



Sixth
Framework
Programme

KNAPPE

Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters

Contract n°036864

Operative commencement date of the project: February 1st 2007

Final date of the project: July 2008

D0.5&D0.9 Executive & Scientific Committee meeting minute Brussels, 23 June 2008

The deliverable authors are responsible for the content

AUTHOR:	Evelyne TOURAUD
AFFILIATION:	ARMINES - Ecole des Mines d'Alès
ADDRESS:	Boulevard Saint-Michel, 60 F-75272 Paris Cedex 06, France.
TEL.:	+33-4.66.78.27.12
EMAIL:	evelyne.touraud@ema.fr
FURTHER AUTHORS:	

Document Information

DOCUMENT TYPE	<i>Meeting Minute</i>
DOCUMENT NAME:	<i>Executive Committee meeting minute 23 June 2008</i>
REVISION:	
REV.DATE:	
CLASSIFICATION:	<i>public</i>
STATUS:	

Participants: Alistair Boxall, Dagmara Buntner, Mark Cronin, Valéria Dulio, Marinella Farré, Daniel Gouy, Paul Houeto, Marie-Laure Janex-Habibi, Romain Journal, Eleftheria Kampa, Pascal Michoux, Graham Mills, Michael Murray, Alain Pericaud, Gwenn Regnault, Benoît Roig, David Taylor, Anne Togola, Evelyne Touraud, Valentine Vierne, Sébastien Zabczynski .

Apologies : Alexa Sadezky (BfG), Véronique Molières (C2DS)

B. Roig introduces the session by welcoming all the participants and addressing many thanks to EFPIA for its welcome in their building and for the facilities it offers in the organisation of this meeting.

Then, he reminds the main expectations of Knappe project. There has been a big increase of literature on pharmaceutical products (PPs) in the environment. Knappe project aims to collect and integrate the different data, considering the whole life cycle of PPs (www.knappe-eu.org). During Knappe events and Executive Committee meetings, obtained data have been discussed and integrated into to propose to European Community priority actions to lower occurrence and impacts of PPs in the environment. **B. Roig** reviewed the list of deliverables and meetings during the project and informed that European Commission has accepted the extension of the duration of the project (at the end of September).

The main key findings of Knappe workshops are summarized in a document that is given to the attendees for discussion.

After this introduction, **S. Zabczynski** presented the main results of WS1 (WP1 and WP2).

- Indicator substances are available for wastewater, but still missing for unwanted ecotoxicological effects. Indicator substances for the determination of the wastewater share are diatrizoate and iopamidol (iodinated X-ray contrast medium), carbamazepine (antiepileptic), erythromycin (antibiotic), metoprolol (betablocker). Indicator substances showing the presence of non or poorly treated wastewater are ibuprofen, paracetamol, salicylic acid (analgesic) and bezafibrate (lipid regulator).
- Today's wastewater treatment achieves only partial pharmaceutical removal (optimum sludge retention time range:10 – 20 days, optimum hydraulic retention time range:12 to 25 hours)
- Advanced removal options for pharmaceutical removal in WWTPs are feasible (ozonation, reverse osmosis, activated carbon), but the cost-benefit analysis is missing. During reverse osmosis, removed pollutants are concentrated in the waste stream, which must be treated itself. Advanced oxidation processes may lead to toxic transformation products
- There is a lack of data concerning PPs concentration in sludges
- Solution in future should be based on the combination of centralized and source control/source separation measures. Source control can contribute significantly to pharmaceutical load reduction by:
 - Avoiding persistent compounds e.g. by substitution with degradable ones
 - Source treatment e.g. hospital wastewater

Then, **A. Boxall** presented the key findings of the workshop WS2 dedicated to environmental effects of pharmaceuticals. The attendees (academics, regulators, industrials) have been split in two groups, risk issues and effect issues, with the following discussion points to tackle:

- Risk issues
 - What are the impacts of recently studied pharmaceuticals on environmental health?
 - What are the risks of mixtures?
- Effect issues

- How can we better assess ecotoxicity?
- What is the relevance of the ecotoxicity data?
- What is the significance of these data in terms of ecological functioning?

The main conclusions can be summarized as follows:

- Large body of literature is now available on the ecotoxicity of pharmaceuticals (different taxonomic groups, species sensitivity)
- Analysis of this standard data (lowest reported standard acute or chronic or novel test endpoint) and monitoring data (maximum measured concentration) indicates that risks of most substances (and mixtures) are low
- Range of subtle effects are reported at environmentally realistic levels, many of these novel endpoints can be related to important ecological functions
- While traditional predictive approach work poorly for the endpoints of most interest, by drawing on mammalian data and using molecular information, it could be possible to identify those substances of most concern and design risk assessment accordingly

E. Kampa presented the key findings of WS3 dedicated to policy instruments design to limit pollution from PPs. The participants came from NGOs, politics, environment agencies and industry. The key points that have been tackled are:

- Definition of „problem“ due to PP discharge into the water environment
- Adequacy of current policy framework
- Options for good management practice as focus of possible future action
- Polluter pays principle
- Recommendations for future research on instrument choice & design

Concerning the problem definition, it is necessary to be able to say which types of PPs are of most concern.

From the policy point of view, all in all, the current policy framework (ERA guidelines and Technical Guidance Documents) is considered to be sufficient, if allowed to operate properly. ERA has to continually improve.

A main part of discussion has been focussed to the options of good management practices. Several ones can be envisaged such as improvement of prescription practices, environmental classification schemes of PPs (according to hazard and risk,) take-back schemes of surplus or unused drugs, targeted environmental monitoring around wastewater treatment plants, source limitation, upgrading of wastewater treatment... Nevertheless, emphasis has been made on the need of balance between the costs and the efficiency of the proposed actions. One has to check and compile literature on cost, methodology and effectiveness in the environment.

Regarding the polluter pays principle, the question was “who should pay in case of water pollution from PPs?” It is admitted that pharmaceuticals in the environment is a societal problem and that costs should be borne by all. A common approach might be useful for several micropollutants as cost for additional treatment could be very high. Society decision to remove all micropollutants or not (local or national government issue) has to be assessed.

Finally, some points for future research have been highlighted:

- Costs and benefits of different options
- Do take back schemes bring any benefit to the environment? Can this be assessed?
- Can we learn more about the behavioural impact of measures on doctors or vets?
- Develop research on public risk perception & tolerance
- How to ensure current levels of PPs do not increase further (population increase & increased consumption)?

- Evaluation of new drugs may give us indication & help us reflect back on “old” products with similar modes of action

G.Mills reported on ecopharmacovigilance and monitoring strategies that have been discussed during the workshop WS4. The main conclusions are as follows:

- There is a chemical cocktail in the environment and substances like PPs are difficult to monitor. Due to high cost, there is a need to focus monitoring efforts on compounds of concern, and different classes of STP,
- Dealing with monitoring methods, there is a need for more careful design of monitoring programmes and toxicological assessments. This need to use more fit for purpose methods (e.g. passive sampling linked with toxicity bioassays),
- A post-registration reporting scheme for adverse environmental effects of medicines for human use similar to that for veterinary medicines would be a useful safeguard,
- Concerning ecotoxicology, there is a need for new, well designed assays for the ecotoxicological assessment of pharmaceuticals since classical mortality end-points are not applicable for most of these substances,
- A central registry for the collection of data (chemical, environmental, toxicological, pharmacological, and ecotoxicological) could assist dissemination of information and help in improving and refining models of the fate, distribution, and environmental behaviour and toxicology and in optimising the use of costly data. Moreover, this centralised data repository could help to improve communication with the public, and to address (often unfounded) anxieties.

Finally, **A. Boxall** gave an overview of the discussion on ecopharmacostewardship during the workshop WS4. Three sessions have been carried out in parallel:

- Towards greener pharmaceutical products
- Driving uptake of ecopharmacostewardship
- Classification & labelling and new strategies

The main conclusions can be summarized as follows:

- PPs cannot be addressed as a whole and when considering ecopharmacostewardship approaches, PPs must be split into three categories:
 - On patent prescription drugs
 - Off patent prescription drugs
 - Over the counter (OTC) drugs
- Pharmaceutical industry must have a driver : consumer, regulator or cost
- Standardised method for measuring green?
- Stockpiling and over prescription are important issues surrounding the environmental impact of PPs
- The Swedish system, considered as a pilot, must be rigorously evaluated before being extended elsewhere in Europe
- Ecolabels may be effective on OTCs
- Back catalogue of drugs is the major issue

After these presentations, **B. Roig** opened the discussion. For the end of the project, we need to envisage all the main conclusions of the workshops prioritise them and tell if they are relevant or not. **D. Taylor** suggested expressing clearly what is known and which have evidence for, gaps in knowledge and actions that should be taken. Interesting issues will be conclusions, things that are specific to PPs and need to be done. Recommendations are often very general issues (e.g. mixture is an issue for lot of compounds).

A. Pericaud said that water managers do not have way to assess real effects of PPs on the environment, especially for mixtures. There is a research need to find a common method in order to select substances and possibly put them in a priority list. **P. Houeto** wondered how to choice the relevant species to make studies in order to validate mammalian study. **D. Gouy** answered that pharmacological effect on a lower concentration than environmental effect is known. These data can be combined with the usual toxicology. The majority of drugs can be anticipated from an ecological point of view from the dossier. **E. Touraud** asked if the data are available. **D Gouy** said that for old compounds, they are available in literature. For new ones, they are only in the dossier (so restricted). **A. Boxall** asked how to extrapolate from receptor response to ecological evidence: what all these data mean for an end effect? **D. Taylor** said that there is a big research area, too, in extrapolation to a human impact, risk assessment for human population. Do we know relation between impact on individual and impact on population? It is a major role in the environmental/ecological research area. **P. Houeto** asked if QSAR may predict chronic toxicity. **A. Boxall** conclusion is that is impossible. **M. Cronin** added that PPs chronic toxicity prediction is very difficult. Acute toxicity is possible with limits.

B. Roig wondered if there is an interest to study environmental factors as potential of increase toxicity. **A. Boxall** answered that they will effect. **D. Taylor** added that it is difficult to suggest more work on PPs toxicology when studies are saying that there is no ecological effect. Nevertheless, there is a lack of information on the area of sewage sludge and PPs that are removed: do they appear again? It could be useful to identify if there is any risk. **A. Boxall** answered that a paper from Erapharm project just came out. **M.L. Janex-Habibi** informed that SUEZ-ENVIRONNEMENT is running a research project on the fate of about 100 compounds on 20 wastewater treatment plants equipped with various processes (conventional and advanced). There will be data available, even on sewage sludge. They want to know the impact on treatment plant and cannot focus on all individual PPs. A big need to identify relevant indicators of risk of presence in the environment is needed. The potential impact on the plant is useful, too, for the operator to adjust the treatment. **P. Houeto** said that omics approach could be interesting to get indicator in terms of environmental endpoint.

M. Cronin proposed to look in a broader content. As stakeholder, he said that useful presentations summarising information have been carried out. He appreciates the idea of a data base on effects which could get support from chemical industry. He is fascinated about the concept of publicity and education (toxicology is no longer taught but what side effects are): public education is a big aspect. Ecolabels is a nice idea but wait for 20 years for a safer industrial environment. The economic impact of this has to be studied.

V. Dulio said that in the conclusion of Knappe project should be a though about what to do in the future for the national agencies and structures.

Concerning potential partnership between water managers and healthcare community (doctors, pharmacists), **A. Pericaud** said why not but why for. Such partnership is only reasonable in a project such as Knappe. **E. Touraud** answered that such a partnership is to inform healthcare community about what residues after the use are recovered in order to change in prescription. An holistic approach is required. **M. Murray** said we have to be careful if we want to change behaviour of doctors: not reduce prescription where needed but reduce the waste of over-prescription. **E. Touraud** said that part of these over-prescribed PPs can contribute to the diffusion in the environment. **M. Murray** added that it is what we have

to target. **D. Taylor** said that prescription should be based on need and not on environment significance.

Then, **E. Touraud** presented the leaflet of information letter and the first remarks concerning the targeted audience, purpose, cartoon, translation in European languages, diffusion modes. We are late now to finalise the document. She asked to send more comments before mid July. Finally, she gave first information about Knappe Final Conference: agenda (two days, mid September) and venue (Paris, School of Mines). The dates have to be confirmed.

ANNEX 1: AGENDA OF THE EXECUTIVE COMMITTEE

14:00	<p><i>KNAPPE project progress</i></p> <p>General overview</p> <ul style="list-style-type: none"> - WS1: Occurrence of PPs in the environment: key findings - WS2: Toxicological significance of PPs: key findings - WS3: Policy instruments design to limit pollution from PPs: key findings - WS4: Environmental stewardship of PPs: key findings <ul style="list-style-type: none"> - <i>Ecopharmacostewardship</i> - <i>Ecopharmacovigilance</i> - WP6 : Knappe Final Conference 	<p>B. Roig</p> <p>A.Sadezky / S. Zabczynski</p> <p>A. Boxall</p> <p>E. Kampa</p> <p>A Boxall G. Mills</p> <p>E. Touraud</p>
15:15	<p><i>Discussions and exchanges with stakeholders</i></p>	
16:15	<p><i>Conclusion</i></p>	<p>B. Roig</p>
16 :30	<p>END OF MEETING</p>	

ANNEX 2: LIST OF PARTICIPANTS

NAME	INSTITUTION	
BOXALL Alistair	University of York (UK)	a.boxall@csl.gov.uk
BUNTNER Dagmara	SUT (PL)	dagmara.buntner@polsl.pl
CRONIN Mark	SCI (UK)	M.T.Cronin@ljmu.ac.uk
DULIO Valéria	INERIS (F)	Valeria.DULIO@ineris.fr
FARRE Marinella	CSIC (SP)	mfugam@cid.csic.es
GOUY Daniel	SANOFI AVENTIS (F)	Daniel.Gouy@sanofi-aventis.com
HOUETO Paul	AFFSAPS (F)	Paul.HOUETO@afssaps.sante.fr
JANEX-HABIBI Marie-Laure	Suez Environment (F)	Marie-Laure.JANEX-HABIBI@suez-env.com
JOURNAL Romain	SANOFI AVENTIS (F)	ROMAIN.JOURNAL@sanofi-aventis.com
KAMPA Eleftheria	ECOLOGIC (D)	kampa@ecologic.de
MICHOUX Pascal	MSD (F)	pascal_michoux@merck.com
MILLS Graham	Portsmouth University(UK)	Graham.Mills@port.ac.uk
MURRAY Michael	ABPI (UK)	mmurray@abpi.org.uk
PERICAUD Alain	SAUR(F)	apericau@saur.fr
REGNAULT Gwenn	AFSSA (F)	g.regnault@AFSSA.FR
ROIG Benoît	ARMINES Alès (F)	benoit.roig@ema.fr
TAYLOR David	AstraZeneca (UK)	David.Taylor4@astrazeneca.com
TOGOLA Anne	BRGM (F)	a.togola@brgm.fr
TOURAUD Evelyne	ARMINES Alès (F)	evelyne.touraud@ema.fr
VIERNE Valentine	ARMINES Paris (F)	vierne@ensmp.fr
ZABCZYNSKI Sébastien	SUT (PL)	sebastian.zabczynski@polsl.pl

KNAPPE contractual partners