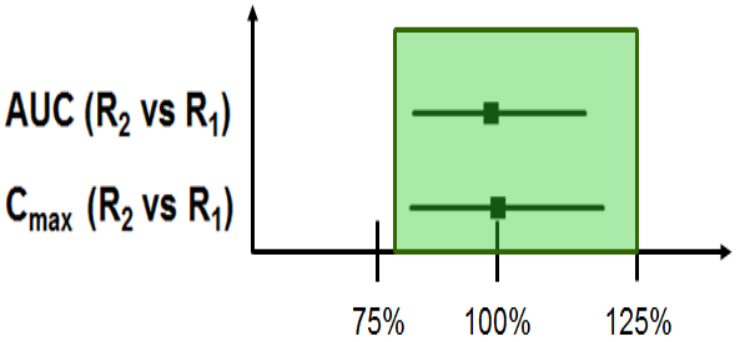




Clinical Bioavailability
Reference versus Reference

✓ **Bioavailability: AUC and C_{max} of Zoriax US are highly reproducible**

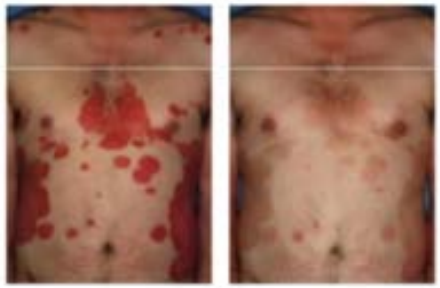




BE

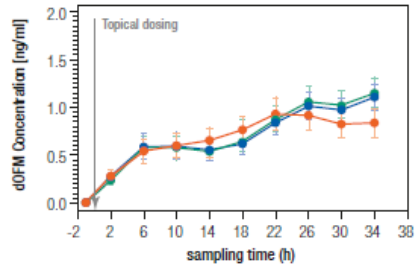
Conclusion

In-vivo



PD endpoint study

In-vivo



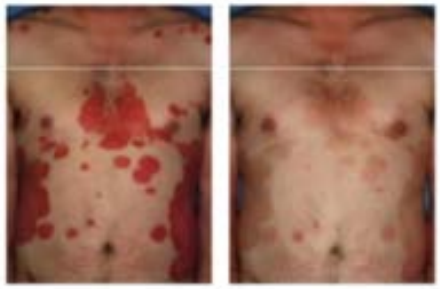
PK healthy subjects

Bodenlenz et al. Clin Pharmacokinet, 2016

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

Conclusion

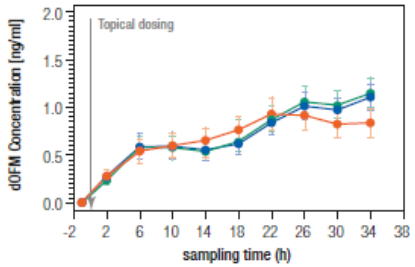
In-vivo



PD endpoint study

dOFM

In-vivo



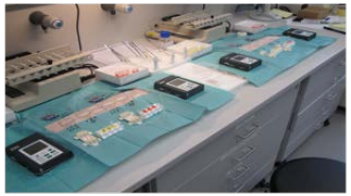
PK healthy subjects

dOFM allows to reduce your development risk

➔ check your skin-PK in ex-vivo skin and/or in vivo pig experiment first

Animal studies

Ex-Vivo



Healthy Human Skin

Outlook

RFA-FD-16-028: Bioequivalence of Topical Products - Awarded to Joanneum Research (U01FD005861)

Joanneum Research will use dOFM to assess the pharmacokinetics of topically applied drug products.

➔ The study results will help support the development of an accurate, sensitive and reproducible methodology to monitor and compare the dermal pharmacokinetics of topically administered drug*

* http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM526210.pdf

One-Stop-Shop

for tissue specific PK and PD

EN ISO 9001 | EN ISO 13485:2003 | GLP | Data management | statistic

GCP

A big thank you!

Katrin Tiffner
IVRT and dOFM ex-vivo

Manfred Bodenlenz
Clinical dOFM BE Study

Reingard Raml
Analytics

Thomas Pieber
Clinical PI

Isadore Kanfer
BE expert

Sam G. Raney
FDA Project Officer

Bernd Tschapeller
Data Mangaement

Thomas Augsutin
Statistics

More than 20 other persons

Priyanka Ghosh
Bryan Newman
Elena Rantou
Youngsook Lee
Lisa Ko
Jill Coker

Many thanks also to **Mike Roberts** (Princess Alexandra Hospital, Brisbane, Australia) and **Chris Anderson** (Region Östergötland, Sweden) for great scientific discussions

Thank you for your attention

Dr. Frank Sinner
JOANNEUM RESEARCH
Forschungsgesellschaft mbH
HEALTH – Institute for Biomedicine
and Health Sciences
Neue Stiftingtalstrasse 2, 8010 Graz, Austria
+43 316 876-4000
frank.sinner@joanneum.at
www.joanneum.at/health