Drug Profiling – a toolbox for candidate selection, preclinical and pharmaceutical development

Across Barriers GmbH
Sciencepark 1
66121 Saarbrücken
Germany
Phone: +49 681 959 188 00
Fax: +49 681 959 188 02
Dr. Udo Bock: u.bock@acrossbarriers.de
Dr. Eleonore Haltner: dr.haltner@acrossbarriers.de

Company profile Across Barriers

- Foundation by Prof. C.-M. Lehr and Dr. E. Haltner in 1998
- 900 m² working area
- S2 labs for biological and radioactive operations
- 30 Employees (pharmacists, chemists, biologists)
- Permissions and quality standards
  - 11/00 Permission for radioactive work
  - 07/01 GLP certified, 3 categories (Good Laboratory Praxis)
  - 07/02 Test of drugs and drug products; GMP
  - 02/03 Permission to work with Narcotic Agents
- Independent quality assurance, double check of all data, frequent training for our employees
Intelligent Drug Profiling
Analytics – Physicochemistry – In vitro techniques (cell cultures, tissue) – regulatory support

- Chromatographic method development and validation
- Optimization and Adaptation of analytical methods and analytical method transfer
- Physicochemical characterization (lipophilicity, aqueous solubility, pKa)
- Chemical and biological stability (gastrointestinal fluid, serum, plasma etc.)

Regulatory support (GMP services)
Stability testing; release analytics; Common Technical Document (consulting, coordination; data acquisition; preparation of documents)

Factors influencing absorption

**formulation factors**
- dosage form, absorption enhancers
  - Coating, ...

**disintegration**
- aggregates
- fine particels

**physicochemical factors**
- size, solubility, molecular weight, charge (pKa), H-bonding potential, molecular surface area, stability, ...

**dissolution**
- drug in solution

**biochemical factors**
- Metabolism, efflux, active transporters, ...

**permeability**
- drug in blood
### Physicochemical characterization: a toolbox equipped from screening tools to methods according guidelines

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Method</th>
<th>Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKa</td>
<td>Sirius (Health Scientific)</td>
<td>3 mg, 98% purity</td>
</tr>
<tr>
<td>lipophilicity</td>
<td>kIAM, Sirius (Health Scientific) shake flask (miniaturized)</td>
<td>DMSO solution 3 – 5 mg</td>
</tr>
<tr>
<td>aqueous solubility</td>
<td>nephelometric (pH dependent) shake flask (limit, saturation)</td>
<td>DMSO solution</td>
</tr>
<tr>
<td>protein binding</td>
<td>HSA chromatography ultrafiltration</td>
<td>DMSO solutions</td>
</tr>
<tr>
<td>solubility/stability</td>
<td>aquous, gastrointestinal fluids, serum, physiol. buffers (FASIF, FESIF), metabolic (CYPs, microsomes), chemical</td>
<td></td>
</tr>
<tr>
<td>substance characterization</td>
<td>identity, purity, assay, water content, loss of drying</td>
<td></td>
</tr>
</tbody>
</table>

---

### Across Barriers’ in vitro models

- **In vitro permeability** (standardized and customized assays)
- Investigation of transport mechanisms
  - Identification of active transport mechanisms
  - Identification of efflux mediated transport
  - Interaction of drug substances
  - Influence of excipients on permeability and/or transport mechanism
  - Proof of drug delivery concepts
- **Dermal Barrier** (porcine, human, reconstructed skin)
- **Gastrointestinal Barrier** (Caco-2, porcine gut)
- **Blood Brain Barrier** (primary endothelial cells)
- **Pulmonary Barrier** (bronchial cells, lung cells)
- **Buccal and nasal Barrier** (excised tissue)
- Classification of drug substances according Biopharmaceutics classification system (FDA)
Stress stability and preformulation screening for liquid, solid and semisolid formulations

**Benefit**
- Low sample amounts (approx. 30 mg of API for a set of 20 excipients)
- Very fast result (usually within 5 working days full report available)
- Chromatographic Impurity Profile available for each API-excipient mixture

**Information we get**
- Purity of drug
- Influence of conditions (acid, base, oxidation)
- Influence of API/excipient ratio
- Influence of excipient quality resp. purity
- Influence of process
- No information about kinetic

**Two step procedure**
- Assessment of API stability
- Assessment of API-excipient interaction

---

Analytical services

- Chromatographic method development and validation
- Stability indicating methods according to the ICH principles (forced degradation)
- Optimization and Adaptation of analytical methods and analytical method transfer
- Bioanalytics

**Detectors:**
- UV VIS
- Photodiode Array
- Fluorescence
- Electrochemical
- LC-ESI-MS coupled with PDA
- LC-MS-MS coupled with UV

**Separation:**
- Isocratic methods
- Gradient methods
- Size exclusion
Stability testing and proof of drug products

**Stability conditions**
- 5°C
- 25°C/60% RH
- 30°C/60% RH and 30°C/65% RH
- 40°C/75% RH
- Photo stability

**Stress testing**
- High temperature, acid and base hydrolysis
- Oxidative and photo stress
- Exploratory and definitive studies

**Dissolution testing**
- Apparatus 1 and 2
- Method transfer, development and validation

**Quality control**
- Labwatch system with continuous temperature and humidity monitoring
- Email and SMS alarm system over night and during weekends
- Backup generator
- Redundant operating systems
- Frequent calibration

**Experience**
- Stability studies for drug registration
- Follow up stability studies
- Container studies
- Compatibility studies

Services for Pharma: from research to market

**Drug Product**
**Drug Substance**

- **Analytical Method Development and Validation**
- **Physicochemical Profiling**
- **In vitro Pharmacokinetics (cell cultures)**
- **Compatibility Screening And Testing**
- **Pharmacopoeia Methods**
- **Stability Testing (Short Term, ICH)**
- **Method Development and Validation**
- **Registration Documents**
- **Analytics (LC-UV; MS; MS-MS)**
### How to work with us

- **Fee for Services**
- **Strategic Alliances (Co-Development)**
- **Consulting**
  - regulatory support
  - customized study design
  - project planning
  - project management
- **R&D Cooperations**
- **Frame Work Agreements**

### Your benefits....

- **High quality standards**
  - Good laboratory praxis, Good manufacturing praxis
- **Approved methods**
  - working according guidelines, validated in vitro models, close contact to authorities and regulators
- **Customized assays**
  - the needs of our customers are always the focus, individual consulting and project planning
- **Interdisciplinary team**
  - pharmacists, biotechnologists, chemists, biologists
- **High expertise**
  - well educated staff, 60% with university degree
  - university collaborations, involvement in EU and national funded research projects, network of experts
- **Short reaction time**
  - latest two weeks after receiving all necessary information and/or substances
- **Good communication skills**
  - professional project management, weekly customer reports during project