

# Dermal drug testing

## Pharmacokinetic, pharmacodynamic and bioequivalence studies in the dermis



We investigate the transport and effects of APIs/drugs in the dermis after local, topical or systemical application in the dermis – in-vivo and ex-vivo. We perform tissue-specific preclinical and clinical pharmacokinetic (PK) and pharmacodynamic (PD) studies of APIs/drugs as well as mechanistic studies of diseases.

We can also investigate bioavailability/bioequivalence and perform metabolomic studies in-vivo and ex-vivo. For these investigations, we use microdialysis and our patented technique – open flow microperfusion (OFM).

*“Our unique and patented method of ‘open flow microperfusion – OFM’ enables access to the entire biochemical information of the dermal interstitial fluid compartment directly from the site of action – in-vivo and opens up new horizons in preclinical and clinical drug testing.”*

*Thomas Pieber, MD, Professor of Medicine  
Director*



## Quality standards

---

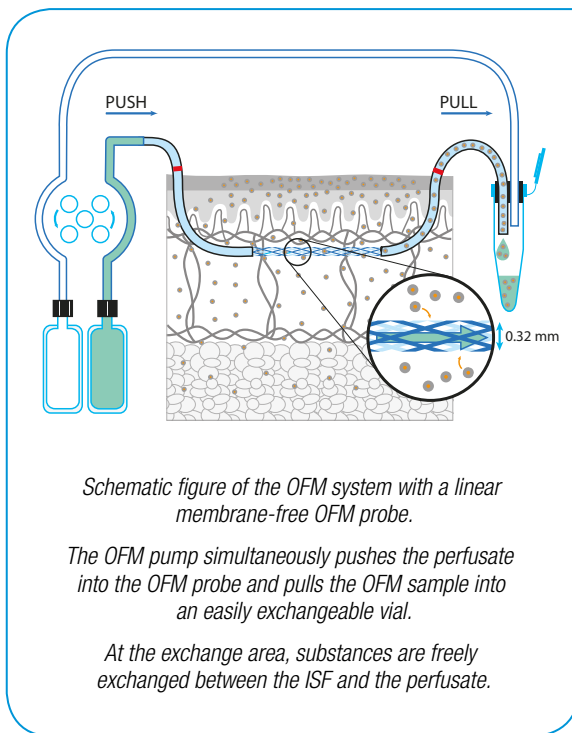
- EN ISO 9001:2008
- EN ISO 13485:2012
- GLP – Good Laboratory Practice

## Our partners

---

- Biobank Graz
- Clinical Research Center Graz  
(Medical University of Graz, Austria)
- Biomedical Research Unit  
(Medical University of Graz, Austria)

## The method – open flow microperfusion



### Dermal ISF sampling without limitations

- OFM is a catheter based method
- a linear membrane free OFM probe is inserted into the skin and lies right beneath the dermis
- the OFM probe is continuously perfused
- at the exchange area (sampling mesh) substances are freely exchanged between the ISF and the perfusate

### Benefits

- ➔ direct contact with the dermal interstitial fluid compartment (ISF)
- ➔ continuously collect ISF samples in-vivo
- ➔ no limitation in size: from single molecules to antibodies
- ➔ no limitation regarding lipophilicity
- ➔ simultaneous analysis of multiple substances (e. g. biomarkers)



### OFM material

- CE-certified OFM probes, pump and accessories for preclinical and clinical use
- minimally invasive membrane free probe with a sampling mesh and a 0.5 mm insertion needle
- wearable pump (0.1 – 10 µl/min) allowing delta push-pull operation
- 3 OFM probes per pump
- OFM probes patented and patent for pump pending

## Active Pharmaceutical Ingredients (API)

### Our services

Your question	Our approach
<i>Which biochemical effects are caused by an API in the dermis?</i>	<p><b>We investigate potential effects as well as any side effects of your API by</b></p> <ul style="list-style-type: none"> <li>■ directly administering unformulated API via OFM probes into the dermis</li> <li>■ continuously sampling dermal interstitial fluid</li> <li>■ analyzing a wide PD marker panel in the dermal interstitial fluid samples to provide a continuous PD profile for your API.</li> </ul>
<i>Is your API targeting the intended biochemical pathway in the dermis?</i>	<p><b>We investigate the intended mechanism of action in-vivo in the dermis by</b></p> <ul style="list-style-type: none"> <li>■ directly administering unformulated API via OFM probes into the dermis</li> <li>■ continuously sampling dermal interstitial fluid</li> <li>■ analyzing a customized PD marker panel in the dermal interstitial fluid samples to provide a continuous PD profile for your API.</li> </ul>
<i>Which API concentration in the dermis achieves the intended therapeutic effect?</i>	<p><b>We investigate the local dose-response relationship in-vivo in the dermis by</b></p> <ul style="list-style-type: none"> <li>■ directly administering unformulated API via OFM probes into the dermis</li> <li>■ continuously sampling dermal interstitial fluid</li> <li>■ analyzing a customized PD marker panel in the dermal interstitial fluid samples to provide dose-response information for your API.</li> <li>■ applying different concentrations of the API to the dermis to determine <ul style="list-style-type: none"> <li>➤ the relevant API concentration in the dermis that achieves the intended therapeutic effect.</li> <li>➤ potential local toxicity of the API.</li> </ul> </li> </ul>

### Your benefits

- In-vivo dose-response directly in the dermis instead of surrogate parameters in blood.
- At the earliest possible stage in drug development you can demonstrate intended therapeutic effects of your unformulated API in-vivo in the dermis.
- No need to formulate the API.
- Reduce your time and costs by reducing risk of failure in drug development.
- Receive a highly resolved time profile of API action for up to 36 hours.
- Identical trial set-up in preclinical and clinical experiments.

## Dermal drugs

### Our services

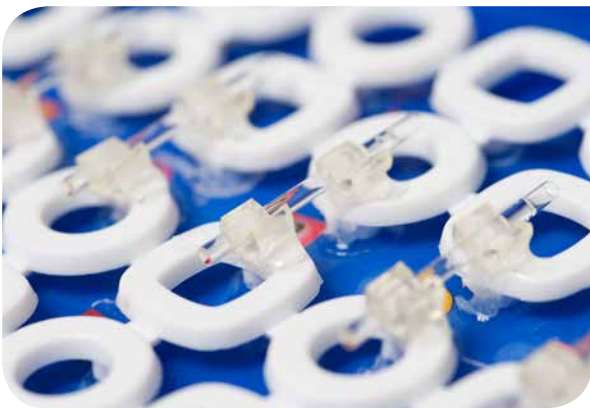
Your question	Our approach
<i>In what concentration does a dermal drug reach the dermis?</i>	<p><b>We provide a cross-sectional profile of your dermal drug in all skin layers by</b></p> <ul style="list-style-type: none"> <li>■ applying formulated drug via the intended route (e.g. topical, subcutaneous, intravenous, oral)</li> <li>■ using specialized in-vivo/ex-vivo skin biopsies</li> <li>■ slicing the biopsies parallel to the skin surface</li> <li>■ analyzing the drug concentration separately in each slice</li> </ul> <p><b>We investigate the continuous pharmacokinetic profile in the skin by</b></p> <ul style="list-style-type: none"> <li>■ continuously sampling dermal interstitial fluid</li> <li>■ quantifying drug concentrations in the dermal interstitial fluid samples.</li> </ul>
<i>Which biochemical effects are caused by the dermal drug?</i>	<p><b>We investigate potential effects and any side effects of your drugs directly in the skin by</b></p> <ul style="list-style-type: none"> <li>■ applying formulated drug via the intended route (e.g. subcutaneous, intravenous, oral, topical)</li> <li>■ placing OFM or microdialysis probes in the dermis</li> <li>■ continuously sampling dermal interstitial fluid</li> <li>■ analyzing a wide PD marker panel in the dermal interstitial fluid samples for a continuous PD profile of the drug.</li> </ul>

### Your benefits

- Spatial and temporal pharmacokinetic profiles for your drug in the dermis.
- Receive a highly resolved time profile in a preclinical or clinical set-up for up to 36 hours.
- Reduce the risk of failure by access to in-vivo PK/PD data at the earliest possible stage in drug development.
- Reduce your time and costs by reducing risk of failure in drug development.
- Identical trial set-up in preclinical, ex-vivo and clinical experiments.
- At the earliest possible stage in drug development you can demonstrate intended mechanisms of action and possible side effects for your drug directly in the dermis.



**GCP**  
EN ISO 9001:2008 | EN ISO 13485:2012 | GLP – Good Laboratory Practice



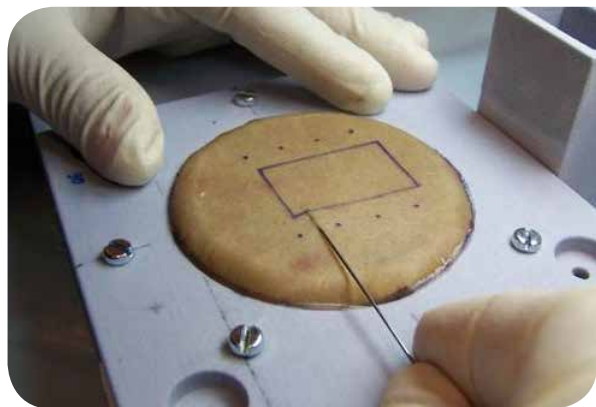
### In-vitro validation

In-vitro testing precedes any in-vivo or ex-vivo study, to ensure reliability of quantitative sampling. We investigate compound stability in the sample matrices, including freeze-thaw cycles, followed by tests for stability of compound recoveries; i.e., we verify the adsorption-free passage of the compounds from sampling probe to sampling vial by analysing simulated perfusates and test solutions. The obtained data can help prevent misinterpretation of in-vivo or ex-vivo results.

### Preclinical ex-vivo testing in excised human skin

For our preclinical ex-vivo PK studies we can use excised human skin (healthy and diseased). After preparation and cultivation, ex-vivo experiments are performed under controlled conditions.

We can investigate the absorption and liberation of topically applied active pharmaceutical ingredients (API). Human excised skin is provided by the Biobank at the Medical University of Graz.



FOTOLIA, Vitaliy Pakhnyushchyy

### Preclinical in vivo studies

We perform preclinical in-vivo PK and PD studies using our OFM technique or microdialysis. We examine how the API/drug is absorbed, metabolized and excreted by the body when introduced transdermally, intravenously, intraperitoneally or in other ways. In-vivo studies in rodent and porcine skin can be carried out on conscious or anaesthetized animals for up to 12 hours.

These studies are performed in cooperation with the Institute for Biomedical Research at the Medical University of Graz.

clinical  
in-vivo  
studies

PK/PD-  
bioanalysis

data  
manage-  
ment

statistics

reporting

GCP

EN ISO 9001:2008 | EN ISO 13485:2012 | GLP – Good Laboratory Practice



### Clinical in-vivo testing

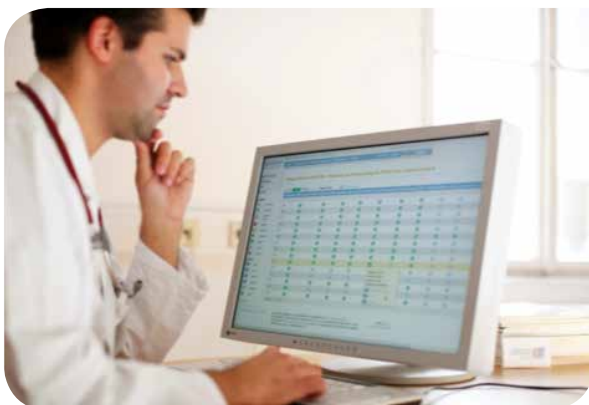
OFM is minimally invasive and enables prolonged dermal ISF sampling for up to 36 hours in patients or volunteers. Multiple probes per application site allow streamlined study designs that can deliver powerful data in a relatively small number of subjects for PK/PD and bioavailability/ bioequivalence studies.

Clinical trials are conducted according to ICH-GCP standards at the local Clinical Research Centre of the Medical University of Graz.

### PK/PD-bioanalysis

We have implemented 92 screening methods for 92 cytokines and 75 eicosanoids and we can perform highly sensitive quantification of selected PD markers including cytokines and eicosanoids.

We develop, optimize, qualify, validate and automate all PK/PD-bioanalysis for high-throughput analysis. All PK/PD-bioanalysis is performed with highly sensitive state-of-the-art mass spectrometry analytics according to GLP guidelines.



### Data management and statistics

We develop Source Data Forms and electronic Case Report Forms using Open Clinica according to your database requirements.

We perform comprehensive data management including user training, data cleaning, plausibility checks, outlier handling, query management, data base release meetings, data base lock and archiving.

We develop the Statistical Analysis Plan (including sample size calculation) and perform and validate the clinical statistics.

## CONTACT

JOANNEUM RESEARCH  
Forschungsgesellschaft mbH

Institute for  
Biomedicine and  
Health Sciences

**Dr Frank Sinner**

Neue Stiftingtalstrasse 2  
8010 Graz, Austria

Phone +43 316 876-4000  
Fax +43 316 8769-4000

[frank.sinner@joanneum.at](mailto:frank.sinner@joanneum.at)

[health@joanneum.at](mailto:health@joanneum.at)  
[www.joanneum.at/health](http://www.joanneum.at/health)