Data Requirement and Risk Assessment in Pharmaceuticals

Where can we use extrapolation tools?

Gerd Maack
Department of Pharmaceuticals
CONTENT

➢ What are the guidelines asking for?
  ▪ Human Pharmaceuticals
  ▪ Veterinary Pharmaceuticals

➢ Assessment and Possibilities outside the Regulatory Context

➢ General Conclusions
Guideline on the environmental risk assessment of medicinal products for human use
(EMEA/CHMP/SWP/4447/00)  (Came into effect 01. December 2006)

- Tiered Approach
- „Trigger“- values

Relevance and Exposure

Phase I

PEC_{sw} \geq 0,01 \mu g/L

Log K_{ow} > 4,5

PBT-Screening

PEC <0,01 \mu g/L

Effect in the environment at concentrations below 10 ng/L expected („however“-clause)

In-depth Assessment of Fate and Effects

Phase II

STOP

33 % of all applications
(EMA 2014)
**Guideline on the environmental risk assessment of medicinal products for human use**
(EMEA/CHMP/SWP/4447/00)  
(Came into effect 01. December 2006)

**Assessment of Fate and Effects**

**Phase II Tier A**

- **Risk**
  - PEC/ PNEC
  - no risk

**Phase II Tier B**

- **PEC/ PNEC**
- **STOP**

**Base data Set**
- **Chronic** data for Algae, Daphnia and Fish
- Sludge, Respiration Inhibition
- Adsorption / Desorption
- Ready Biodegradability
- Transformation in Sediment Systems
- ...

- Terrestrial effect studies
- Nitrogen Transformation Test
- Transformation in soil
- PEC-Refinement
- Metabolite studies

Depending on the MoA, a tailored ERA might be necessary
Data Requirement for Pharmaceuticals

Guideline on the environmental risk assessment of medicinal products for human use
(EMEA/CHMP/SWP/4447/00)  (Came into effect 01. December 2006)

Table 3: Physical-chemical, fate and effects studies recommended in Phase II Tier A

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Recommended Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adsorption - Desorption Using a Batch Equilibrium Method</td>
<td>OECD 106/ OECD 121/OPPTS 835.1110*</td>
</tr>
<tr>
<td>Ready Biodegradability Test</td>
<td>OECD 301</td>
</tr>
<tr>
<td>Aerobic and Anaerobic Transformation in Aquatic Sediment Systems</td>
<td>OECD 308</td>
</tr>
<tr>
<td>Algae, Growth Inhibition Test</td>
<td>OECD 201</td>
</tr>
<tr>
<td>Daphnia sp. Reproduction Test</td>
<td>OECD 211</td>
</tr>
<tr>
<td>Fish, Early Life Stage Toxicity Test</td>
<td>OECD 210</td>
</tr>
<tr>
<td>Activated Sludge, Respiration Inhibition Test</td>
<td>OECD 209</td>
</tr>
</tbody>
</table>

* One study is generally sufficient

Table 5: Terrestrial fate and effects studies recommended in Phase II Tier B:

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Recommended Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic and anaerobic transformation in soil</td>
<td>OECD 307</td>
</tr>
<tr>
<td>Soil Micro organisms: Nitrogen Transformation Test</td>
<td>OECD 216</td>
</tr>
<tr>
<td>Terrestrial Plants, Growth Test</td>
<td>OECD 208</td>
</tr>
<tr>
<td>Earthworm, Acute Toxicity Tests</td>
<td>OECD 207</td>
</tr>
<tr>
<td>Collembola, Reproduction Test</td>
<td>OECD 232</td>
</tr>
</tbody>
</table>
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Veterinary Medicinal products assessed according to VICH Guideline

Phase I

- Decision tree
- Exposure assessment
- Comparison with trigger values to identify those products, for which a Phase II assessment is required

- No exposure – no further assessment
Veterinary Medicinal products assessed according to VICH Guideline

**Phase I**
- Decision tree
- Exposure assessment
- Comparison with trigger values to identify those products, for which a Phase II assessment is required

- No exposure – no further assessment

**Phase II**
- Base data set
- Refinement of information on fate and effects

**Tier A**
- $\text{PEC}_{\text{SOIL}} \geq 100 \, \mu g/kg$

**Tier B**
- $\text{PEC}_{\text{Discharge, aquaculture}} \geq 1 \, \mu g/l$

**Tier C**
- Parasitcides for pasture animals and aquaculture
- Substances of high concern, e.g. EDs

**Non-OECD tests, e.g. field tests**
VICH Guideline – Phase II Tier A Testing

• Physical- chemical properties

• Tier A environmental fate studies and PEC calculation

• Tier A effects testing
  aquatic effect studies (short term)
  terrestrial effect studies

• Risk Assessment at Tier A
  - Soil
  - Water (Direct entry and runoff)
  - Dung
Data Requirement for Pharmaceuticals

# VICH Guideline – Phase II Tier A Testing

## Table 1. Physical-chemical Properties Studies at Tier A

<table>
<thead>
<tr>
<th>Study</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Solubility</td>
<td>OECD 105</td>
</tr>
<tr>
<td>Dissociation Constants in Water</td>
<td>OECD 112</td>
</tr>
<tr>
<td>UV-Visible Absorption Spectrum</td>
<td>OECD 101</td>
</tr>
<tr>
<td>Melting Point/Melting Range</td>
<td>OECD 102</td>
</tr>
<tr>
<td>Vapour Pressure*</td>
<td>OECD 104</td>
</tr>
<tr>
<td>n-Octanol/Water Partition Coefficient **</td>
<td>OECD 107 or 117</td>
</tr>
</tbody>
</table>

## Table 2. Environmental fate studies at Tier A

<table>
<thead>
<tr>
<th>Study</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soil Adsorption/Desorption*</td>
<td>OECD 106</td>
</tr>
<tr>
<td>Soil Biodegradation (route and rate)**</td>
<td>OECD 307</td>
</tr>
<tr>
<td>Degradation in aquatic systems**</td>
<td>OECD 308</td>
</tr>
<tr>
<td>Photolysis (optional)</td>
<td>Seek regulatory guidance***</td>
</tr>
<tr>
<td>Hydrolysis (optional)</td>
<td>OECD 111</td>
</tr>
</tbody>
</table>

## Table 3. Aquatic effects studies at Tier A

<table>
<thead>
<tr>
<th>Medium</th>
<th>Studies</th>
<th>Toxicity endpoint</th>
<th>AF</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freshwater</td>
<td>Algal growth inhibition*</td>
<td>EC₅₀</td>
<td>100</td>
<td>OECD 201</td>
</tr>
<tr>
<td>Freshwater</td>
<td><em>Daphnia</em> immobilization</td>
<td>EC₂₀</td>
<td>1000</td>
<td>OECD 202</td>
</tr>
<tr>
<td>Freshwater</td>
<td>Fish acute toxicity</td>
<td>LC₂₀</td>
<td>1000</td>
<td>OECD 203</td>
</tr>
<tr>
<td>Saltwater</td>
<td>Algal growth inhibition</td>
<td>EC₅₀</td>
<td>100</td>
<td>ISO 10253</td>
</tr>
<tr>
<td>Saltwater</td>
<td>Crustacean acute toxicity</td>
<td>EC₅₀</td>
<td>1000</td>
<td>ISO 14669</td>
</tr>
<tr>
<td>Saltwater</td>
<td>Fish acute toxicity</td>
<td>LC₄₀</td>
<td>1000</td>
<td>Seek regulatory guidance</td>
</tr>
</tbody>
</table>

If applicable

## Table 4. Terrestrial effects studies at Tier A

<table>
<thead>
<tr>
<th>Study</th>
<th>Toxicity endpoint</th>
<th>AF</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen Transformation (28 days)*</td>
<td>≤ 25% of control</td>
<td>**</td>
<td>OECD 216</td>
</tr>
<tr>
<td>Terrestrial plants</td>
<td>EC₅₀</td>
<td>100</td>
<td>OECD 208</td>
</tr>
<tr>
<td>Earthworm Subacute/reproduction</td>
<td>NOEC</td>
<td>10</td>
<td>OECD 220 / 222</td>
</tr>
</tbody>
</table>

## Table 5. Additional effects studies recommended for endo/ectoparasiticides used for pasture treatments at Tier A

<table>
<thead>
<tr>
<th>Study</th>
<th>Toxicity endpoint</th>
<th>AF</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dung fly larvae</td>
<td>EC₅₀</td>
<td>100</td>
<td>Seek regulatory guidance*</td>
</tr>
<tr>
<td>Dung beetle larvae</td>
<td>EC₅₀</td>
<td>100</td>
<td>Seek regulatory guidance*</td>
</tr>
</tbody>
</table>
Summary - Data Requirement according to the Guidelines

Both guidelines are quite strict regarding the data requirement for an Environmental Risk Assessment

Accepted are:
- Study reports according to OECD guidelines
- Literature of a similar quality level

Not accepted is:
- Read Across
- AOP
- Extrapolations
- QSAR
- Modelling e.g. Fish Plasma Model
- Fish Embryo Test (OECD 236) as a replacement of the Fish Acute Test (OECD 203)
- .....
Data sets are not complete for many substances especially for substances already on the market before 2006

1285 APIs of environmental relevance in Germany, currently in use (no vitamins, proteins etc.)

<table>
<thead>
<tr>
<th>API group</th>
<th>Complete Aquatic Data Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasiticides</td>
<td>4 %</td>
</tr>
<tr>
<td>Contrast Agents</td>
<td>5 %</td>
</tr>
<tr>
<td>Neuroactive Substances</td>
<td>9 %</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>10 %</td>
</tr>
<tr>
<td>Vascular / Cardiac System</td>
<td>11 %</td>
</tr>
<tr>
<td>Various</td>
<td>12 %</td>
</tr>
<tr>
<td>Antimycotics</td>
<td>13 %</td>
</tr>
<tr>
<td>Analgetics / Anaesthetics</td>
<td>14 %</td>
</tr>
<tr>
<td>Endocrine Active Substances</td>
<td>15 %</td>
</tr>
<tr>
<td>Antineoplastics</td>
<td>26 %</td>
</tr>
<tr>
<td>Alimentary / Metabolic System *</td>
<td>33 %</td>
</tr>
<tr>
<td>Virostatics</td>
<td>38 %</td>
</tr>
</tbody>
</table>

* antidiabetics, lipid regulators, laxatives

Schwarz et al. 2018, SETAC Rome
Data Requirement for Pharmaceuticals

**Data sets are not complete for many substances**
especially for substances already on the market before 2006

1285 APIs of environmental relevance in Germany, currently in use
(no vitamins, proteins etc.)

- Metformin
- Ibuprofen
- Diclofenac
- Carbamazepine
- Contrast agents (e.g. garbapentin)
- Several antibiotics
- ....

Schwarz et al. 2018, SETAC Rome

Dataset with no or incomplete data sets include “blockbuster” like

- > 30% of the pharmaceutical consumption in Germany in 2015
Summary - Data Requirement according to the Guidelines

- The guidelines are asking for OECD studies. Read Across and extrapolations from *in vitro* or even more *in silico* calculation is not foreseen.


- Every applicant has to conduct own studies or submit a written consent from the originator.

* A substance based monographic system, comparable to the e.g. Plant Protection Products and a system similar to the REACH regulation (SIEF) is not accepted by the pharmaceutical companies and at the moment legally not foreseen.
The challenge: Do pharmaceuticals present a risk to the environment, and what needs to be done to answer the question?

Although human pharmaceuticals are currently considered as emerging contaminants, many have been present in the aquatic environment for decades. Two facts make pharmaceuticals in the environment an issue of concern. One is that there are a few thousand different pharmaceuticals, and the other is that all of them are biologically active, at least in humans. These 2 facts lead us, in turn, to the 2 key unresolved issues related to pharmaceuticals in the environment. First, how should we conduct a prioritization exercise to identify those pharmaceuticals likely to be of the greatest environmental risk? Second, are typical environmental concentrations of those pharmaceuticals anywhere close to the concentrations that produce adverse effects in ecotoxicity tests?

John P. Sumpter
Data Requirement for Pharmaceuticals

Extrapolations outside of regulatory requirements

- Extrapolations outside of regulatory requirements
- QSAR
- Fish Embryo Test
- Drug target Orthologues
- Gene expression analysis
- Pharmacological studies
- Fish Plasma Modell
- Ecotoxicological tests
- AOP Wiki
- QSAR

Diagram showing relationships between different data requirements and regulatory tests.
Intelligence-led Assessment of Pharmaceuticals in the Environment (iPiE)

- Prioritize the environmental testing requirements for pharmaceuticals, which are already on the market, but currently lack sufficient environmental information
- Assess environmental risk earlier in the development of new human-use pharmaceuticals

By using information from existing datasets on environmental fate and effects of APIs, toxicological studies, pharmacological mode of action and in silico models
Participants

EFPIA (European Federation of Pharmaceutical Industry and Associations)

• AstraZeneca AB, Sweden
• Bayer AG, Germany
• Boehringer Ingelheim International GmbH, Germany
• Bristol-Myers Squibb Company, USA
• Eli Lilly and Company, Ltd., United Kingdom
• F.Hoffmann-La Roche Ltd, Switzerland
• GlaxoSmithKline plc, United Kingdom
• Janssen Pharmaceutica NV, Belgium
• Merck Sharp & Dohme, Corp., USA
• Novartis Pharma AG, Switzerland
• Pfizer Limited, United Kingdom
• Sanofi Recherche & Développement, France
• TEVA Pharmaceutical Industries Ltd, The Netherlands

Universities, Research organisations, Public bodies, non-profit groups

• German Environment Agency, Germany
• Fundació Institut Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain
• Helmholtz Centre for Environmental Research GmbH, Germany
• Liverpool John Moores University, United Kingdom
• Stichting Katholieke Universiteit Nijmegen, The Netherlands
• Universitat Pompeu Fabra, Barcelona, Spain
• University of Exeter, United Kingdom
• University of York, United Kingdom

SMEs

• ECT Oekotoxikologie GmbH, Germany
• Molecular Networks GmbH, Germany
• Synapse Research Management Partners S.L., Spain
• Lhasa Limited, Leeds, United Kingdom
How to achieve this?

- Environmental fate, ecotoxicological effects, and physicochemical information has been collected from industry reports and entered into a database.
- Models development to estimate concentrations of pharmaceuticals in surface waters, sediments and soils across Europe.
- Models development for predicting effects of pharmaceuticals on aquatic organisms.
- Software has been developed to allow the database to be searched and predictive models to be run.
**Fish Plasma Model**
(Hugget et al. 2004)

- A theoretical model aiming to assess whether an API present in the environment is likely to have an effect in fish
- Most human drug targets are conserved in fish
- Assumption: A pharmacological effect in fish will be seen at similar plasma concentrations (biological read-across)
Fish Plasma Model
(Hugget et al. 2004)

Limitations

• For antimicrobial (antifungal, antiviral or antibacterial) APIs the drug target is not present in human and fish. The observed ecotoxicological effects in fish are expected to be caused by non-target-related side effects.  
  → FPM human to fish model should be applied

• For anticancer drugs side effects in humans are acceptable  
  → Results not transferable to effects in fish

• Most pharmaceuticals are ionisable  
  → pH adjustment is critical

FPM is a theoretical read across concept that is based on simplified assumptions of underlying complex processes
Is the Fish Embryo Test (OECD 236) suitable to replace the Fish Acute Test (OECD 203) in the assessment of pharmaceuticals?

Belanger, S. E. et al. (2013). *E To& C* 32(8), 1768-1783
Is the Fish Embryo Test (OECD 236) suitable to replace the Fish Acute Test (OECD 203) in the assessment of veterinary pharmaceuticals?

“Analysis of the relevance and adequateness of using Fish Embryo Acute Toxicity (FET) Test Guidance (OECD 236) to fulfil the information requirements and addressing concerns under REACH”
Conclusions

• Experiments assessing the effects of pharmaceuticals at higher levels of biological organisation are largely lacking, while insight in these effects are needed for a proper risk assessment.

• The guidelines are clearly asking for OECD like studies. Read Across and extrapolations from in vitro or even more in silico calculation is not foreseen.

• Extrapolation from in vitro experiments, Read Across, etc.. are not sufficient validated to be used as a replacement or failed to be generally used for pharmaceuticals.
Thank you very much for your attention

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