Sixth Framework Programme

KNAPPE

Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters

Contract n°036864

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D0.4 & D0.8 - Executive & Scientific Committee meeting minute
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Participants: Alistair Boxall, Dagmara Buntner, Hélène Darras, Valéria Dulio, Bernard Ferré, Daniel Gouy, Richard Greenwood, Paul Houeto, Eleftheria Kampa, Birgit Mertens, Michael Murray, Alain Pericaud, Gwenn Regnault, Benoît Roig, Alexa Sadezky, David Taylor, Evelyne Touraud, Valentine Vierne, Sébastian Zabczynski .

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. This third Executive & Scientific meeting offers the opportunity to include new member (AFFSAPS) in the stakeholders group.
Then, he gives an overview of Knappe project progress. Three reports have been delivered: D1.1, D2.1 for WP1 and WP2, D5.1 for WP5. Two newsletters have also been produced. The documents are all available on Knappe web site (www.knappe-eu.or). Three other reports (D1.2, D2.2 and D5.1) will be available very soon.

The main results of WP1&2 have been presented in the previous Executive Committee meeting (17 July 2007).
During this meeting, WP3, WP4 and WP5, which began on month 6, are going to be presented.
The main future milestones are:

- the two workshops, WS1 "Occurrence of PPs in the environment" and WS2 "Toxicological significance of PPs" and the International Conference "Pharmaceutical Products in the Environment : Trends toward lowering occurrence and impact" will be held before the end of February,
- WS3 "Regulatory instrument design to limit pollution from PPs" and WS4 "Environmental stewardship of PPs" and the Final Dissemination Conference" will be held before the end of the project.
- The third newsletter will be delivered at the end of February.

After this introduction, **E. Kampa** presented the first outputs of WP3, dedicated to the development of cornerstones of a European prevention action to limit the discharge of PPs into environmental water. A first study reviewed existing policy instruments at EU level and a second one aims to propose options for a future European approach using various instruments (regulation, taxes, ecolabels…).
Key existing policy instruments, links to EU WFD, the Groundwater Directive…and possible gaps in current approaches have been studied. Concerning products authorization and ERA, experts say that one should look beyond authorization (lack of data). Moreover, in depth assessment of drug take back returns is missing (France and Sweden have quite comprehensive schemes). Public awareness and education has to be improved. With regard to water and risk mitigation, currently PPs are mostly not directly considered in WFD**.** Sewage Sludge Directive aims is to promote the safe use of sewage sludge, to reduce the risks associated with it but only refers to heavy metals. Case studies have been carried out in specific countries (Sweden, United Kingdom and Germany).
Some points are still under discussion for regulations in product authorization (long term and low effect, cumulative effect, …). Concerning environmental protection, no further directive is needed for PPs (adapt the existing one). A framework is missing for "old" drugs. Another point is to clarify who is the polluter (it could be crucial for animal level).
E. Kampa concluded by the presentation of the further steps and WP3 activities (draft document of activity 2 in April 2008 and WP3 Expert Workshop in York on 28 April).

A discussion followed the presentation of E. Kampa. **D. Taylor** mentioned the importance to identify the polluter and the user (pharmacists, patients, doctors?). What criteria could be used to decide if new policy for environment is needed? **B. Roig** asked for the number of new medicines on the market every year**. M. Murray** is not aware of any data giving these information. The only way is to analyze prescriptions. About 70% of used medicines are old ones. **R. Greenwood** confirmed that old drugs are dominant and a new drug is becoming old in the ten following years. **A. Boxall** added that for old drugs, one have to distinguish between human and veterinary drugs.
P. Houeto asked if the user is a basic patient and if it is useful to know it. **D.Taylor** answered that, primary, the patient is the first to put the drug in the environment but do it because of doctor. It is difficult to define the responsibility: patient, doctor, authorization agency? **E. Kampa** said that an issue for further research was to find an answer. The same issue existed before for heavy metals.
Concerning PPs environmental impact, **B.Roig** asked for the impact of metabolites and degradation products and the opinion of the stakeholders. **D. Taylor** answered that, it is too complicated at the moment, even if it is an interesting issue. Product goes through patient but is not always metabolized. Some transformation products are metabolized. Generating sufficient metabolites for test is very difficult but metabolized molecules is generally less active than original one. **P. Houeto** confirms that it is a big deal to access to this information but why not study very active metabolites. Making the parallel with pesticides, **D. Taylor** said that it seems to be sure that pharmaceutical activity decreases with metabolism. **A. Boxall** added that, within Erapharm, a document has been developed, looking at transformation products, which could be used. **D. Taylor** is interested to know if some metabolites have a high pharmaceutical activity. **H. Darras** added that sometimes, metabolites are used as indicators of the occurrence of the parent compound (i.e. ibuprofen).

A. Boxall presented the objectives and the adopted approach in WP4 dedicated to health and environmental impacts/effects related to PPs. The objectives are to:

- Review the data on the effects of PP's on aquatic and terrestrial organisms and humans
- Explore the significance of the reported effects in terms of environmental and human health
- Further our understanding of the impacts of PP transformation products and mixtures of PP's on ecosystem functioning and human health.

The approach is based on literature review and database development. An Expert workshop (28 – 31 January 2008, Harrogate, UK) will be organised to discuss and comment the available data. 12 invited attendees from Europe, Switzerland, USA and Canada are expected to come from industry, regulators, academics and research institutes.

Currently, an intensive literature review has been performed and the relational database will contain chemical information (CAS No., therapeutic class(es), molecular weight, molecular formula, pKa, Kow, solubility) species information (common name, phylum or division, sub-phylum, class, habitat, cell type), test data (duration, endpoints, results and'omics' (DNA sequences for the receptors proteins for 500 compounds). The database contains around 20 000 study endpoints for both human and veterinary pharmaceuticals including both acute and chronic endpoints. Reported ecotoxicity endpoints for the majority of studies are in the low to high mg/l range. It is also possible to identify which therapeutic classes are most potent to a particular endpoint. Data base allow exploring the predictive power of existing QSARs for acute effects of pharmaceuticals and comparisons can be made with experimentally derived acute toxicity data.

The database will be available to participants during workshop. Two groups have been constituted: “Risk issues” and “Ecotoxicity issues”. A draft manuscript, developed by the end of the workshop, will be submitted to *Reviews in Environmental Contamination and Toxicology* for publication.
Following the presentation, a discussion took place. **P. Houeto** said that, concerning ‘omics’, one don’t have a background profile of genes and wondered if it is useful to use it. **A. Boxall** answered that it is useful for some substances and that it is an opportunity to explore it. **P. Houeto** wondered if there is any validation of the software used for QSAR data. **A. Boxall** answered that validation exists for substances but can still be explored. **E. Touraud** asked how to take into account the uncertainty of experimental data. **A. Boxall** said that for some of the data, one can have a huge variability so it is a real issue. **B. Roig** added that another objective of the WP4 will be to make links with WP1 and WP2 data. Is it possible to lead to an “environmental” classification of PPs (different from “therapeutic” one)?
R. Greenwood said that when QSAR crossed series became complicated, one need to have a huge number of compounds covering large chemicals space to be able to do it. Regarding toxicology data, sanity of data need to be looked at.

In J. Clark and L. Summerton absence, **E. Touraud** presented the first results of ecopharmacostewardship within WP5. The related discussion document is available on Knappe web site (www.knappe-eu.org) and provides:

- Review of the potential role & significance of eco-pharmacostewardship over the lifecycle of PPs
- Understanding of how & where stewardship schemes can be adopted to improve the overall sustainability of PPs
- Identification of existing examples of good practice and drivers for increased uptake.

The content of the document deals with:

- Application of eco-pharmacostewardship approaches to minimise the environmental impacts of PPs throughout their lifecycle
- Designing ‘greener’ PPs: the adoption of benign-by-design clean synthesis methods and green production technology
- Assessing sustainability implications of PPs
- Towards greener drugs
- Classification and labelling schemes for PPs
- Drug take back schemes
- Approaches to communicate methods of ‘good practice’.

Through WP5 a number of eco-compatibility criteria have been identified to measure the overall environmental footprint of PPs:

- Derived from sustainable raw materials
- Safe and clean synthesis
- Maintained or enhanced efficiency
- Reduced environmental impact at end of life.

It is recommended that these criteria could be used to develop a classification and labelling scheme to provide relevant & practical information for prescribers and users of PPs. This could be based upon an expansion of the Swedish scheme and implemented in other countries. Further key recommendations for the increased development of greener PPs have been suggested among which implementation of tax or other incentives, campaign to increase awareness of the benefits of eco-pharmacostewardship approach, raise public awareness of

the issues surrounding environmental impacts of PPs, promote extended responsibility for PPs within producers and distributors…
As a conclusion, **E.Touraud** presented the results of a survey carried out by the University of Waterloo (Canada) to give the view of expert stakeholders (from academia, government and industry) on management of pharmaceuticals in the environment. In terms of effectiveness and feasibility, the most "scored" strategies were:

- Advanced wastewater treatment technologies
- Education of medical professionals to reduce overprescription
- Pharmaceutical-return programs coupled with public education
- Requirements for all municipalities to have a minimum of secondary wastewater treatment
- Among these, pharmaceutical-return programs and requirements for secondary municipal wastewater treatment are seen as the most feasible.

Other management strategies have been examined:

- Development of green drugs are seen as ineffective and infeasible
- Environmental risk assessment legislation is the main instrument for the governments in Europe, recommended by many interviewees but yet seen as ineffective in mitigating environmental impacts
- Wastewater and drinking water treatments: there is a pressure to produce cleaner water (public perception of tap water), avoid negative environmental side effects (AOP).

Finally, WP5 workshop will be organized to discuss the document.

A rather strong discussion about "green drugs" followed this presentation. **D. Taylor** made assumption that environmental impact is when only a real "proof" exists, i.e feminization of fish by endocrine disruptors. The first action is to assess if the risk is realistic and accurate because, at the moment, few or none assessments are available. Moreover, **D. Taylor** adds that he is not aware of green drugs that have been marketed. **M. Murray** added that the prime purpose of pharmaceutical industry is to produce efficient and safe drugs for humans. It can do it in a greener way but it is not the first preoccupation. **B. Mertens** wondered: green process or green PP? **D. Taylor** added that green manufacturing already exists in all industries but not a drug with no impact at all on environment…: it is already difficult to develop drugs that works so, it would not be appreciate to add the "green" status of the drug. **B. Roig** answered that from an environmental chemist point of view, the approach cannot be limited. Some examples of micro pollutants discharged in the environment (pesticides, heavy metals) show some effects on humans: so it can be imagined that the continuous discharge of PPs in the environment may have adverse effects at long term. **D. Taylor** said that the point is to decide what an acceptable concentration in the environment is. If the threshold value is 0, there is a huge problem! In everybody interest, we have to decrease the amount of micro pollutants in the environment but has to be careful if no clear evidence that any impact exists. **M. Murray** added that we should look to the authorization process and have to bear in mind what is the relation risk/benefit. Do we know that more and more pharmaceuticals occur in water? **D. Taylor** answered that there is no evidence on this point but more and more people are looking and testing. **B. Mertens** drawn attention on the no effect concentration as a part of risk assessment. The purpose for **B. Roig** is to try to anticipate possible damage: **D. Taylor** answered that the only way to avoid this will be zero presence. **H. Darras** added that the situation has evolved with the improvement of analytical methods.

Then, within WP5, **R. Greenwood** presented the role of eco-pharmacovigilance, the aim of which is to review sources, pathways and sinks that determine exposure. The work is quite fitted to the environmental life cycle of drugs (eco-pharmacostewardship). He presented a simplified schematic of the entry, distribution and fate of human pharmaceuticals in the aquatic environment. In order to assess the risk of any particular pharmaceutical in the aquatic environment it is necessary to have knowledge of the toxicity of the compound, the distribution of the compound and the bioavailability of the compound in the environment. Monitoring strategies need to take these factors into account in order to manage the risk and detect and assess environmental impact and finally to optimise the use of water resources. Existing drugs and medicines that are identified as a potential high risk during the market authorisation process will be looked at. A series of monitoring scenarios will be proposed.

Finally, **B. Roig** concluded the meeting by presenting progress on the preparation of the International Conference in Nîmes (19-20 February). 4 topics are tackled:

- Pharmaceutical degradation products
- Environmental stewardship
- Regulatory perspectives
- Industrial perspectives

Five invited specialist will give plenary lectures : Pr. Klaus Kümmerer, University Medical Center of Freiburg (Germany), Pr. Åke Wennmalm: Stockholm County Council (Sweden), Dr. Ettore Zuccato Mario Negri Inst. for Pharmacol. Research, Milan (Italy), Dr. Susan T. Glassmeyer US EPA, Cincinnati (USA) and Dr. Florian Keil, Inst. for Social-Ecological Research, Frankfort (Germany)**.**

20 conferences and 20 posters are planned. Currently, 50 participants coming from industry, academia and research institutes are registered.

The preliminary program of the conference is added to this minute.

ANNEX 1: AGENDA OF THE EXECUTIVE COMMITTEE

	KNAPPE project progress General overview - WP3: **Develop cornerstones of an EU prevention action:** primary action - WP4: **Health and environment impacts/effects of PPs:** workshop preparation and discussion - WP5**: Eco-Pharmacostewardship and vigilance** discussion document - WP6: **Communication and dissemination :** International conference	B. Roig E. Kampa A. Boxall E. Touraud, R. Greenwood B. Roig
15:00	- Discussions and exchanges with stakeholders	
16:15	***Conclusion***	B. Roig
16 :30	**END OF MEETING**	

ANNEX 2: LIST OF PARTICIPANTS

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KNAPPE contractual partners

*K*nowledge and *N*eed *A*ssessment of *P*harmaceutical *P*roducts in *E*nvironmental waters

FP6 European project Contract n°036864

www.knappe-eu.org

Pharmaceutical Products in the Environment: Trends Toward Lowering Occurrence and Impact
19-20 February, 2008, Hotel Atria Nîmes, France

Conference Day One: Tuesday 19 February 2008

08.30 Registration

08.55 Chairman's welcome and opening remarks

09.00 ***United States Environmental Protection Agency. Research on Pharmaceutical and Personal Care Products***
Dr. Susan Glassmeyer, United States Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory, Cincinnati, USA

Session 1: Pharmaceuticals degradation and by products

09.40 ***Transformation products in the environment: how can we assess the risk ?***
Dr. Alistair Boxall, EcoChemistry Team, York University/CSL, UK

10.20 ***Measurements and removal options of pharmaceuticals in European WWTPs - outcome of the EU project KNAPPE***.
Thomas Ternes, German Federal Institute of Hydrology, Koblenz, Germany

10.45 ***Occurrence and fate of PPs and by-products from resource to tap water***
Olivier Thomas, Laboratoire d'analyse, Ecole des Hautes Etudes en Santé Publique (EHESP), Rennes, France.

11.10 Morning coffee and Poster session

11.40 ***Fate of Macrolide Antibiotics Used in Human Medicine in Natural Surface Waters***
Juliana Feitosa-Felizzola, Laboratoire Chimie de Provence, Université de Provence, Marseille, France

12.05 ***Improvement of ecotoxicity tests to evaluate relevance of membrane bioreactor process (MBR) for treatment of hospital water waste contaminated by cyclophosphamide***

Virginie Faucet-Marquis, Laboratoire de génie chimique, UMR CNRS/INPT/UPS 5503, Départment BioSyM F 31106 Toulouse, France

12.35 ***Time of Flight (ToF) and Hybrid Quadrupole-Time of Flight (QqToF) studies of biodegradation pathways of pharmaceuticals: membrane bioreactor (MBR) vs. conventional activated sewage sludge***
Jelena Radjenovic, Continental Waters and Soils Quality Unit Department of Environmental Chemistry Institute of Chemical and Environmental research of Barcelona (IIQAB) Spanish Council for Scientific Research (CSIC), Spain

13.00 (Title to be confirmed))
Pr. Klaus Kümmerer, Department of Environmental Health Sciences, University Medical Centre, Freiburg, Germany

13.25 Lunch

Session 2: Environmental stewardship for pharmaceuticals: a practical approach

15.00 ***Pharmaceutical management through environmental product labelling in Sweden***
Pr. Ake Wennmalm, Environmental Director, Stockholm County Council, Sweden

15.25 ***Ecopharmacostewardship – An EFPIA Perspective***
David Taylor, Chairman EFPIA Environment, Health & Safety Working Group and Director Environment & Sustainability, AstraZeneca, United Kingdom

15.50 ***Unused Prescription drugs***
Bo Gunnarsson, Apoteket AB, Sweden and **Matilda Persson**, The Swedish Association of the Pharmaceutical Industry (LIF), Sweden

16.15 Afternoon coffee and Poster Session

16.40 ***Evaluation of the Swedish environmental information and classification scheme of pharmaceuticals***
Marlene Ågerstrand, Dept. of Philosophy, Royal Institute of Technology, Teknikringen, Stockholm, Sweden

17.05 ***Precautionary and Integrated Risk Management for Pharmaceuticals in the Water Cycle - a Perspective from Sustainable Pharmacy***
Dr. Florian Keil, Institute for Social-Ecological Research ISOE GmbH, Germany

17.45 Closing remarks from the chairpersons

18.00 End of day one and networking drinks

20.00 Knappe Diner

Conference Day Two: Wednesday 20 February 2008

09.00 Poster session

Session 3: Regulatory perspectives: toward environmental priority lists of pharmaceuticals

09.40 ***Prioritization and risk assessment of the pharmaceuticals for human use***
Dr. Ettore Zuccato, Food Toxicology Laboratory, Department of Environmental Health Sciences, "Mario Negri" Institute for Pharmacological Research, Milan, Italy

10.20 ***Development of an International Priority List of Pharmaceuticals relevant for the Water Cycle***
P. de Voogt, Kiwa Water Research, Nieuwegein, The Netherlands

10.45 ***Experiences gained through the environmental risk assessment program for human pharmaceuticals in Sweden at www.fass.se***
Dr. Andreas Woldegiorgis, Analysis group, IVL Swedish Environmental Research Institute Ltd, Sweden

11.10 Morning coffee and Poster session

11.40 ***Environmental assessment of Norwegian priority pharmaceuticals based on the EMEA guideline***
Merete Grung, NIVA (Norwegian Institute for Water Research), Oslo, Norway

12.05 ***Assessment of daphnia chronic ecotoxicity data for a wide selection of human pharmaceuticals***
Dr Jim J Ryan, GlaxoSmithKline, Corporate Environment, Health & Safety, Ware Research & Development Site, United Kingdom

12.30 ***Experiences with the EMEA Environmental Risk Assessment Guideline for a New and Novel Human Pharmaceutical***
Dr. Keith Silverman, Director, Risk Assessment, Global Safety & the Environment, Merck & Co., Inc., Whitehouse Station, USA

13.00 Lunch

Session 4: Trends in industrial practices and environmental management

14.30 ***The Environmental Impact of Pharmaceuticals: From the Problem to the Solution - Green Pharmacy***
Pr. Klaus Kümmerer, Department of Environmental Health Sciences, University Medical Centre, Freiburg**,** Germany

15.10 ***Pilot-scale study on the removal of pharmaceuticals by LECA based SSF-constructed wetlands***
Ana Dordio, Department of Chemistry, University of Évora, Portugal

15.35 ***Green chemistry at Pfizer***
Peter J Dunn (Pfizer)

16.00 ***Green Chemistry to Improve Environmental Credentials of Pharmaceuticals***
Simon Breeden, Green Chemistry Centre of Excellence, University of York, United Kingdom

16.30 ***Strategy for modeling pharmaceuticals fluxes in hospital wastewaters***
Yves Levi, Université Paris Sud 11, Faculté de pharmacie, Laboratoire Santé publique-environnement, Chatenay-Malabry, France

16.55 General discussion

17.20 Chairman's closing remarks

17.30 End of conference