Environmental Risk Assessment of Pharmaceuticals

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Environmental Risk Assessment of Medicinal Products for Human Use

Replacement of Chlorofluorocarbons (CFCs) in metered dose inhalation products
Entry Paths into the Environment

Entry paths into the environment for most medicinal products when prescribed to patients

Air

- Excretion
  - Sewage
    - Sewage treatment plant
      - Soil
        - Surface water
          - Ground water
            - Drinking water
      - Excretion
    - Incineration
      - (Air)
  - Storage
  - Disposal
    - Waste
      - Landfill site
        - Storage
      - Incineration
        - (Air)
The environmental impact should be assessed and, on a case-by-case basis, specific arrangements to limit it should be envisaged. In any event this impact should not constitute a criterion for refusal of a marketing authorisation.

The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:

- Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.
- Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment.
<table>
<thead>
<tr>
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<tr>
<td>Transmission to the CPMP</td>
<td>January 2001</td>
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<tr>
<td>Release for Consultation</td>
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<td>July 2001</td>
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<td>June 2003</td>
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<td>Adoption by CHMP</td>
<td>01 June 2006</td>
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<td>Date for Coming into Effect</td>
<td>01 December 2006</td>
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The CHMP Guideline

CHMP – Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (CHMP/SWP/4447/00)

- Legislative basis: Article 8(3) of Directive 2001/83/EC, as amended

- An ERA is **REQUIRED** for all new MAAs for a medicinal product through a centralised, mutual recognition, decentralised or national procedure.
The CHMP Guideline

✓ Scope

❖ Exemptions

• Vitamins
• Electrolytes
• Amino acids, peptides and proteins
• Carbohydrates and lipids
• Herbals
• Vaccines

Q: ERA needed for peptides?
The CHMP Guideline

✓ Scope

• **NOT** to risks arising from the synthesis or manufacture of medicinal products.

• Does **NOT** apply to GMO-derived medicinal products (EMEA/CHMP/BWP/135148/04)

• Radio-pharmaceutical precursors and radio-pharmaceuticals note additional requirements on emission standards (Dir 96/29/Euratom and 97/43/Euratom)
## Step-Wise Approach

<table>
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<tr>
<th>Stage in regulatory evaluation</th>
<th>Stage in risk assessment</th>
<th>Objective</th>
<th>Method</th>
<th>Test /Data requirements</th>
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<td>Pre-screening</td>
<td>Estimation of exposure</td>
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<td>Consumption data, logK_{OW}</td>
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<td>Screening</td>
<td>Initial prediction of risk</td>
<td>Risk assessment</td>
<td>Base set aquatic toxicology and fate</td>
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<tr>
<td>Phase II Tier B</td>
<td>Extended</td>
<td>Substance and compartment-specific refinement and risk assessment</td>
<td>Risk assessment</td>
<td>Extended data set on emission, fate and effects</td>
</tr>
</tbody>
</table>
Phase I

- In phase I, the estimation should be based only on the **drug substance**, irrespective of its route of administration, pharmaceutical form, metabolism and excretion.
- With reference to the OSPAR Convention, drug substances with a $\log K_{ow} > 4.5$ should be screened, in a step-wise procedure, for persistence, bioaccumulation and toxicity.
- In Phase I the PEC calculation is restricted to the **aquatic compartment**.
The *OSPAR Convention*

- OSPAR Commission for the Protection of the Marine Environment of the North-East Atlantic
- Concern about whether some EC directives (2001/83/EC and others) contain appropriate provisions to ensure the risk assessment under them take adequately account of possible impacts on the marine environment.
Phase I

Calculation of the Predicted Environmental Concentration (PEC)

\[ PEC_{\text{SURFACE WATER}} = \frac{\text{DOSE}_{\text{ai}} \times F_{\text{pen}} \times WASTE_{\text{Winhab}} \times \text{DILUTION}}{\text{DILUTION}} \]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum daily dose</td>
<td>( \text{DOSE}_{\text{ai}} )</td>
<td></td>
<td>mg\text{*inh}^{-1}\text{d}^{-1}</td>
</tr>
<tr>
<td>Market penetration</td>
<td>( F_{\text{pen}} )</td>
<td>0.01 (default)</td>
<td></td>
</tr>
<tr>
<td>Amount waste water</td>
<td>( WASTE_{\text{Winhab}} )</td>
<td>200 (default)</td>
<td>L\text{*inh}^{-1}\text{d}^{-1}</td>
</tr>
<tr>
<td>Dilution factor</td>
<td>( \text{DILUTION} )</td>
<td>10 (default)</td>
<td></td>
</tr>
<tr>
<td>Predicted concentration</td>
<td>( PEC_{\text{SURFACE WATER}} )</td>
<td>(OUTPUT)</td>
<td>mg\text{L}^{-1}</td>
</tr>
</tbody>
</table>

Phase I

The initial calculation of $\text{PEC}_{\text{SURFACE WATER}}$ assumes:

- A fraction of the overall market penetration ($F_{\text{pen}}$).
- The predicted amount used per year is evenly distributed over the year and throughout the geographic area.
- The sewage system is the main route of entry of the drug substance into the surface water.
- There is no biodegradation or retention of the drug substance in the STP.
- Metabolism in the patient is not taken into account.
Phase I

Action limits

✓ $\text{PEC}_{\text{SURFACEWATER}} < 0.01 \, \text{µg/L}$
  and no other environmental concerns apparent
  ⇒ Assume that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients

✓ $\text{PEC}_{\text{SURFACEWATER}} \geq 0.01 \, \text{µg/L}$
  ⇒ Phase II environmental fate and effect analysis
Phase IIA

Tier A – Considerations

✓ Aquatic effect studies

- Standard long-term toxicity test set on fish, daphnia and algae
- Substances with anti-microbial activity
Phase IIB

Tier B – Considerations

☑ Several options to refinement of PEC and PNEC for the parent compound and/or relevant metabolites (≥ 10% of amount excreted)

☑ Environmental transformation, when relevant

☑ Information from refined and expanded data set
  ❖ Route(s) of excretion and metabolites
  ❖ Long-term toxicity
  ❖ Microbial inhibition
  ❖ Biodegradability
Labelling

✔ Labelling should generally aim at minimising the quantity discharged into the environment by appropriate mitigation measures.

✔ PIL: Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

✔ Additional labelling should be employed only when warranted (e.g. radioactive isotope preparations or medicines concentrated in devices) in which circumstances the measures to be taken should be practical and realistic given the anticipated use of the product.
The contraceptive patch product XY contains 0.75 mg ethinyl estradiol and 6.0 mg norelgestromin hormones in a single patch. The gradual release of hormones over the course of each week (approximately 20 µg/day ethinyl estradiol and 150 µg/day norelgestromin) act much like contraceptive pills do.

Residual amount ~ 80%
Disposal frequency of drugs in the household

- 42% promptly
- 21% half-yearly
- 18% yearly
- 12% every 2-5 years
- 5% less than 5 years
- 2% unknown

www.start-project.de
Unused Medicines
Disposal over the water-closet?
Disposal of tablets over the water-closet

- Yes, always - 1.0%
- Yes, frequent – 2.1%
- Yes, sometimes – 6.8%
- Yes, rare – 5.8%

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Disposal of liquid drugs over the water-closet

- Yes, always – 10.2%
- Yes, frequent – 8.3%
- Yes, sometimes – 13.1%
- Yes, rare – 11.8%

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Replacement of Chlorofluorocarbons (CFCs) in metered dose inhalation products

HFA 134 A / HFA 227

- No significant pharmacological effects
- Less cardiac sensitisation than CFC's
- No significant biotransformation
- Chronic toxicity, high safety margin
- Reprotoxicity, no special risk
- Genotoxicity, negativ
- Carcinogenicity, negativ
European Strategy for Phaseout of CFCs in MDIs

Members of the ad hoc working group

- European Commission (DG III and DG XI)
- Management Committee of Member States
- European Federation of Pharmaceutical Industries Associations (EFPIA)
- International Pharmaceutical Aerosol Consortium (IPAC)
- European Chemical Industry Council (CEFIC)
- Standing Committee of European Doctors
- European Federation of Asthma and Allergy Association (EFA)
- Further Experts
European Strategy for Phaseout of CFCs in MDIs

'essential uses'

• it is necessary for the health, safety or is crucial for the functioning of society and

• there are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of environment and health
European Strategy for Phaseout of CFCs in MDIs

Categories

A  Short acting beta agonist bronchodilators e.g. salbutamol terbutaline, fenoterol

B  Inhaled Steroids e.g. beclomethasone, budesonide, fluticasone

C  Non Steroidal anti-inflammatories e.g. cromoglycate, nedocromil

D  Anticholinergic bronchodilators e.g. ipratropium bromide

E  Long acting beta agonists bronchodilators e.g. salmeterol, eformoterol

F  Combination drugs
European Strategy for Phaseout of CFCs in MDIs

The need for MDIs

- 25 million patients with asthma in Europe
- 16000 deaths per year in Europe
- 80% of prescribed inhalers are MDIs
European Strategy for Phaseout of CFCs in MDIs

Education programme

Post-marketing surveillance

Transition is not optional

• Doctors, nurses and pharmacists should be prepared to help patients

• During a period of 12 months, the CFC product and the CFC-free alternative are both available
European Strategy for Phaseout of CFCs in MDIs

Conclusion

- Stepwise reduction of CFCs
- Temporary exemption ('essential use')
- European strategy for phaseout of CFCs
- Two CFC replacement have been developed
- Reformulation needs 'bridging studies'
Acknowledgements

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Back-Up Slides (reference)
## Abbreviations

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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
</tr>
<tr>
<td>CSTEE</td>
<td>Scientific Committee on Toxicity, Ecotoxicity and the Environment (European Commission)</td>
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<td>EMEA</td>
<td>European Medicines Agency</td>
</tr>
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<td>ERA</td>
<td>Environmental Risk Assessment</td>
</tr>
<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
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<tr>
<td>GLP</td>
<td>Good Laboratory Practise</td>
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<td>ISO</td>
<td>International Organization for Standardization</td>
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<tr>
<td>MAA</td>
<td>Marketing Authorisation Application</td>
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<tr>
<td>OECD</td>
<td>Organization for Economic Co-operation and Development</td>
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<tr>
<td>PIL</td>
<td>Patient Information Leaflet</td>
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<tr>
<td>PEC</td>
<td>Predicted Environmental Concentration</td>
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<tr>
<td>PNEC</td>
<td>Predicted No Effect Concentration</td>
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<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>STP</td>
<td>Sewage Treatment Plant</td>
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<td>SWP</td>
<td>CHMP Safety Working Party</td>
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<td>TGD</td>
<td>Technical Guidance Document</td>
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Regulatory References

CHMP – Guideline on Environmental Risk Assessment for Human medicinal Products containing, or consisting of, genetically modified organisms (GMOs) (EMEA/CHMP/BWP/135148/04)

CHMP – Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (CHMP/SWP/4447/00) (finalisation expected)

Common Technical Document, Module 1.6 (EU)

Council Directives 96/29/Euratom and 97/43/Euratom (Radiopharmaceuticals)


EMEA - Procedure for European Union Guidelines and Related Documents within the Pharmaceutical Legislative Framework (EMEA/P/24143/2004)

Notice to Applicants (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm)
Regulatory References


**OECD** - Chemicals Testing – Guidelines ([http://www.oecd.org/department/0,2688,en_2649_34377_1_1_1_1_1_1,00.html](http://www.oecd.org/department/0,2688,en_2649_34377_1_1_1_1_1_1,00.html))


The European Union System for the Evaluation of Substances (**EUSES**) ([http://ecb.jrc.it](http://ecb.jrc.it))
Guideline Note on Fpen

Fpen

A 95 percentile of 0.954% was calculated as the default penetration factor (Fpen). It is proposed to use a Fpen of 0.01 (1%) in the risk assessment.

The penetration factor (Fpen) represents the proportion of the population being treated daily with a specific drug substance. The default penetration factor was derived from a wide range of individual market penetration factors, which were calculated as follows:

$$\text{Fpen} [\%] = \frac{\text{consumption [mg*year}^{-1}] \times 100}{\frac{\text{DDD [mg*d}^{-1}*\text{inhab]} \times \text{inhabitants [inhab]} \times 365 \text{ d*year}^{-1}}{}}$$

The following data were used:

- Institut für Medizinische Statistik, Frankfurt/M., (IMS Health): IMS Health maintains a data bank “Chemical Country Profil” containing statistics for annual German consumption of about 2700 drug substances. This database was considered representative for the drug consumption in the European Union.

- Defined daily dose values (DDD) values of the World Health Organization (WHO). In total DDD-values for about 1450 drug substances were available.

- German population: 82 012 000 inhabitants in 2001

For the evaluation of the market penetration factor about 800 drug substances were taken into account. Those substances were established on the German market in 2001 and a DDD-value was available.

(18) The environmental impact should be assessed and, on a case-by-case basis, specific arrangements to limit it should be envisaged. In any event this impact should not constitute a criterion for refusal of a marketing authorisation.
Directive 2001/83/EC, as amended: Art 8 (3)

- The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:
  - (ca) Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.
  - (d) Description of the manufacturing method.
  - (e) Therapeutic indications, contraindications and adverse reactions.
  - (f) Posology, pharmaceutical form, method and route of administration and expected shelf life.
  - (g) Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment.

...
Directive 2001/83/EC, as amended: Art 10(1) (Definition of “generic”)

- By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.

- A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product.

- The first subparagraph shall also apply if the reference medicinal product was not authorised in the Member State in which the application for the generic medicinal product is submitted. In this case, the applicant shall indicate in the application form the name of the Member State in which the reference medicinal product is or has been authorised. At the request of the competent authority of the Member State in which the application is submitted, the competent authority of the other Member State shall transmit within a period of one month, a confirmation that the reference medicinal product is or has been authorised together with the full composition of the reference product and if necessary other relevant documentation.

- The ten-year period referred to in the second subparagraph shall be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.
EU Guidelines

✓ What is a Guideline?

❖ Community document, which is considered to provide advice to applicants or marketing authorisation holders, competent authorities and/or other interested parties on the best or most appropriate way to fulfil the obligation laid down in the community pharmaceutical legislation.

❖ In the case of scientific guidelines, these may relate to specific scientific issues reflecting a harmonised EU approach and based on the most up-to-date scientific knowledge.

Ref.: EMEA/P/24143/2004
Legal Status of Guidelines

- To be considered as harmonised Community position
- If followed by relevant parties such as applicants, marketing authorisation holders, sponsors, manufacturers and regulators will facilitate assessment, approval and control of medicinal products in the EU.

Nevertheless, alternative approaches may be taken, provided that these are appropriately justified.