KNAPPE
Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters

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“Proceedings of the Expert Workshop on the design of instruments to limit pollution from PPs”

The deliverable authors are responsible for the content

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## Contents

1. **Introduction** ..................................................................................................................... 1  
   1.1 Objectives of the workshop ...................................................................................... 1  
   1.2 Structure of the workshop ...................................................................................... 2  
   1.3 Structure of the proceedings .................................................................................. 2  

2. **Résumé of plenary blocks** ............................................................................................... 3  

3. **Break-out sessions on “Policy Instruments”** ................................................................... 4  
   3.1 Introduction ............................................................................................................... 4  
   3.2 Key questions for discussion ................................................................................... 4  
   3.3 Discussions and conclusions .................................................................................... 5  

Acknowledgements .................................................................................................................. 8  

Annex I:  **Workshop programme** ......................................................................................... 9  
Annex II:  **List of participants in Policy Instruments sessions** .......................................... 10  
Annex III:  **Full list of workshop participants** .................................................................... 11  
Annex IV:  **Presentations** .................................................................................................... 13
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>EMEA</td>
<td>European Medicines Agency</td>
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<tr>
<td>ERA</td>
<td>Environmental Risk Assessment</td>
</tr>
<tr>
<td>KNAPPE</td>
<td>EU Project “Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters”</td>
</tr>
<tr>
<td>PPs</td>
<td>Pharmaceutical products</td>
</tr>
<tr>
<td>PEC</td>
<td>Predicted Environmental Concentration</td>
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</table>
1 Introduction

1.1 Objectives of the workshop

The workshop “Environmental Stewardship of Pharmaceuticals & Policy Instruments” (29/30 April 2008, York, UK) took place in the context of the EU FP6 project KNAPPE (Knowledge and Need Assessment of Pharmaceutical Products in Environmental Waters). More information on the KNAPPE project, which is funded by the European Commission DG Research (Contract No. 036864), is available on [http://www.knappe-eu.org/](http://www.knappe-eu.org/).

The event combined various sets of break-out sessions on different topics, which took place in parallel and shared key plenary blocks:

a) A set of sessions was dedicated to issues of ecopharmacostewardship and ecopharmacovigilance (relevant to workpackage 5 of KNAPPE). The aim was to explore:
   - How the impact of pharmaceutical products (PPs) can be reduced at all stages in their lifecycle
   - Approaches to monitor the potential impacts of a PP on the environment post-authorisation

b) Another set of sessions was dedicated to discussions on the design of policy instruments that can be applied to limit the discharge of PPs into the water environment (relevant to workpackage 3 of KNAPPE).

The detailed programme of the workshop is available in Annex I.

The present deliverable (D3.2) focuses on the outcomes of the workshop relevant to the design of policy instruments to limit pollution from PPs. A separate deliverable (D5.3) has been prepared to report on the outcome of the parallel sessions held on ecopharmacostewardship and ecopharmacovigilance (check [http://www.knappe-eu.org/](http://www.knappe-eu.org/)).

Focus of the workshop on the issue of policy instruments was the exchange of information on strengths and possible shortcomings of current policy approaches used to limit water pollution from PPs. The opportunity was also given to delegates to discuss future options for policy instruments in Europe, such as regulations and economic instruments.

In order to assist participants to prepare for the workshop, an introductory note was prepared and made available prior to the event. This note outlined in brief the key elements and directives of the EU policy framework, which are relevant for current discussions on PPs in the aquatic environment. It also provided a discussion of the current policy framework and its instruments to limit PPs in water, finally, setting out possible questions to be put forward for discussion at the workshop. The introductory note is available online on the KNAPPE project website:


The list of delegates participating in the workshop sessions on “Policy Instruments” is available in Annex II. The full list of delegates attending the York workshop is available in Annex III. Delegates included representatives of the pharmaceutical industry, academia, national and European authorities as well as one NGO.
1.2 Structure of the workshop

Workshop Day 1, 29 April 2008
On Day 1 of the workshop, introductory plenary speeches provided background information on the KNAPPE project with particular reference to workpackages 3 and 5. Plenary presentations were given by Prof. David Taylor (AstraZeneca), Dr. Christian Daughton (US EPA) and Dr. Åke Wennmalm (Stockholm County Council).

Subsequently, two break-out sessions on “Policy Instruments” took place (in parallel to other break-out sessions on ecopharmacostewardship and ecopharmacovigilance topics). The break-out sessions were introduced with a presentation by Ecologic (lead partner of KNAPPE workpackage 3) on the framework of policy instruments to limit the discharge of PPs into European waters, followed by group discussions and information exchange among the participants.

Workshop Day 2, 30 April 2008
On Day 2 of the workshop, a plenary presentation was given by Mr. Jordi Torren Edo (EMEA). This was followed by further break-out sessions on ecopharmacovigilance and ecopharmacostewardship topics (WP5 of KNAPPE).

In the last plenary of the workshop, concluding discussions also included a summarising presentation of discussions during the Day 1 break-out sessions on “Policy Instruments”.

1.3 Structure of the proceedings

This report summarises the main workshop discussions on the issue of policy instruments.

In the following, section 2 gives an overview of the keynote presentations given in the workshop plenary blocks. Section 3 summarises discussions of the break-out sessions on “Policy Instruments”. The Annexes to this report include the complete workshop programme, lists of participants as well as slides of key presentations at the event (plenary presentations as well as the introductory presentation to the sessions on “Policy Instruments”).
2 Résumé of plenary blocks

Day 1

In the first plenary block of the workshop, KNAPPE project partners gave welcoming speeches. Alistair Boxall (CSL/University of York) introduced participants to the general background and aims of the workshop. Richard Greenwood (University of Portsmouth) introduced the topic of ecopharmacovigilance, while Louise Summerton (Green Chemistry Network) introduced the topic of ecopharmacostewardship in the context of workpackage 5 of KNAPPE. Eleftheria Kampa (Ecologic) gave an introduction to workpackage 3 of KNAPPE (Developing cornerstones of EU prevention action to limit discharge of PPs into water) outlining also the workshop objectives related to this workpackage.

Following the introductory presentations, Prof. David Taylor (AstraZeneca) gave a presentation of the industry perspective on ecopharmacostewardship and how the potential environmental impact of pharmaceuticals can be minimised whilst continuing to maximise patient benefit. This presentation provided examples of where the pharmaceutical industry is already working towards environmental sustainability. Practical issues surrounding ecopharmacovigilance were discussed, and an overview of current policy requirements was also given (see detailed slides in Annex IV).

After a first set of break-out sessions, Dr. Christian Daughton (US Environmental Protection Agency) gave a keynote presentation via teleconference, giving a US perspective on the environmental stewardship of pharmaceuticals. His presentation provided an overview of the lifecycle of PPs and summarised the driving forces for source control and pollution prevention, highlighting scientific gaps and needs (see detailed slides in Annex IV).

In the final plenary of Day 1, Dr. Åke Wennmalm (Stockholm County Council) gave a keynote presentation on pharmaceuticals in the environment from the health care perspective. He referred to key environmental aspects in EU pharmaceutical directives as well as to work carried out in Sweden on hazard and risk assessment of PPs in the frame of the Swedish environmental classification system of medicine (see detailed slides in Annex IV).

Day 2

The second day of the workshop started with a keynote plenary presentation by Mr. Jordi Torren Edo (European Medicines Agency, EMEA), who talked about the mandate and role of the EMEA, the authorisation and ERA of PPs highlighting the differences between human and veterinary medicines, pharmacovigilance, the availability problem of medicine as well as the communication of critical information to the public via the European Public Assessment Reports (EPARs) (see detailed slides in Annex IV).

After a final set of break-out sessions, all participants convened in the plenary for final discussions and summing up presentations on the break-out sessions on Policy Instruments, Ecopharmacovigilance and Ecopharmacostewardship.
3 Break-out sessions on “Policy Instruments”

3.1 Introduction

An introductory presentation was given by Eleftheria Kampa (Ecologic) to set the scene on the current European policy framework, which is relevant to discussions on PPs in the aquatic environment (see detailed slides in Annex IV). The presentation was largely based on the results of the first deliverable produced in the context of KNAPPE workpackage 3, providing a state-of-art review of policy instruments to limit the discharge of PPs into European waters. This deliverable is available online on the KNAPPE project website:


Discussions in the sessions on “Policy Instruments” were moderated by Mr. Thomas Dworak (Ecologic Vienna).

3.2 Key questions for discussion

The key questions proposed for discussion were the following:

<table>
<thead>
<tr>
<th>Session I: EU policy framework – Setting the scene</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What does the industry think about the current framework?</td>
</tr>
<tr>
<td>2. Is current EU policy sufficient to protect the environment and European waters from PPs? Where are key gaps in legislation and/or implementation?</td>
</tr>
<tr>
<td>3. Is human health protection adequately considered in EU policy on PPs (issue of chronic intake)? Is any further action needed?</td>
</tr>
<tr>
<td>4. Is further policy needed to link the ERA of PPs more clearly to management actions? How to improve implementation of risk mitigation?</td>
</tr>
<tr>
<td>5. How can the approach of EU medicinal &amp; water protection policy to environmental risk management become more harmonised? Could ERA regulations for PPs be linked to water quality standards?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session II: Design and application of different instruments</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. How to deal with unknown environmental impacts from “old medicine” on the regulatory level? Chances &amp; obstacles?</td>
</tr>
<tr>
<td>7. How can the polluter-pays-principle under the WFD be applied? How to define the “polluter”: industry – doctors – patient – local government?</td>
</tr>
<tr>
<td>8. Which instruments could be used to enforce the polluter-pays-principle?</td>
</tr>
<tr>
<td>9. Which research &amp; knowledge gaps should be addressed in the near future (relevant to socio-economic issues)?</td>
</tr>
</tbody>
</table>
3.3 Discussions and conclusions

The following summarises the main discussions and conclusions of the two break-out sessions on “Policy Instruments” at the York workshop.

### Defining the problem

Initial discussions focused on the question of “whether there is a problem or not” due to the discharge of PPs in water, which is key for any ensuing discussions on possible policy action. The main points can be summarised as follows:

- There is no clear picture yet within industry of potential risks from PPs. However, it cannot be excluded that there might be a risk, which is why the use of the precautionary principle is called for in relevant policy discussions.
- In the same time, some participants suggested that it is important to be sure that the appropriate level of scientific evidence of risk be accumulated before costly precautionary measures are invoked.
- Communication of relevant criteria and more transparency is required for proposed actions, e.g. ”why is carbamazepine proposed for priority substance list?” Further it should be clarified which kind of risk should be given priority (e.g. single pollutant or accumulation). In general, the industry (but also government) need to know what is defined as a problem, before it can give an opinion on what types of PPs are of most concern.
- Other key relevant questions arising were: “Where do we set the limit to start taking action? Where does problem start and end? Is the simple presence of PPs in water already a problem or should we set safety margins?”. Within this context, also rising costs of possible action need to be considered.
- It was also pointed out that we should differentiate between pollution from peak use of PPs (e.g. in cases of flu, when more PPs are released due to extreme events) and pollution from the systematic use of PPs.

### Current policy framework

As far as the current policy framework is concerned:

- The right mechanisms are there already to deal with environmental impacts of PPs. The ERA guidelines and Technical Guidance Documents (TGDs) in Europe were praised as very complete and the most strict in the world.
- Additionally, the EU Water Framework Directive provides an overall framework for water protection from chemicals.
- All in all, the current policy framework is considered to be sufficient, if allowed to operate properly.
- There may be some gaps for particular compounds. If there is a class of compounds that has not been tested at all for environmental risk, it was proposed that a representative compound should be tested.
- Environmental risk assessment (ERA) has to continually improve. In the same time, we should not ignore what we already know; for instance, some studies already exist on chronic exposure effects. However, more information is needed on other issues such as metabolites.
Options for good management practice

Several good management practice options, which should be focus of possible action, were discussed:

- Good prescription practices (e.g. wise use of animal antibiotics in a balanced way for prophylaxis and treatment).
- Environmental classification schemes (such as the one currently run in Sweden).
- Take-back schemes, which are a legal requirement based on EU directives:
  - Take-back schemes are supported by the industry as concept.
  - However, the enforcement of current legislation is still a problem in most countries.
  - An EU guideline on how to set up and operate take-back schemes could further support this measure.
- Procurement and market tenders on the basis of environmental risk criteria: This would involve making large orders of PPs, e.g. by hospitals, based also on environmental criteria.
- Targeted environmental monitoring, e.g. around urban wastewater treatment plants in order to detect risks early. Although there was no general agreement, this was proposed as one possible action.
- Upgrading of wastewater treatment plants:
  - It was commented that although limitation of PPs at source should be our first choice, this would not be enough considering the very large amounts of PPs in circulation already (3000 PPs registered).
  - The upgrade of treatment plants would also bring benefits in terms of reducing other micro-pollutants.
  - However, if action is limited to treatment only (most likely with government financial support), there would be no incentives to change PP release at source.
- Partnerships were also proposed as a good management practice option, e.g. between operators of urban wastewater treatment plants (for whom water pollution with PPs is an “upstream” issue) with pharmacists and doctors in their region to reduce discharge at “source”.

Assessment of options

The various options proposed for future action have to be assessed on the following:

- Environmental benefits.
- Environmental consequences: E.g. upgrading wastewater treatment raises energy demand in the treatment process.
- Costs: This is related to the fact that no action is cost-free and the issue of shifting costs to options that are more acceptable or less acceptable should be considered. It was commented that thinking of possible action “holistically” is important.
- Cost-effectiveness.

Polluter pays principle

The polluter pays principle, which is promoted in the field of water protection across
Europe, was discussed pointing out the following:

- In the case of water pollution from PPs, who should pay for it?
  - There seemed to be agreement that PPs are a societal problem and the cost should be borne by all, not the supplier or the consumer only.
- In terms of economic instruments that could be used to apply this principle, it was proposed that a sewage treatment fee seems to be the less complex solution.
- It was also commented that market stimulating instruments seem to work better than tax-systems due to the creation of advantages (cf. ecolabels, classification systems). For the way forward, the impacts of both approaches need to be assessed in a more detailed way.
- Finally, it was pointed out that there are many other micro-pollutants in water except for PPs. For this reason, a common approach for all micro-pollutants might be useful:
  - It would/should be a societal decision whether to remove all micropollutants from water or not (in most cases, this being a local or national government issue).
  - Although several pollutants would be removed from water, the cost of such additional treatment action could be very high. Relevant costs need to be assessed.

**Further research**

Several areas of further research and future work were identified:

- How to tackle increased PPs in the environment due to population increase & increased consumption? How to ensure that current levels of PP concentrations do not increase further?
- What type of assessment do we need to put PPs on the priority substances list? Should this be based on trends or current concentrations?
- Do take back schemes bring any benefit to the environment? Can this be assessed?
- In general, before applying new policy instruments, much (socio-economic) research is needed to assess the effectiveness of existing management tools.
- What are the costs and benefits of different options? Money should be spent on most effective approaches, which could be take-back schemes, upgraded wastewater treatment and/or additional research.
- Safety levels of PPs in soil (as set in current EU guidelines on environmental risk assessment) may have to be reconsidered, especially in view of new detection findings.
- The evaluation of new drugs might give us some indication & help us reflect back on “old” products with similar modes of action.
- Can we learn more about the behavioural impact of different measures on doctors or vets?
- Finally, research on public risk perception & public risk tolerance would be valuable. This would help us deliver information in a way that is understandable to the public.
Acknowledgements

Many thanks to Thomas Dworak (Ecologic Vienna) for valuable comments on the summary of the workshop sessions on “Policy Instruments”. Thanks also to all participants of the policy sessions for their active contributions and comments as well as to the local organisers of CSL for great coordination and support.

Finally, financial support from DG Research of the European Commission under the Sixth Framework Programme for Research, Technological Development and Demonstration Activities for the Specific Support Action “KNAPPE” (Contract No. 036864) is greatly acknowledged.
**Annex I: Workshop programme**

**Tuesday 29th April**

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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<tbody>
<tr>
<td>09:30</td>
<td>Coach departs from Hotel 53, York City Centre</td>
</tr>
<tr>
<td>10:00</td>
<td>Registration and Coffee</td>
</tr>
<tr>
<td>10:30</td>
<td>Welcome &amp; background to the KANPPE project with particular reference to Work Packages 3 &amp; 5</td>
</tr>
<tr>
<td>11:00</td>
<td>Plenary – <em>Ecopharmacostewardship</em>: Minimising the potential environmental impact of pharmaceuticals whilst continuing to maximise patient benefit</td>
</tr>
<tr>
<td></td>
<td>Prof. David Taylor, Director of Environment and Sustainability, AstraZeneca</td>
</tr>
<tr>
<td>11:35</td>
<td>Parallel Sessions</td>
</tr>
<tr>
<td>11:35</td>
<td>Monitoring strategy scenarios</td>
</tr>
<tr>
<td>12:50</td>
<td>Lunch &amp; Networking</td>
</tr>
<tr>
<td>14:20</td>
<td>Plenary – <em>Environmental Stewardship of Pharmaceuticals</em> - an Overview of Sources, Control, and Science Questions, Dr Christian Daughton, Chief, Environmental Chemistry Branch, US EPA</td>
</tr>
<tr>
<td>14:55</td>
<td>Parallel Sessions</td>
</tr>
<tr>
<td>14:55</td>
<td>Monitoring and Analytical Methodology</td>
</tr>
<tr>
<td>16:10</td>
<td>Summing up: Ecopharmaco-vigilance and –stewardship</td>
</tr>
<tr>
<td>17:00</td>
<td>Plenary – Pharmaceuticals in the environment - from the health care perspective</td>
</tr>
<tr>
<td>17:25</td>
<td>Dr Åke Wennmalm, Environmental Director, Stockholm County Council</td>
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<tr>
<td>Close</td>
<td></td>
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<tr>
<td>18:00</td>
<td>Drinks Reception, Bedern Hall</td>
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</table>

**Wednesday 30th April**

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:30</td>
<td>Coach departs from Hotel 53, York City Centre</td>
</tr>
<tr>
<td>09:00</td>
<td>Arrival and coffee</td>
</tr>
<tr>
<td>09:30</td>
<td>Plenary – Role of the EMEA in the Environmental Risk Assessment for medicines in the EU</td>
</tr>
<tr>
<td>09:30</td>
<td>Mr Jordi Torren Edo, Scientific Administrator, Safety of Veterinary Medicines, European Medicines Agency</td>
</tr>
<tr>
<td>10:05</td>
<td>Parallel Sessions</td>
</tr>
<tr>
<td>10:05</td>
<td>Ecotoxicology identification of relevant information</td>
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<tr>
<td>11:20</td>
<td>Group discussion and Summing up (including policy instrument report and further steps)</td>
</tr>
<tr>
<td>12:30</td>
<td>Lunch &amp; Networking</td>
</tr>
<tr>
<td>Close</td>
<td></td>
</tr>
<tr>
<td>18:00</td>
<td>Coach departs for York City Centre</td>
</tr>
</tbody>
</table>
## Annex II: List of participants in Policy Instruments sessions

<table>
<thead>
<tr>
<th>NAME</th>
<th>INSTITUTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr David Gee</td>
<td>European Environment Agency</td>
</tr>
<tr>
<td>Dr Ake Wennmalm</td>
<td>Stockholm County Council</td>
</tr>
<tr>
<td>Dr Roger Meyerhoff</td>
<td>Eli Lilly &amp; Company</td>
</tr>
<tr>
<td>Dr Les Heelam</td>
<td>Eli Lilly &amp; Company</td>
</tr>
<tr>
<td>Mr Mike Murray</td>
<td>ABPI</td>
</tr>
<tr>
<td>Mr Christopher Drew</td>
<td>SORIS</td>
</tr>
<tr>
<td>Mr Jordi Torren Edo</td>
<td>EMEA, Safety of Veterinary Medicines</td>
</tr>
<tr>
<td>Dr Nicole Adler</td>
<td>German Federal Environment Agency</td>
</tr>
<tr>
<td>Dr Staffan Castensson</td>
<td>Apoteket AB</td>
</tr>
<tr>
<td>Mr Andy Stubbings</td>
<td>EHS Wyeth</td>
</tr>
<tr>
<td>Ms Birgit Mertens</td>
<td>Janssen Pharmaceuticals</td>
</tr>
<tr>
<td>Mr Frank Mastrocco</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Dr Eleftheria Kampa</td>
<td>Ecologic</td>
</tr>
<tr>
<td>Mr Thomas Dworak</td>
<td>Ecologic Vienna</td>
</tr>
<tr>
<td>Mr Jamie Page</td>
<td>Health Care Without Harm</td>
</tr>
</tbody>
</table>
Annex III: Full list of workshop participants

Dr Nicole Adler - Environmental Risk Assessor, Federal Environment Agency
Prof. Maria De Fatima Alpendurada - Director, Iaren-Water Institute of the Northern Region
Dr Katie Barrett - Programme Director, Huntingdon Life Sciences
Dr Steve Binks - Director, Hazard Assessment, GlaxoSmithKline
Mr Steven Bousfield - EHS Advisor, GlaxoSmithKline
Dr Alistair Boxall - Head of Ecochemistry Team, Central Science Laboratory/ University of York
Dr Simon Breeden - Senior Researcher, University of York
Dr Staffan Castensson - Senior Scientist, Apoteket AB
Prof. James Clark - Director, Green Chemistry Centre of Excellence, University of York
Mr James Comerford - PhD student, University of York
Dr Fabien Deswarte - Green Chemistry Associate, University of York
Dr Erica Donner - Research Fellow, Urban Pollution Research Centre, Middlesex University
Mr Christopher Drew - Chief Executive, SORIS
Mr Thomas Dworak - Director, Ecologic Vienna
Mr David Ford - Sustainable Procurement Specialist, PASA (NHS)
Mr Chibuzo Franklin Llogu - International Masters student of Environmental Protection and Agricultural Food Production, Universität Hohenheim
Mr David Gee - European Environment Agency
Mr Jon Goddard - Director, Environment Agency
Mr Anthony Gravell - Technical Specialist, Environment Agency
Dr Richard Greenwood - University of Portsmouth
Dr Melanie Gross - Senior Consultant, Watts and Crane Associates
Dr Les Heelam - Environmental Advisor, Eli Lilly & Co Ltd
Dr David Hollinshead - Associate Director, AstraZeneca
Dr Paul Houeto – Non-clinical assessor, AFSSAPS
Mr Tim Jarvis - Environment Advisor, GlaxoSmithKline
Mr Romain Journal - Environment Engineer, Sanofi-Aventis
Dr Eleftheria Kampa - Fellow, Ecologic
Dr Barbara Kasprzyk-Hordern - Lecturer in Forensic and Analytical Science, University of Huddersfield
Prof. Klaus Kümmerer - Head of Applied Environmental Research Section, Department of Environmental Health Research Section, University Hospital Freiberg
Miss Sarah Lumley-Holmes - Green Chemistry Events Admin Asst, University of York
Ms Alexandra Lux - Researcher, Institute for Social-Ecological Research (ISOE)
Ms Birgit Mertens - Environmental Manager, Janssen Pharmaceutica
Dr Roger Meyerhoff - Senior Research Advisor, Eli Lilly and Company
Dr Graham Mills - Reader, University of Portsmouth
Mr Frank Mostrocco - Director, Environmental Toxicology, Pfizer
Mr Mike Murray - Head of Manufacturing and Environment, ABPI
Mr Adebola A. Oketola - Lecturer, University of Ibadan
Mr Jamie Paige - Executive Director, HCWH
Dr Benoit Roig - Armines -EMA
Dr Jim Ryan - Principal Scientist, Product Environmental Risk Assessments, GlaxoSmithKline
Mr M. Farhad Laman Shaheen - Marketing Director, Skylab Pharma
Mr Busudev Sharma - Secretary of Baglung District, NEFIN
Mr Pasang Sherpa - Chair Person, NEFIN
Dr Rebecca Slack - Environmental Scientist, Institute of Environment and Health, Cranfield University
Mr Edd Smith - Central Science Laboratory
Dr Jürg Oliver Straub - Corporate Safety, Health and Environmental Protection, F. Hoffmann-La Roche Ltd
Mr Andrew Stubbings - Regional Director, EHS Wyeth
Mrs Louise Summerton - Green Chemistry Networks Manager, Green Chemistry Network
Mr Kazi Tariqul - Sales Manager, Skylab Pharma
Prof. David Taylor - Director, Environment and Sustainability Agency
Ms Emma Teuten - Research Fellow, University of Edinburgh
Dr Helen Thompson - Team Leader, CSL
Mr Jordi Torren Edo – Scientific Administrator, Safety of Veterinary Medicines, EMEA
Dr Evelyne Touraud - Armines-EMA
Mr James Treadgold - Imperial College London
Dr Åke Wennmalm - Environmental Director, Stockholm County Council
Mr Ralf Arno Wess - Sales Manager, IBACON GmbH
Dr Rich Williams - Senior Research Fellow, Pfizer Global Research and Development
Annex IV: Presentations

Plenary presentations

• **Prof. David Taylor**, Astrazeneca: "Ecopharmacostewardship: Minimising the potential environmental impact of pharmaceuticals whilst continuing to maximise patient benefit"

• **Dr Christian Daughton**, US Environment Protection Agency: "Environmental stewardship of pharmaceuticals - An overview of sources, control and science questions"

• **Dr Åke Wennmalm**, Stockhom County Council: "Pharmaceuticals in the environment - from the health care perspective"

• **Mr Jordi Torren Edo**, European Medicines Agency: "Role of the EMEA in the environmental risk assessment for medicines in the EU"

Introductory presentation to break-out sessions on Policy Instruments

• **Dr Eleftheria Kampa**, Ecologic: "Framework of policy instruments to limit the discharge of pharmaceutical products into European waters"
Ecopharmacostewardship
Minimising the potential environmental impact of pharmaceuticals whilst continuing to maximise patient benefit.

Product stewardship
- is a principle that directs all participants involved in the life cycle of a product to take shared responsibility for the impacts to human health and the natural environment that result from the production, use, and end-of-life management of the product.
  - The greater the ability of a party to influence the life cycle impacts of a product, the greater the degree of that party’s responsibility.
  - The stakeholders typically include manufacturers, retailers, consumers, and government officials.

OUTLINE
- Where do new drugs come from?
- Towards environmental sustainability
- Towards ‘greener’ pharmacy
- Ecopharmacovigilance?
- Policy Requirements?
The path to a single new medicine

Years

No. of compounds

Up to

10,000

10-15

1-8

1-3

1

First patent application

Clinical trial application

Product licence application

Drug Discovery

Drug Development

Target and lead identification

Lead optimisation

Concept testing

Development for launch

Launch

Clinical Development

Phase I

50-150 people

Phase II

100-200 people

Phase III

500-5,000 people

Phase IV

studies continue

Product life cycle support

Toxicology and pharmacokinetic studies

(absorption, distribution, metabolism, excretion)

Pharmaceutical and analytical development

Process chemistry and manufacturing

Registration and regulatory affairs

Sales and marketing (preparation, promotion, advertising and selling)

The innovation problem

Research Pharma Industry

Projected revenue loss 2010-12 from patent expiry

The Pharmaceutical Industry in Perspective

Generic Pharmaceutical Company

Patent Expiry

Research Pharmaceutical Company

The innovation problem

In the 10 years since 1995 R&D expenditure has trebled whilst success rate has halved.

Research Pharma Industry

Projected revenue loss 2010-12 from patent expiry

OUTLINE

Where do new drugs come from?

Towards environmental sustainability

Towards ‘greener’ pharmacy

Ecopharmacovigilance?

Policy Requirements

Clarke J et al. (2008)
Improving Manufacturing Sustainability
Use of Green Chemistry in process development

Reduction in waste generation (L waste / kg product) over 13 years

Properties of Existing Pharmaceuticals

46 % weren’t P, B or T

Acute Toxicity of the Top 60 APIs
Used in UK - Worst Case PEC/PNEC Ratios

Towards Greener Pharmacy
Framing the question is vital

"We should only develop (bio)degradable drugs!"

"We should be developing drugs that leave lower environment residues"

Towards ‘greener’ pharmacy
Why degradable drugs may not be the answer.

• Rapid biodegradation is often synonymous with liver metabolism.
• This can produce reactive metabolites or oxygenated species that can then cause serious side effects in patients.
• At least 11 drugs have been withdrawn from the market for this reason.
• In order to function, drugs need to have a realistic ‘shelf-life’ and, in most cases, sufficient stability to pass through the stomach.
• Degradable drugs will still be detectable in the environment due to continuous input.

Pseudo Persistence
Time for degradation of a chemical to the last molecule after a single release of one tonne of material, assuming first order kinetics

Towards ‘greener’ pharmacy
The needs of the patient and the environment coincide

• 100% oral absorption
  ✓ Lower emissions from patients
• Diseased receptor specific
  ✓ No impact on healthy receptors
• No effects other than the therapeutic one
  ✓ No non-target effects
• Metabolised in patient to inert substances
  ✓ Releases only inert residues
• Effective in all patients treated
  ✓ Produces lower overall drug usage
Towards ‘greener’ pharmacy
Current drug developments are already leading to reduced potential for environmental impact

• Improved understanding of metabolism and excretion resulting in less drug being used
  • shorter duration of therapy
  • better targeting & delivery
  • increased specificity
  ✓ lower environmental residues

AstraZeneca Tuberculosis Project
Existing TB therapy is 40 yrs old & requires 5 drugs to be taken for 6-8 months
✓ Shortening the duration of therapy to improve patient compliance
✓ Eradicating disease, even latent disease, to reduce the chances of relapse

Desired endpoint: A single drug therapy effective within 4 months.

Human medicines in the 21st Century will leave even smaller environmental residues

• Personalised Medicines
  • Molecular screens combined with clinical data will point to more precise treatment options for each patient sub-group.

• Biopharmaceutical Revolution
  • 1st product 1980, 200+ products already approved. Now 30+% of industry pipeline.
    ✓ High specificity, Low excretion, v. low environmental residues

• Ecopharmacology ?? (‘ab initio’ design of ‘GREEN’ medicines.)
  • Very challenging and requires major advances in knowledge

Attrition in the Drug R&D Process

~100 Discovery Approaches
7,000,000 Compounds Screened
1,001 Screening Hits
12 Candidates
1 Product
12 - 24 Years

“"In medicinal chemistry we’re still fundamentally an observational science. (That should have been obvious given how little math any of us need to know).

We have broad theories, trends, rules of thumb - but none of it is enough to help us very much, and we’re constantly surprised by our data.

That can be enjoyable, if you have the right personality type, but it sure isn’t restful, and a lot of the time it isn’t very profitable, either”

Derek Lowe, (2007)

Exploring Chemical Space
Drugability & Lipinski’s Rule of 5

To determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans

1. Not more than 5 hydrogen bond donors
   • (nitrogen or oxygen atoms with one or more hydrogen atoms)
2. Not more than 10 hydrogen bond acceptors
   • (nitrogen or oxygen atoms)
3. A molecular weight under 500 g/mol
4. A partition coefficient log P less than 5

"Them’s more like guidelines than actual rules"

Capt Barbosa, Pirata of the Caribbean

OUTLINE
✓ Where do new drugs come from?
✓ Towards environmental sustainability
✓ Towards ‘greener’ pharmacy
✓ Ecopharmacovigilance?
✓ Policy Requirements
Ecopharmacovigilance

Theory & Practice

• We already have a process to report suspected adverse reactions of drugs on patients (pharmacovigilance).
• In theory a process to report similar Adverse Reactions of drugs in the environment or non patient populations (ecopharmacovigilance) could be developed.
• This is much more complicated than it appears
• Ecopharmacovigilance may actually not be possible for all practical purposes.

Pharmacovigilance in Practice

• Potential adverse effects are usually reported by patients themselves
• In other words this is a reactive self monitoring process
• Although the exposed population is well supervised and multiple exposure is unlikely the process is not very efficient
• Only a small proportion (1-10%) of adverse effects are thought to be reported by patients, usually relatively acute in their nature
• Data analysis is manpower intensive and may require complex statistical trend analysis to identify effects.
• Many signals of potential adverse effects turn out to be false positives
• Some post approval monitoring trials are now taking place
• This is only possible if a specific risk is already suspected
• Monitoring all potential reactions using clinical studies is not feasible

Differences between Pharmacovigilance and Ecopharmacovigilance

• EXPOSURE
  • Restricted to identifiable number of a single well characterised species
  • Unrestricted: potentially all species in all environments
• DOSE
  • Accurately known since defined by medication regime
  • Regional average is predictable but actual exposure unknown
• OBSERVATION
  • Exposed population under regular supervision
  • Exposed populations monitored irregularly if at all
• CONFOUNDING FACTORS
  • Can usually be identified by discussion with patient
  • A potentially very large and unknown number

Ecopharmacovigilance

Some practical difficulties to be overcome

• Identification of Suspected Adverse Reactions (SARs)
  • Signal to noise ratio
    • Natural variability, disease, predation, climate etc.
  • You only find things if you are looking
    • There are > 1.5m species of plants and animals
• Acute responses vs Chronic responses
• Attribution of SAR to cause
  • There are >30,000 other synthetic chemicals in use
  • Species are exposed to multiple and variable stressors
• Co-ordination
  • Multiplicity of environmental monitoring groups

A Comment on Exposure Monitoring

• Pharmaceuticals can now be detected at pg l-1 concentrations.
• However, this needs highly trained analysts and sophisticated equipment (LC MS/MS) which severely constrains sample throughput.
• Exposure models such as PhATE™ and GREAT-ER are now capable of making worst case predictions of concentrations at catchment scale.
• Experimental data has demonstrated their output to be precautionary
• These models continue to be developed and improved.

Conclusion:
Routine monitoring of pharmaceutical residues in the environment is not precautionary and an unnecessary use of time and resources.

Ecovigilance

A possible way forward?

• Adverse environmental effects can occur at the population level
  • These can be caused naturally or anthropogenically
  • Cause and effect are frequently difficult (impossible) to determine
• Many scientists are involved with ecological monitoring
  • Similar adverse environmental responses are sometimes observed in different locations.
  • There is currently no mechanism for such observations to be shared or recorded.
• A case can be made for a single data collation system
  • This would be the first step to the identification of cause and effect
  • At the EU level this might be a task that the European Environment Agency could fulfil.
Existing EU Policy Instruments

- Directive 2001/83 Article 8(3)b Medicinal products for human use
  - Requires 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.

- Directive 2008/1 Annex 1(4.5) Integrated pollution prevention & control
  - Requires manufacturers of APIs to use BAT to control emissions.

- Directive 2001/83 Article 127b Medicinal products for human use
  - Requires the establishment of collection systems for unused medicines.

  - Member States shall protect, enhance and restore all bodies of surface water, ... with the aim of achieving good surface water status at the latest 15 years after the date of entry into force of this Directive.

Environmental Residues

How low is low enough?

- Drinking water may contain ng L⁻¹ concentrations of pharmaceuticals
  - But to receive a therapeutic dose you need to drink impossible amounts.
  - Metoprolol: DDD is 150 mg, Stockholm DW contains 0.4 ng L⁻¹
  - Need to drink 4 x 10⁸ litres to receive one daily dose.
    - Half an Olympic size swimming pool

- Advanced water treatment may reduce these by 90%
  - Resulting drinking water still contains detectable 40 pg L⁻¹ concentrations
  - Now you need to drink 4 x 10⁹ litres to receive one daily dose.

There may still be uncertainties but safety factors are enormous

- The only way to be certain that there are no pharmaceutical residues in drinking water is not to use pharmaceuticals.

Reducing the uncertainties

- The research based pharmaceutical companies are continuing to explore the remaining uncertainties in this issue.

- AstraZeneca is currently working with industry, academics and regulators to better understand

  - How drugs are removed in wastewater treatment & how this could be improved
  - What happens to drugs in the environment and how this could be better predicted
  - How the ecotoxicology of drugs could be informed by data from mammalian studies
  - How the chronic impacts of ‘atypical’ drugs might be predicted

FOCUSING ON PROTEIN TARGETS AT THE CORE OF MODE-OF-ACTION

ECOTOXICOLOGY: ECETOC CASE STUDIES

Tom Hutchinson (AstraZeneca), Dan Caldwell (J&J), Andreas Hartmann (Novartis), Martin Holt (ECETOC), Duane Huggett (U. North Texas; formerly of Pfizer), Christian Oberwalder (BASF), Frank Mastrocco (Pfizer), Steve Maund (Syngenta) & Don Versteeg (P&G)

SETAC - Porto (2007)

PIE - A problem to be solved? or a solution looking for a problem?

- 1994 PIE emerged as a potential issue
  - Significant data gaps needed filling to enable any risk to be assessed.

- 2008 Substantial progress has been made
  - Consensus is that current residue levels in water pose no significant risk to human health and will not cause short-term impacts on aquatic life.
  - There are, and will continue to be, uncertainties e.g.
    - How do we improve the evaluation of chronic impacts on aquatic life.
    - How do we optimise existing wastewater treatment

- Industry, Regulators and Academia are continuing to improve their understanding of potential issues.

- Existing regulations are capable of managing remaining issues.

- New pharmaceuticals will have a smaller environmental footprint
  - But analytically detectable residues may still be found

- Application of “hard” precaution may lead to untreated patients
Questions?

David Taylor
AstraZeneca Director Environment & Sustainability
Environmental Stewardship of Pharmaceuticals - an Overview of Sources, Control, and Science Questions

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Objectives

➢ Provide an overview of the life cycle of medications.
➢ Focus on the sources and their control.
➢ Highlight the scientific gaps and needs.
➢ Summarize the driving forces for source control and pollution prevention.

Outline

➢ Origins
➢ Sources
➢ Occurrence
➢ Transport
➢ Fate
➢ Exposure
➢ Effects
➢ Stewardship
➢ Monitoring
➢ Risk Communication

Other materials and links are available at the U.S. EPA's PPCPs Web Site:

http://www.epa.gov/ppcp/

US EPA’s Mission:
Protect Human Health and the Environment

• Dual role - provide state-of-the-art scientific research on which regulatory and enforcement actions can then be based.
• A major objective - minimize the impact of stressors (e.g., chemical pollutants) on the environment and human health.
• EPA’s Office of Research and Development (ORD):
  — Approximately 2,000 employees (or 17,000 total)
  — Wide spectrum of scientific backgrounds
  — Interdisciplinary approach to examining environmental issues
  — Risk paradigm is used as a organizing principle
  — No regulatory authority

EPA Notice

Although this work was reviewed by EPA and approved for publication, it may not necessarily reflect official Agency policy.
Published literature continues to expand in breadth and depth.
Numbers of publications have been exponentially increasing since 2003. Literature covers more aspects of the risk paradigm (in particular eco/aquatic toxicology).
No longer possible for individual investigators to keep current with literature. Over 4,000 publications (2008).
http://www.epa.gov/ppcp лит.html
Vastly increased transfer of knowledge throughout the scientific community.
Issue is far-reaching and has many ramifications with respect to our understanding of the world’s relationship with chemicals in general.

PPCPs – has morphed into the much larger issue of "emerging contaminants," a term having a variety of different meanings.
Issue intersects with other categories of pollutants, especially EDCs and nanomaterials (which will be used with increasing frequency in medicine).
Much of what has been learned regarding conventional pollutants is applicable to PPCPs, but some is not.
Significant differences between PPCPs and traditional pollutants across the risk paradigm (origins, occurrence, transport, treatment removal technologies, exposure, effects...).

What are the primary concerns pertinent to exposure outcomes?
“Inappropriate” exposures (e.g., ingestion of medications intended for dermal or intravenous use; fetal exposure to chemotherapeutants)
Risk perception:
- trust in water supplies
- acceptance of water reuse/recycling
Can the significance of potential exposure be evaluated in a holistic manner given that all organisms live in an extremely large, expanding universe of chemicals?

Focus shifting to the role of the individual consumer as a source of pollutants
confined only by where people live or visit
collective significance derives from seemingly insignificant contributions from multitudes of individuals
pollutants originating from substances generally viewed as widely desirable or beneficial, and sometimes essential
wide expanse of distinct chemical entities (thousands of different drugs), many hundreds of which are used routinely worldwide in health-care and for personal care
**Origins**

- human medications: generic and brand name, OTC and prescription
- illicit drugs (comparatively fewer bioactive substances, but perhaps very large quantities)
- veterinary medications - primarily steroids, antibiotics, and anti-inflammatories
- CAFOs (local impacts more measurable but also more limited geographically)
- thousands of distinct APIs formulated into many thousands of commercial products
- personal care products (commercially formulated products exceed 10,000)

**Sources**

- excretion, bathing, and disposal to sewage (and therefore waste treatment facilities) play a central role
- significant percentage of sewage receives minimal or no treatment (septic systems, straightpiping)
- larger numbers can occur (at lower concentrations) in any given watershed compared with regulated pollutants
- possible that exponentially more chemicals will become evident as the limits of analytical detection are further reduced
  - not just parent chemicals, but also a wide array of metabolites (carbamazepine is one example) and degradates, some of which are biologically active; this may multiply the scope of concern by more than several fold

**Occurrence**

- Emerging? There is no reason to believe that PPCPs have not existed in the environment for as long as they have been used commercially.
- PPCPs and other trace ECs demonstrate how we live in a chemical sea
- ubiquitous occurrence but types and relative quantities differ between locales
  - primarily in watersheds receiving treated wastewaters and agricultural areas treated with recycled water or sewage solids
  - constant input via sewerage leads to continual presence: imparts pseudo-persistence for chemicals having ordinarily short half-lives
**Occurrence**

- PPCPs reported to date as routinely occurring in the environment are not necessarily the most important ones. The distinction between target and non-target is very important.
- Many fewer PPCPs detected in finished drinking water, and concentrations are orders of magnitude lower than in treated sewage (usually less than 10-100 ppt).
- Examination of such low concentrations (sub-ppt - ppb) has been made possible solely by advances in analytical chemistry.
- How important are episodic, transient surges in concentrations? Poses problems for discrete samples versus time-weighted averages.

**Transport**

- In general, volatility is not an issue: not subject to global distillation.
- Inhalation is usually only an exposure issue occupationally (medicated feed dust) and perhaps trace levels entrained in repairable mists (showers).
- PPCP removal from sewage and water by conventional treatment techniques ranges widely from near-nil to almost complete (compound-specific).
- Major route of removal from STPs is via sorption to solids (concentrations can extend into ppt, e.g., biosolids).
- Sorption not necessarily predicted by O-W partitioning.
- Biosolids are the primary mechanism for introducing human medications to land (AGRICULTURAL). Environmental life cycle of drugs is extremely complex.
- Drug disposal might be significant with respect to introducing transient, episodic spikes in concentrations at STPs or effluents.

**Pharmacokinetics and Predicting Environmental Fate**

Using carbamazepine (CBZ) as but one example, the following generalities emerge:

- Pharmacokinetics essential to understand complexity of metabolites that can be excreted (CBZ has at least 30 different human metabolites).
- Wide spectrum of metabolites can be created from a single active ingredient.
- Many of these metabolites are excreted and can become pollutants themselves.
- Excreted conjugates can serve as hidden reservoirs of the parent chemical, residues sorbed to sediments and particulates but not measurable.
- Waste and water treatment oxidative technologies, usually used for disinfection (chlorine, ozonation, UV irradiation) can be effective but also can create a wide array of by-products.

**Exposure**

- Pseudo-persistence leads to continual exposure for certain aquatic organisms.
- Exposure concern centers around sewage outfalls and downstream reaches.
- Bioconcentration can occur for certain PPCPs in aquatic life (plants and fish/shellfish).
- Low-level exposure to multiple chemical stressors simultaneously or sequentially.
- Importance of duration and timing of dose (exposure trajectory or history).
- Importance of multiple exposures to stressors with similar MOAs and with different MOAs.
- We live in a chemical sea of continually changing composition - both anthropogenic and naturally occurring chemical stressors.
- Exposure to chemical stressors must be placed into context with exposure to all other non-chemical stressors.
- Acute exposures in special circumstances possible for both humans and wildlife.
Effects

- Except for hormonal agents, unknown what effects might occur from exposure to trace (sub-ppt) levels.
- Minute antibiotic residues not known to select for resistance in ambient environment; no evidence that exposure of bacteria in the environment to trace levels of antibiotics is a major concern.
- Sable effects are a primary concern (e.g., behavioral).
- Additive or interactive (antagonistic, synergistic) effects.
- Multi-Phase MOA: type of effect changes with the dose.
- Hormetic effects (paradoxical dose-response).

Decline of Gyps spp. Vultures in Pakistan & India – Conclusively Linked with Diclofenac

- Beginning in the early 1990s, vultures (especially white-backed vultures such as Gyps bengalensis) experienced dramatic population declines (as great as 95%) in Southern Asia – particularly India and spreading to Pakistan and Nepal.
- Various hypothesized causes ranged from pathogens to pesticides. The causative agent(s) resulted in acute renal failure transformed to renal tissue accumulation of uric acid, leading to death of the breeding population.
- Prof. J. Lindsey Obama (Washington State University) et al. first discovered (in Pakistan) the disease to be linked to the exposure to diclofenac (also known as Diclofenac). The disease caused the death of vultures, resulting in a decline in the population of vultures in Pakistan.
- Diclofenac, primarily a human NSAID, was used in veterinary medicine in certain countries. In India, diclofenac was used for cattle, whose carcasses were a major food source for Gyps.
- Diclofenac seems to be selectively toxic to Gyps spp. versus other carrion-eating raptors.
- Gyps bengalensis are sensitive to diclofenac, which is a nonsteroidal anti-inflammatory drug (NSAID) used in veterinary medicine.
- Other vulture populations, such as Gyps indicus and Gyps africanus, are also affected by diclofenac, leading to population declines.

Animal Euthanasia and Secondary Poisoning of Wildlife

- Various drugs are used to euthanize domestic pets and other animals.
- The principle drug is pentobarbital. High doses are used. Most of the body burden residue escapes excretion and persists indefinitely. The carcass, if not disposed of according to local regulations, can be consumed by scavengers.
- Wilderness areas require special attention and disposal.
- Various hypothesized causes ranged from pathogens to pesticides. The causative agent(s) resulted in acute renal failure transformed to renal tissue accumulation of uric acid, leading to death of the breeding population.
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- Other vulture populations, such as Gyps indicus and Gyps africanus, are also affected by diclofenac, leading to population declines.

Effects (cont'd)

- Significant acute effects for both humans and wildlife are possible in special situations.
- Accumulated leftover drugs awaiting disposal may be responsible for significant human morbidity and mortality.
- Unintended chronic exposure: Concern for human health centers around fetal exposure, especially for APIs not ordinarily intended for use by pregnant women. *Færo words*: Question of exposure via routes never tested (e.g., ingestion of dermal drugs).

Stewardship, Pollution Prevention & Source Control
Drug disposal is a high-profile topic because accumulated household drugs are an acute diversion/abuse issue for humans as well as a major source of unintentional poisonings in children, the elderly, and pets. Very important to the public and local regulators and water industry.

Poisoning and abuse were the driving forces for the 2007 White House ONDCP/EPA guidance on disposal: http://www.whitehousedrugpolicy.gov/drugfact/factsht/proper_disposal.html

Issues surrounding drug disposal are deceivingly complex; in the U.S., the CSA and RCRA pose special challenges.

Need to proceed beyond local drug collection programs (such as take-back events) to achieve a nationwide solution (EPA's OCHP issued grants for two pilot projects in 2007)

Important perspective: unknown as to what fraction of drug residues in the ambient environment are contributed by drug disposal. If all leftover medications were prudently collected, would there be any measurable reduction in environmental residues? The answer probably depends on the API.

Reliable data on leftover drugs is completely lacking (being addressed at EPA-ORD)

Stewardship involves much more than prudent disposal of leftover drugs

Actions taken to reduce PPCPs in the environment will have collateral benefits in also capturing chemicals we are currently not aware of.

Drug disposal - not just an environmental issue, but also an acute human health concern (e.g., poisonings). But further yet, the very fact that excess drugs accumulate and need disposal points to problems in the way health care is administered.
Stewardship, Pollution Prevention & Source Control

- A major objective should be the design of prescribing/dispensing practices that do not lead to the accumulation of leftover or drugs to begin with. Leftover drugs represent wasted medical care resources and sub-optimal therapeutic outcomes.
- MANY other ways to reduce the types and quantities of PPCPs entering the environment (outlined in the “Green Pharmacy”: http://epa.gov/nerlesd1/bios/daughton/green1.pdf)
- Aging water infrastructure means BAT technology can be widely employed.

Environmental Pharmacology
Ecopharmacology
Pharmacovigilance
PharmEcovigilance
Pharmacoenvironmentology

- Extended the focus to the environmental aspects of drugs once they become pollutants, and the stewardship approaches for lessening these impacts

Pharmacovigilance

- "... the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other (possible) drug-related problems.”
- Awareness and practice of many of the aspects of pharmacovigilance (especially that medicinal products could cause undesired effects) had existed for hundreds of years - first formally discussed in the 1700s.
- The term "pharmacovigilance" was coined in France, and the concept was first formally used in the French open literature (1974-1976) - largely prompted by the 1960's thalidomide-pheochromocytoma affair.
- Focus is primarily on undesired effects in humans and animals resulting from their therapeutic/lifestyle treatment.

pharmEcovigilance

- pharmEcovigilance would merge traditional pharmacovigilance with ecopharmacovigilance - encompassing the many dimensions of both ecological and human health.
- Emphasized that human and ecological health are intimately connected.
- Seek to optimize design of the life cycle of drug manufacturing, sale/distribution & usage:
  - prescribe the most effective medications in efficacious minimal doses for each patient
  - dispense in quantities and for durations that ensure patient compliance (full consumption)
  - minimize/esinate the generation of leftover medications — so the need for disposal is avoided.
- Major objectives:
  - minimize impacts on the environment from APIs as pollutants
  - minimize exposure of humans via consumption of APIs "recycled" from the environment (trace residues drinking waters and foods)
  - minimize hazards posed to safety and health from residues or scavenging of medicinal products by humans, pets, and wildlife.

Environmental Stewardship & Pharmaceuticals: U.S. EPA Publications

Many of the principles underlying environmental stewardship and pharmaceuticals (including the concept of the Green Pharmacy) were set forth at the US EPA beginning in 2002:


Outcomes

- Single most important outcome from the focus on PPCPs and EDCs over the last 15 years or so:
  - Catalyzed a sea-change to look past the regulated world of chemicals.
- PPCPs and EDCs have now morphed into the larger issue of so-called “emerging” contaminants.
- PPCPs in the environment demonstrate for the public the connections between the health of ecology and the ecology of health.
- PPCPs as pollutants show the intimate connections between the health of humans and our environment.

Outcomes (cont’d)

- Enhanced focus being placed on problems that have long challenged toxicology: the significance of low-level exposure to multiple chemical stressors.
- Use of PPCPs as tools to solve other problems (e.g., sewage tracers, estimating illicit drug use).
- Catalyzed a nationwide discussion regarding disposal of unwanted medications (e.g., take-backs & mail-backs).
- Fostering recognition in the medical and pharmacy communities that prescribing and dispensing have ramifications for both the environment and for human health.

Drug Disposal: A Major Unknown

- What fractions of drug residues occurring in the ambient environment result from discarding leftover drugs?
  - No studies exist that provide objective data from well-defined populations to support any type of conclusion.
  - Data are needed on the types, quantities, and frequencies with which drugs accumulate as household waste.

Drug Disposal (cont’d)

- First published methodology for cataloging the types and amounts of APIs released to the environment from disposal to sewerage.

New Approach to Mining Data for Types and Quantities of Disposed Drugs

- Coroner cases are those in which the decedent died alone or when there were unusual circumstances regarding the death.
  - Standard definition of coroner cases as used nationally.
  - Population demographics from which coroner cases are derived do not differ from the general population.
- Coroner inventory is the only ready source of accurate data that:
  - Indicates what types of drugs accumulate.
  - Indicates which drugs may result in disposal.
  - Indicates what categories of drugs are actually disposed of (by the coroner).
  - Encompasses all medication – OTC and prescription.

Records Clark County (NV) Coroner

- Based on Clark County Coroner Cases for 13-month period (January 2005 – January 2006)
  - Population: 2 million people
  - 1,623 cases reviewed
  - Approximately 325,000 pills/tablets/capsules disposed into sewage system.
  - Controlled substances/Non-controlled substances
  - Greater than 102,000,000 mg (102 kg) of APIs disposed into the environment.
  - 92% flushed into sewage system.
  - 7% trash disposal.
  - 1% incinerated.

† from unpublished dissertation research of I. Ruhoy, 2008, UNLV.
New Data from Clark County Coroner

- Greater than 600,000 mg of beta-blockers disposed
- Greater than 1,200,000 mg of antimicrobials disposed
- Greater than 11,500,000 mg of analgesics disposed
  - NSAIDs
  - Non-opioids
  - Opioids

*from unpublished dissertation research of I. Ruhoy, 2008, UNLV.*

Coroner Drug Inventories Can Be Used To DETERMINE:

- Types and relative amounts of APIs disposed
- Actual quantities of APIs disposed
- Fraction of APIs disposed by various routes (e.g., sewerage vs. trash)
- Minimum limits on amounts of individual APIs disposed by entire population
- Putative maximum limits on amounts of individual APIs disposed
- Predicted concentrations introduced to WWTPs
- Relative significance of disposal with respect to the overall environmental occurrence of an individual API
- Those APIs for which disposal is insignificant with respect to their overall environmental occurrence
- Those APIs for which disposal might play a significant role in their overall environmental occurrence
- Those medications for which patient compliance rates are low

Coroner Drug Inventories Can Be Used To GUIDE:

- Selection of APIs for targeted monitoring in sewage streams and the environment in specific geographic locales
- Recognition of APIs that are being over-prescribed
- Recognition of medications with poor patient compliance

Questions

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prepared for:

KNAPE workshop on Environmental Stewardship of Pharmaceuticals & Policy Instruments

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prepared: 17 April 2008
Pharmaceuticals in the environment - from the health care perspective

Åke Wennmalm

Environmental Stewardship of Pharmaceuticals & Policy Instruments
April 29-30 2008, York

the health care perspective

Long-term target:
Protect drinking water from contamination with synthetic chemicals

Guiding principle:
All patients should have the right to best available treatment

Pharmaceuticals (ng/L) in three water treatment plants in the Stockholm region, samples taken 2007-04-02

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Plant N intake</th>
<th>Plant L intake</th>
<th>Plant G intake</th>
<th>Plant N outlet</th>
<th>Plant L outlet</th>
<th>Plant G outlet</th>
</tr>
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<tbody>
<tr>
<td>Citalopram</td>
<td>&lt;0.3</td>
<td>1.4</td>
<td>0.5</td>
<td>&lt;0.3</td>
<td>&lt;0.3</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>Atenolol</td>
<td>1.0</td>
<td>0.5</td>
<td>1.5</td>
<td>&lt;0.3</td>
<td>&lt;0.3</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1.1</td>
<td>1.5</td>
<td>2.5</td>
<td>0.3</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1.4</td>
<td>1.4</td>
<td>2.0</td>
<td>0.7</td>
<td>0.2</td>
<td>1.3</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>&lt;0.2</td>
<td>0.4</td>
<td>1.2</td>
<td>0.5</td>
<td>0.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>0.6</td>
<td>0.8</td>
<td>0.7</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Trimeperprim</td>
<td>0.4</td>
<td>&lt;0.3</td>
<td>0.4</td>
<td>&lt;0.3</td>
<td>&lt;0.3</td>
<td>&lt;0.3</td>
</tr>
</tbody>
</table>

Pharmaceuticals in liver from perch caught in the Stockholm region in May, 2007

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Central Stockholm</th>
<th>10 km east</th>
<th>30 km east</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram*</td>
<td>0.1 µg/kg</td>
<td>&lt;0.1 µg/kg</td>
<td>&lt;0.1 µg/kg</td>
</tr>
<tr>
<td>Propoxyphen**</td>
<td>0.25 µg/kg</td>
<td>0.16 µg/kg</td>
<td>&lt;0.1 µg/kg</td>
</tr>
</tbody>
</table>

* recipient levels <1 ng/L
** recipient levels 0.1-0.6 ng/L

a global problem?

<table>
<thead>
<tr>
<th>Sampling position</th>
<th>Number of detected pharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paris</td>
<td>14</td>
</tr>
<tr>
<td>Singapore</td>
<td>8</td>
</tr>
<tr>
<td>Paris</td>
<td>7</td>
</tr>
<tr>
<td>Beijing</td>
<td>6</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>4</td>
</tr>
<tr>
<td>Hamburg, Johannesburg</td>
<td>3</td>
</tr>
<tr>
<td>Brussels, Heidelberg, HongKong, Copenhagen, Lyon, Sophia</td>
<td>2</td>
</tr>
<tr>
<td>Dubai, Düsseldorf, Hamburg (NL)</td>
<td>1</td>
</tr>
<tr>
<td>Manchester, New York, Shipol</td>
<td>0</td>
</tr>
</tbody>
</table>

EU and pharmaceuticals

European Commission

DG SANCO

Environment DG

EMEA

Enterprise and Industry DG

European Parliament

Council
Environmental aspects in the new directive

<table>
<thead>
<tr>
<th>New reality:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental impact should be assessed and, on a case-by-case basis, specific arrangements to limit it should be envisaged.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk ass/environment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>“any risk as regards patients’ health or public health…” (hum.) &quot;any risk of undesirable effects on the environment” (vet.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Re. documentation to be added to the application:</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Evaluation of the potential environmental risks posed by the medicinal product. The impact should be assessed…”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Re. labelling of package:</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Specific precautions relating to the disposal of unused medicinal products…</td>
</tr>
<tr>
<td>Member states shall ensure that appropriate collection systems are in place for medicinal products that are unused or expired.”</td>
</tr>
</tbody>
</table>

This was good but not enough. Also consider

- to provide simple but accurate information to health care staff about environmental effects of pharmaceuticals
- to give doctors (and patients) possibility to a fair choice between medicines with similar effects but different environmental properties
- to provide an incentive for the pharmaceutical industry to develop future medicines with less environmental impact

The Swedish Association of the Pharmaceutical Industry

invited the Medical Products Agency, Apoteket and representatives of the public health care to jointly develop an environmental classification system for human pharmaceutical substances

The international reference group for “the Swedish initiative”

Risk and hazard assessment?!

Biking without brakes = risk (connected to the use of the object)
**Risk Assessment**

PEC = predicted environmental concentration

\[
\text{PEC}_{\text{SURFACEWATER}} = \frac{\text{sold amount of AI}}{\text{amount of water in which AI is diluted}}
\]

PNEC = predicted no effect concentration
(highest concentration not toxic to aquatic organisms)

\[
\frac{\text{PEC}}{\text{PNEC}} < 1 \text{ (good!)} \quad \frac{\text{PEC}}{\text{PNEC}} > 1 \text{ (bad!)}
\]

**Risk Classification**

Use of the medicine has been considered to result in

- insignificant: PEC/PNEC < 0.1
- low: 0.1 - 1
- moderate: 1 - 10
- high: > 10

Environmental risk

**Outcome of the Risk Classification**

A bike without brakes = hazardous
(a property of the object)

**Hazard Assessment**

Persistence:
The substance is
- degraded in the environment
- slowly degraded in the environment
- potentially persistent

Bioaccumulation:
No significant bioaccumulation potential
Potential to bioaccumulation in aquatic organisms

Does the substance fulfill the criteria for PBT and/or vP/vB?
Outcome of the hazard assessment: bioaccumulation

<table>
<thead>
<tr>
<th>Data missing</th>
<th>No significant bioaccumulation potential</th>
<th>Potential for bioaccumulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>180</td>
<td>200</td>
</tr>
<tr>
<td>40</td>
<td>160</td>
<td>140</td>
</tr>
<tr>
<td>60</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td>80</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>100</td>
<td>40</td>
<td>20</td>
</tr>
</tbody>
</table>

an environmental classification according to the Swedish model comprises

- **Risk assessment:**
  - “Use of the substance has been considered to result in low environmental risk”

- **Hazard assessment:**
  - “The substance is slowly degraded in the environment”
  - “No significant bioaccumulation potential”

Application in daily health care of the environmental information on pharmaceuticals

- political target that outlet concentrations and recipient levels of pharmaceuticals should be lower 2011 than 2005
- environmental information on pharmaceuticals available on the web and in printed material
- all doctors and other prescribers regularly undergoing education on environmental effects of pharmaceuticals
- pharmaceutical committees integrate environmental aspects in their evaluation and recommendation reviews
- patient information sheets developed in collaboration with Apoteket AB

Pharmaceuticals in STP inlets and outlets, average concentrations from three major STPs in the Stockholm region, samples taken 2007–09–03

<table>
<thead>
<tr>
<th>Substance</th>
<th>STP Inlet, ng/L</th>
<th>STP Outlet, ng/L</th>
<th>Elimination, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetaminophen</td>
<td>34400</td>
<td>1700</td>
<td>95</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>4360</td>
<td>146</td>
<td>97</td>
</tr>
<tr>
<td>naproxen</td>
<td>2870</td>
<td>360</td>
<td>87</td>
</tr>
<tr>
<td>furosemide</td>
<td>1540</td>
<td>880</td>
<td>43</td>
</tr>
<tr>
<td>ketoprofen</td>
<td>1190</td>
<td>330</td>
<td>73</td>
</tr>
<tr>
<td>atenolol</td>
<td>1090</td>
<td>750</td>
<td>31</td>
</tr>
<tr>
<td>metoprolol</td>
<td>1010</td>
<td>1160</td>
<td>-14</td>
</tr>
<tr>
<td>codeine</td>
<td>870</td>
<td>200</td>
<td>79</td>
</tr>
<tr>
<td>diazepam</td>
<td>485</td>
<td>120</td>
<td>56</td>
</tr>
<tr>
<td>losartan</td>
<td>370</td>
<td>140</td>
<td>62</td>
</tr>
<tr>
<td>tramadol</td>
<td>320</td>
<td>460</td>
<td>-44</td>
</tr>
<tr>
<td>ceftriaxone</td>
<td>220</td>
<td>280</td>
<td>-30</td>
</tr>
<tr>
<td>naproxctoxicol</td>
<td>200</td>
<td>54</td>
<td>73</td>
</tr>
<tr>
<td>sulphamethoxazole</td>
<td>180</td>
<td>75</td>
<td>58</td>
</tr>
</tbody>
</table>

policymaking in the EU; what are the next steps needed?

- risk assessment should include “public health” and “environment”
- information system on pharmaceuticals and environment in all EU countries
- improved techniques for elimination of pharmaceutical residues in sewage treatment plants
- activate EU legislation on recollection systems for unused pharmaceuticals in all member countries
Role of the EMEA in the Environmental Risk Assessment (ERA) for medicines in the EU

Jordi Torren
Safety of Veterinary Medicines, European Medicines Agency (EMEA)

Thanks to Dr Kornelia Greinan and Dr Jean-Marc Vidal

EMEA
- European Medicines Agency
- Established 1995 by legislation, seat in London
- Mandate and role:
  - Scientific evaluations of applications for centralised marketing authorisations
  - Scientific advice
  - Pharmacovigilance
  - Maximum Residue Limits
  - Referrals

Scientific and regulatory guidelines

Authorisation of Medicinal Products in the EU

3 Routes to Authorisation
- Centralised Authorisation Procedure
  - European Commission through the EMEA-CVMP/CHMP
- National Authorisation Procedure
  - National Authorities
- Mutual Recognition/De-centralised Procedure
  - National Authorities coordinated by the Coordination Group for Mutual Recognition and Decentralised Procedures (CMD(v)/CMD(h))

Scope of the centralised procedure for veterinary medicinal products
- Compulsory for growth promoters/yield enhancers and for products developed using: Recombinant DNA or Monoclonal antibody technology/Gene expression
- Optional for products that
  - Contain new active substances
  - Represent significant therapeutic, scientific or technical innovation
  - Are in the interests of animal health at Community level
  - Are immunological products used against diseases subject to Community Control

EMEA
- Scientific Committees:
  - CHMP
  - CVMP
  - COMP
  - HMPC
  - PDCO
- Working Parties of CHMP and CVMP
  - CMD(h) and CMD(v)

Thank you to Dr Kornelia Greinan and Dr Jean-Marc Vidal

Content
- EMEA – mandate and role
- Authorisation of medicinal products
- Environmental Risk Assessment for medicinal products:
  - Pharmacovigilance
- CVMP ERA Working Party
- Availability of medicines
- EPAR (European Public Assessment Report)
- Conclusions
Scope of the centralised procedure for human medicinal products

- "Compulsory" (Art. 3(1) of Regulation (EC) No 726/2004 & its Annex)
  - "Biotech" products: Recombinant DNA technology/ Controlled gene expression/ Monoclonal antibodies
  - "Mandatory Therapeutic Classes": New active substance for: AIDs/ Cancer/ Neurotroph. Disorders/ Diabetes
  - Orphan Designated Medicinal Products
- Optional scope (Art. 3(2) of Regulation (EC) No 726/2004)
  - New Active Substances
  - Significant Innovation
  - Therapeutic Scientific Technical
  - Interest of Patients at Community Level

ERA for Medicinal Products

- Legal requirements for ERA for medicines since beginning of the 90s
- ERA to be conducted in two phases
  - Phase I: screening
  - Phase II: full assessment
- Further investigations possible
- CHMP/CVMP guidelines on environmental risk assessment
- CVMP guidance for pharmaceuticals phase I and II in 1996, superseded by VICH guidelines

ERA for Medicinal Products

- Relevant legislation:
  - Human medicine: Directive 2001/83/EC, as amended
  - Veterinary medicine: Directive 2001/82/EC, as amended
- An ERA is required for all new MAs
- The environmental impact should be assessed and, on a case-by-case basis, specific arrangements to limit it should be envisaged
- ERA not required for renewals
- For type II variations and extensions required when there is an increase in environmental exposure (not required for type I/II variations).
- For human medicines, the ERA is not part of risk/benefit balance and impact should not constitute a criterion for refusal of a marketing authorisation

Step-Wise Approach Human Medicines

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

<table>
<thead>
<tr>
<th>Stage in regulatory evaluation</th>
<th>Stage in risk assessment</th>
<th>Directive</th>
<th>Method</th>
<th>Test Data requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Pre-screening</td>
<td>Estimation of exposure</td>
<td>Measured (MEC)</td>
<td>Consumption data, HoF, etc.</td>
</tr>
<tr>
<td>Phase I Tier A</td>
<td>Screening</td>
<td>Estimation of effects</td>
<td>Risk assessment</td>
<td>Bioavailability, biokinetics, and fate</td>
</tr>
<tr>
<td>Phase I Tier B</td>
<td>Extended</td>
<td>Estimation and comparison of specific environmental and risk assessment</td>
<td>Risk assessment</td>
<td>Extended data set on exposure, fate, and effects</td>
</tr>
</tbody>
</table>

Phase I Human Medicines

- Action limits
  - PEC_{SURFACEDWATER} < 0.01 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
  - PEC_{SURFACEDWATER} > 0.01 μg/l
    - Phase II environmental fate and effect analysis

ERA Veterinary Medicines

- CVMP guidance from 1996 superseded by VICH guidelines:
  - Phase I (VICH GL6)
  - Phase II (VICH GL38)
- CVMP guideline in supporting VICH GLs 6 & 38 (EMEA/CVMP/ERA/418282/2005)
  - Finalised April 2007
  - Update following discussions with stakeholders to be published shortly + Q&A document
  - Consideration of comments received during public consultation
### ERA Veterinary Medicines

**Phase I:**
- Decision tree.
- Identifies medicines that require further investigation

**Phase II:**
- Full risk assessment based on environmental fate and effect data using a "tiered" approach
- Tier A: Base data set (effects and fate data)
- Tier B: Refinement of assessment
  - further studies for PNEC (aquatic/terrestrial effect studies) and PEC (environmental fate studies)
  - Intensively reared animal branch
  - Pasture animal branch
- Consideration risk mitigation measures

---

### ERA Veterinary Medicines

**Phase II:**
- Candidates:
  - The active is a new compound for mass medication of food producing animals.
  - The active is not extensively metabolised in the animal. It is an antimicrobial applied via feed/water herd medication or a parasiticidal substance applied on pasture or it is a fish medicine.

---

### ERA Veterinary Medicines

**Monographs**
- Earlier proposal by CVMP to consider developing ERA monographs, i.e. documents, in which information on fate and effects of active substances in the environment is summarised
- Use for Phase II assessments
- Monographs would prevent unnecessary repetition of experiments, would save resources and would lead to a more harmonised assessment of environmental risks
- Support availability of veterinary medicines
- It is up to the industry now to make use of the concept and to provide the necessary data
- The CVMP continues to be open to contribute in developing the monographs

---

### Renewals of marketing authorisation of VMPs

- Article 28(2) of Directive 2001/82/EC and Article 39(2) of Regulation (EC) No 726/2004 require a re-evaluation of the risk-benefit balance, but do not foresee the submission of new data
- Renewals require a re-evaluation of the risk-benefit balance
- Recognition that consistent ERA data for all products are not available to Member States.
- ERA data at renewal are normally requested only if:
  - A potential risk to the environment is identified
  - Presence of an active component in the environment has been recorded
  - Data have become available indicating a potential problem.
- If potential risk for the environment is identified more data or risk mitigation measures can be requested (at any time).

---

### Referrals

- Dir. 2001/82/EC, as amended by Dir 2004/28/EC
- Procedure that can be initiated on the grounds of potential serious risk to the environment
  - Art. 33 Referral after MRP/DCP
  - Art. 34 Divergent decision /Harmonisation of SPCs
  - Art. 35 Community interest referral+ Safety concerns

---

### Pharmacovigilance for Veterinary Medicines

- To monitor the safety of medicines through the continuous safety surveillance post authorisation
- Where necessary actions to reduce risk and maintain a favourable benefit/risk balance
- Requirements for reporting of adverse reactions (spontaneous or periodic) and processing of pharmacovigilance data
- Animal safety and human reaction reports
Pharmacovigilance for Veterinary Medicines

Member States (MS) responsible for:
- MRP/DEC/nationally authorised products
- processing reports on centrally authorised products (first contact point)

EMEA responsible for:
- assessing reports for centralised products
- coordination of Pharmacovigilance in the EU via the Pharmacovigilance Working Party
- EudraVigilance

Pharmacovigilance and ERA

“...This system also takes into account any available information related to the lack of expected efficacy, off-label use, investigations of the validity of the withdrawal period and on potential environmental problems...”

- Very few reports on potential environmental problems:
  - Perception and awareness of veterinarians/farmers
  - Difficult to identify as a problem of pharmacovigilance
  - Lack of clear relationship between use of product and effect

*Directive 2001/82/EC as amended

CVMP ERA Working Party

- CVMP group of experts on ERA
- Provide recommendations to the CVMP on environmental risk
- Training for assessors
- Effectiveness of:
  - risk mitigation practices
  - standard risk mitigation recommendations
  - environmental information
- Toxicity of substances to dung fauna
- Degradation of substances in manure

Risk mitigation measures

- Effectiveness of risk mitigation measures - on going activity at the ERA WP
- Guideline on the Summary of Product Characteristics (SPC) for Pharmaceutical Veterinary Medicinal Products, NTA, Volume 6C:
  - “The product should not be allowed to enter surface waters as it has harmful effects on aquatic organisms.”
  - “Do not allow treated animals to swim in watercourses until at least x hours/days after administration.”
  - “The long-term effects of YY on the population dynamics of dung beetles have not been investigated. Therefore, it is advisable not to treat animals on the same pasture every season”

Availability problem

- Availability problem – lack of medicines to treat certain diseases and animals
  - products might be withdrawn possible increased illegal use
- Reasons (from Heads of Medicines Agencies (HMA) report 2007):
  - Costs for bringing product on market /maintenance vs turnover
  - Fragmented and small market
  - Minor species (e.g. goats, bees, rabbits, turkeys)
  - Total market 3-5% of human pharmaceutical market
  - 50% of the market for vet. medicines is agricultural sector

Availability (2)

- Consequences of unavailability of Veterinary Medicines
  - Poses significant problems for animal owners, farmers, veterinarians and governments.
  - Problems regarding residues in foodstuffs of treated animals with implications for consumer health.
  - Possible problem for public health – zoonotic diseases
- Initiatives
  - Review of regulatory procedures and requirements
  - Better harmonisation
  - Fee reductions/fee waivers for products for minor species/minor markets
  - SME legislation
  - Improve co-operation with academia
  - European Technology Platform for Global Animal Health
Communication of critical information to the Public-EPARs

- What is an EPAR? European public assessment report for all products that undergo an assessment by the CVMP
- EPAR's aim: To ensure safe and effective use of the product by providing critical information to public in a consistent, easy to understand manner

Conclusion

- New emphasis on legislation on ERA for medicines
- ERA required for all new products
- Detailed guidance is in place
- Harmonization across EU
- Group(s) on experts on Environmental Risk support task of regulators
- Training Assessors
- Other regulatory tools

Thank you for your attention

http://www.emea.europa.eu/
Frame of policy instruments to limit the discharge of pharmaceutical products into European waters

Eleftheria Kampa
(Ecologic)

Presentation covers:
• Overview of current policy framework in EU
• Possible current gaps
• Concluding remarks
• Thoughts on possible way forward

KNAPPE background document
• State-of-art review of policy instruments to limit the discharge of PPs
  • Available online http://www.knappe-eu.org/
  • Reviews key existing EU policy instruments
  • Explores links to environmental policy (e.g. WFD)
  • State-of-play in 3 countries (on the way to good practice): SE, UK, DE

Policy framework at EU level
• Medicinal policies
  • Product authorisation and environmental assessment
  • Requirements for drug take-back schemes
• Environmental protection policies
  • Key water policies
    • Water Framework Directive
    • Drinking Water Directive
    • Groundwater Directive
  • Other key environmental policies
    • European Soil Strategy
    • Endocrine Strategy
    • REACH
    • IPPC Directive

Drug authorisation and ERA
• Current EU framework
  Recent Directives on human & animal PPs since 2005
• ERA targets water (SW, GW), STPs and soil
  • "Old medicine" still not addressed
    e.g. Precaution instructions for animal PPs not binding for vets & farmers
    No recipe-free circulation & strict take-back could be applied for PPs with proven environmental risk

Drug take-back schemes
• Target accidents, abuse & occurrence in nature
• Set-up & effectiveness differ among countries
  • In-depth assessments of effectiveness are missing to great extent
  • Implementation problems relate to lack of consumer awareness on PP release into the environment & on the scheme operation (reduced visibility in pharmacies and on packaging)
EU water protection policies: WFD

- Water Framework Directive (WFD) as key directive
  - Requires “good status” in all waters by 2015
  - Good status = slight changes in values of relevant quality elements as compared to values found at closely undisturbed conditions
- 2 main WFD elements relate to chemicals:
  - List of 33 priority substances; No PP included (only substances in research & production); 3 PP proposed “subject to identification as possible priority substances”
  - Quality standards for other river-basin specific pollutants (part of good status); PP currently not directly considered (UK: 2 PPs identified as potential specific substances)

Further links of WFD & PPs

- WFD management mechanisms & precautionary principle not fully used yet for “PPs in water”
  - Due to complexity, uncertainties, lack of knowledge
- Important to incorporate PPs in future pressure & impact analysis of water bodies
- Monitoring programmes are being adjusted to WFD
  - PPs mostly not on agenda; But in DE, 3 PP active substances proposed for inclusion in WFD monitoring

Other water protection policies

- Drinking Water & Groundwater Directives
  - PPs not listed yet as substances to be monitored, but frequent requests for more use of precautionary principle
- Urban Wastewater Treatment Directive (end-of-pipe)
  - PP removal not required, it takes place partly as side-effect of treatment process
  - Increased PP removal could result from:
    - better Directive implementation in all EU countries;
    - Directive amendment to include PP emission limits;
    - WFD combined approach of emission limits & EQO;
    - stricter requirements for hospital wastewater treatment
  - Achieving cost recovery for new investments is crucial!
    (e.g. via taxes but definition of polluter needs to be clarified)

Other environmental protection policies

- European Soil Strategy: PPs not part of policy documents but identified as priority research issue
- Sewage Sludge Directive: No limits set for PPs in sludge; limits only for heavy metals; sludge application on fields prohibited in parts of EU
- Endocrine Strategy: ongoing substance evaluation; for water, it refers to WFD anti-pollution strategy
- REACH: PPs exempted
- IPPC: Only related to PP industrial production process

Concluding remarks I

- Precaution & pollution preventive policies should be priority
- Policy framework for end-of-pipe solutions can be improved (UWWTD)
- Closer linkage of medicinal & environmental protection policies needed
  - EU environmental laws (e.g. WFD) must provide common basis for all environmental goals in Europe
  - ERA guidelines do not make reference to EU directives
  - ERA should relate to actual water quality standards

Concluding remarks II

- Legal framework to tackle PPs in the environment is in place; extra directives not needed BUT
  - Precautionary & prevention principles not taken fully into account
  - Partly implementation deficits & partly policy gaps
  - Modification of existing directives may be needed
- PPs are not widely discussed at present
  - We need better understanding, data & further research to close policy and implementation gaps!
Some open issues are:

- **Fate & effects** of PPs in the environment
- **Low-level effects & chronic effects** of PPs on environment and humans
- **Cumulative effects** of multiple PPs on environment and humans
- **Lack of data & restricted data accessibility**
- **Definition of “polluter”** to set regulatory limits on release of PPs into water & to apply the polluter-pays-principle (human & animal PPs)

The way forward?

- **Development or amendment of policy** should consider in a balanced way the following:
  - Precautionary, prevention & polluter-pays principles used in environmental policy making
  - New scientific knowledge on the risks & impacts from the unintended release of PPs into the environment (e.g. see KNAPE & ERPharm projects)
  - **Costs & benefits of different options**
  - Approaches going beyond regulation/policy
  - Risk communication, new product forms etc

Thank you for listening.

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