

MistraPharma

December 2011

Fantastic news! MistraPharma has received continued funding for 2012-2015!

After a very successful evaluation, based on both scientific value and value to users, Mistra (the Swedish Foundation for Strategic Environmental Research) has decided to support MistraPharma for four more years with 52 MSEK (approx. 740 000 USD).

In the second phase we propose to continue to test pharmaceuticals identified as being of concern, focusing our test efforts on reproductive and developmental endpoints. Factors determining bioconcentration, degradation and the kinetics of pharmaceuticals will also be explored.

A new aspect that will be researched is the risk for development of antibiotic resistance; Novel, powerful DNA sequencing approaches will be applied to compare risks for antibiotic resistance promotion in environments with different degrees of pollution.

Substitution processes and suggestions for novel regulatory testing requirements will be further developed, and advanced effluent treatment technologies will be more fine-tuned and brought closer to potential implementation.

New partners in the consortium are Professor John Sumpter at Brunel University (UK), and Professor Gen Larsson and Berndt Björleinius, Royal Institute of Technology, Bioprocess Technology.

The work will be organized in the following six workpackages:
(1) Identification of high risk APIs,
(2) Removal of highrisk APIs in wastewater treatment,
(3) Antibiotic resistance,
(4) Regulatory risk assessment and management,
(5) Analytical determinations,
(6) Stakeholder communication

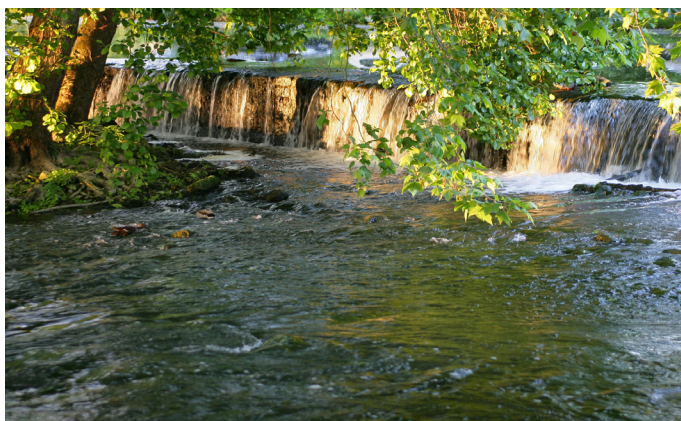
MistraPharma Project Leaders: Ingvar Brandt, Uppsala University, Magnus Breitholtz, Stockholm University. Gen Larsson, Royal Institute of Technology, Joakim Larsson, the University of Gothenburg, Karin Liljelund, Stella Futura, Christina Rudén, Royal Institute of Technology, John Sumpter, Brunel University, Mats Tysklind, Umeå University

Christina Rudén, programme director, KTH

For more information, please contact Christina at cr@abe.kth.se

Make the baltic sea region a lead in sustainable management for pharmaceuticals

In the EU Strategy for the Baltic Sea Region Sweden takes the leadership in a new project to "Make the Baltic Sea Region a lead in sustainable management of pharmaceuticals".



The European Union Strategy for the Baltic Sea Region addresses key challenges and untapped potential of this large region, covering about one third of the total area of the EU. It provides an integrated framework for improving the environmental condition of this shallow enclosed sea, tackling transport bottle-necks and energy interconnections. The Strategy shows that through common action its possible to promote e.g. a sustainable environment.

Make the Baltic Sea Region a Lead in Sustainable Management for Pharmaceuticals is a project (flagship) within Priority Area 3 under the Baltic Sea Strategy. The first meeting for the network was convened 17-18 October 2011, in Stockholm. The work will continue for three years under the Swedish leadership through the MPA.

The result from the meeting is a work plan including 3 areas:

- *Inventory of the status in the in Baltic States:* Summary of ongoing activities related to pharmaceuticals within the health and the environmental sector in relation to sustainable management of pharmaceuticals.

- *Screening:* The amount of pharmaceuticals produced, prescribed and sold in different Baltic States and how many production sites we have in the Baltic Sea area. Next step could be to estimate the amount of active pharmaceutical ingredients (API) that are released in Baltic waters. Screening at the production sites and at the Waste Water Treatment Plants (Publicly own treatment plants). At the present there are no set limits for API:s within EU.

- *Legislation:* The network could be used as an advisory body to the development of legislations concerning health and the environment e.g. water legislation (the Water Framework Directive and the Marine Strategy Framework Directive).

In 2009, during the Swedish Presidency, the Swedish MPA invited people with environmental, health and pharmaceutical knowledge to initiate a platform for exchanging knowledge between the different disciplines. During the meeting in October 2011 it was clear to me that we now had succeeded in finalizing this desirable platform and that we are now ready to make the Baltic Sea Area a lead in sustainable management for pharmaceuticals thanks to committed peoples in all areas.

Charlotte Unger, Medical Products Agency, Sweden

For more information, please contact Charlotte at charlotte.unger@mpa.se

Environmental progestin concentrations disrupt egg development in frogs

MistraPharma researchers at the Universities of Uppsala and Umeå have shown that progestin concentrations found in the aquatic environment impaired egg development in adult frogs. Considering the crucial role of egg formation in female fertility the results imply that progestagenic pollutants may pose a threat to reproduction in wild amphibian populations.

M. Säfholm^{*1}, A. Norder¹, J. Fick², C. Berg¹

Levonorgestrel is a synthetic progesterone commonly used in pharmaceuticals, e.g. in contraceptives. It is found in sewage treatment plant effluents at concentrations up to 30 ng/L, and was recently shown to pose a threat to egg laying in



A juvenile *Xenopus tropicalis*

fish. Information on the susceptibility of adult frogs to progestin toxicity is lacking. The present study aimed to 1) characterize progestagenic effects on the full cycle of oogenesis (egg development) in frogs, and 2) determine female amphibians' susceptibility to reproductive impacts from progestagenic compounds in the environment. Sexually mature female *Xenopus tropicalis* were exposed to levonorgestrel via the surrounding water for 7 days (0, 51 or 307 ng/L) or 28 days (0, 1.3, 18, 160 or 1240 ng/L). Their ovaries were analyzed histologically with respect to frequencies of immature (in early

meiotic prophase I), previtellogenic, vitellogenic, mature, and atretic oocytes. The 28-day exposure caused reduced proportions of oocytes at immature, vitellogenic and mature stages and increased proportions of previtellogenic oocytes, compared with the control. The lowest tested concentration, 1.3 ng/L, increased the proportions of previtellogenic oocytes and reduced the proportions of vitellogenic oocytes, indicating inhibited vitellogenesis. Our results indicate that progestagenic effects on oocyte development include interrupted germ cell progression into meiosis and inhibited vitellogenesis.

Accepted for publication in *Biology of Reproduction*.

For more information, please contact Cecilia Berg at Cecilia.Berg@ebc.uu.se

¹ Department of Environmental Toxicology, Uppsala University, Centre for Reproductive Biology (CRU), Norbyvägen 18A, 75236 Uppsala, Sweden

² Department of Chemistry, Umeå University, SE-90187 Umeå, Sweden

Proactive risk management of emissions of active pharmaceutical ingredients from manufacturing

To ensure our manufacturing discharges are safe, AstraZeneca has proactively developed the concept of Environmental Reference Concentrations (ERCs) and Maximum Tolerable Concentrations (MTCs), which should not be exceeded in the aquatic environment receiving our effluents.

The ERC represents the average concentration of an active pharmaceutical ingredient (API) in the receiving surface water, which would be unlikely to result in any adverse effects. We have also defined MTCs to control short term peak emissions associated with batch-wise production and cleaning activities.

Our approach is based on established environmental quality standard concepts used in national and international legislation, together with published methodologies to protect the aquatic environment (algae, invertebrates and fish), top predators (fish-eating mammals such as otters) and humans. To date we have established ERCs and MTCs for 30 of our APIs.

Last year, we conducted a programme to monitor API emissions at our worldwide sites to compare against the ERC and MTC values. The initial assessment in the middle of 2011 confirmed that all except two sites met with our internal standard. Corrective actions were taken and the position is now that all sites meet the standard we have set ourselves. We are also starting to share the ERC approach with our suppliers who manufacture on our behalf.

We currently have a paper in press describing the ERC methodology, with the intention of encouraging scientific debate on the issue of Pharmaceuticals in the Environment and giving others the opportunity to benefit from the approach we have developed. (Murray-Smith, R., Coombe, V. T., Haag Grönlund, M., Waern, F., Baird, J. A. In press (Accepted 1 Nov 2011). Managing Emissions of Active Pharmaceutical Ingredients from Manufacturing Facilities: An Environmental Quality Standard Approach. Integrated Environmental Assessment and Management (IEAM)).

Gisela Holm, AstraZeneca

For more information, please contact Gisela at gisela.holm@astrazeneca.com



We wish you all a Merry Christmas and a Happy New Year!

Karin Liljelund and Héliene Hagerman

If you have any questions you are welcome to contact us!

Christina Rudén (Programme director) +46 8 790 95 87

Karin Liljelund (Communication manager) +46 730 75 57 50