Pharmaceuticals in the environment

Make ideas work!

Study to inform the development of a strategic approach to PiE in the European Union

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Context and objectives of the study

Context:

- Essential access to pharmaceuticals for public and animal health
- Body of evidence supporting the occurrence of Ps in the environment, at concentrations which may pose risks to the environment, and possibly to human health via the environment.
- Number of gaps and inefficiencies in the way pharmaceuticals are currently managed.

Objectives:

- Identification of policy options based on good practices and concrete proposals for improvement.
- Consultation on these policy options as part of the effort to develop an EU strategic approach to PiE.

Study in collaboration with Milieu Ltd, Ineris and Pr. Kümmerer

Our approach

Scale of the issue

- Literature review → scientific publications from 2013 onwards

Knowledge gaps and drivers of the issue

- Literature review → scientific and grey literature from 2013 onwards

Improvement areas and policy options

- Bio Intelligence Service report (2013)
- 2014 EC Workshop proceedings
- Literature review → grey publications from 2013 onwards and latest policy documents
- Stakeholders' consultation → ~10 experts from health, veterinary and environmental agencies, industry federations, NGOs
- *EC Interservice consultation*

Public consultation

- *Online public consultation – launch planned around the end of September 2016*

Pharmaceutical industry in figures

	Human	Veterinary
EU share of global market	25% (2nd after the United States of America)	31%
EU market	€48 billion (1990) - €220 billion (2014)	€5 billion (2014)
EU expenditure on R&D	€27.5 billion/yr (2014)	€500 million/yr (2014)
Number of companies	~4,200 (mostly large companies, employing 250 persons or more)	
Employment	815,000 jobs full time jobs (incl. R&D)	50,000 full time jobs
EU trade surplus	€55 billion euros (2013)	

Sources: (IFAH-Europe, 2016; EFPIA, 2015a; EFPIA, 2015b; Eurostat, 2013)

Pharmaceuticals production and use

- **3,000 active pharmaceutical substances** on the EU market
- **x 2 increase in the number of Ps** reaching consumers for the last decade (2004-2014)
- **> x 2 increase in the consumption per capita of human Ps** (antimicrobials, ageing and chronic diseases) (between 2000 and 2012) and
- **Significant decrease of antimicrobial consumption for veterinary Ps** (-8% sales in mg/PCU between 2011 and 2013) in the EU/EEA
- **… but 67% increase expected globally** between 2010 and 2030 in the agriculture sector alone
- Average amount of collected pharmaceutical waste reported by Member States **between 10 and 100 tonnes/million capita**.

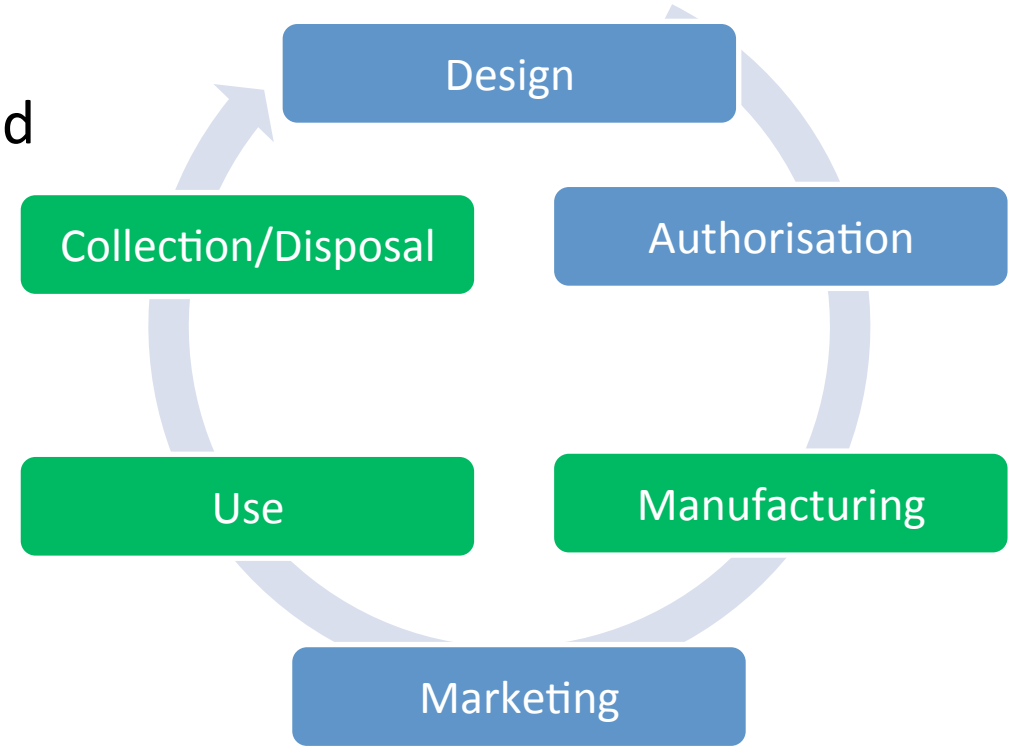
Contamination pathways

Key known pathways:

- Consumer and animal use and excretion
- Improper disposal of unused or expired medicines

2 pathways with recent focus:

- Wastewater discharged from API manufacturing sites
- Application in the field of manure, sludge or reclaimed wastewater?



Latest developments regarding occurrence and fate

Occurrence:

- APIs at concentrations ranging ng/l–µg/l, in particular in rivers and lakes receiving treated WW
- Most documented compartment: fresh surface water
- Increasing attention to PPs in drinking water and seawater
- Still scarce evidence (in general or in the public domain) for:
  - PPs in groundwater
  - PPs in manure and soil, as well as biota.

Fate:

- Increasing efforts to identify transformation products and determine transformation pathways (potentially high concentrations and persistence)
- Still little monitoring of transfers from an environmental compartment to another

Assessment of the risks for the ecosystems

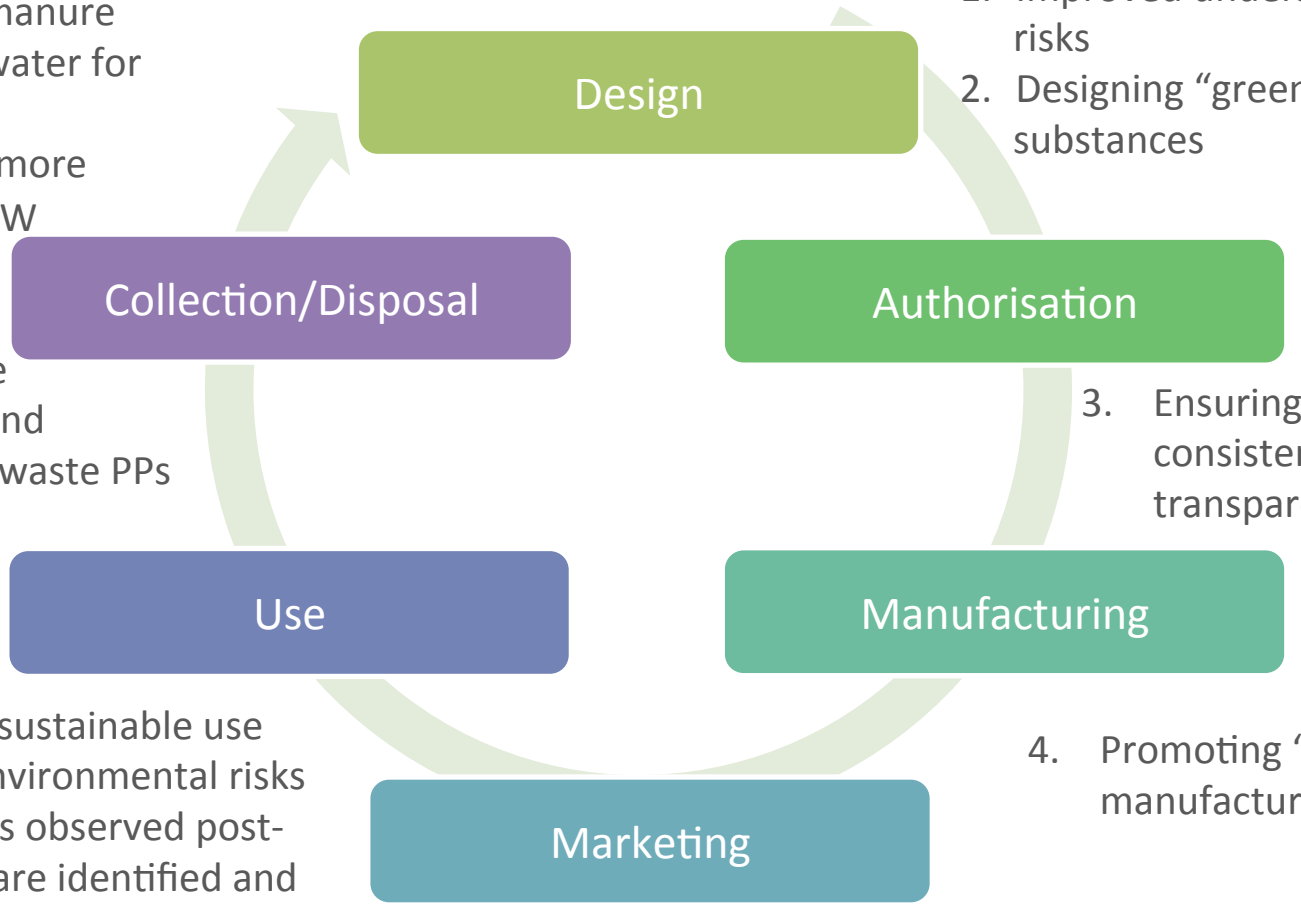
- Based on ERAs performed by Market holders, no environmental risks for a large majority of Ps at predicted environmental concentrations and normal conditions of use
- Yet, still insufficient information about environmental risk for many Ps (environmental occurrence and ecotoxicological data)
- Hot topics in the last 5 years: chronic exposure, mixture effects, non-threshold modes of action, transformation products, Environmental factors
- Recent focus on assessing the risks based on MEC -> Several molecules with a risk quotient > 1
- Observed effects in the environment or at environmental concentrations: diclofenac, ethinylestradiol, benzodiazepine and oxazepam, Ivermectin

Assessment of human health risks via indirect exposure

- Challenge to establish a clear relationship between PiE and adverse health effects
- According to latest studies: low risks for human health via drinking water but potential risks via other routes of exposure
- Particular concerns regarding:
  - antimicrobials and contribution to AMR development (contribution to the 700 000 lives taken in 2014, 10 million by 2050?),
  - exposure to molecules with endocrine-disrupting properties,
  - mixtures.
- Increasing attention but still limited knowledge

→ Long-term effects on human health of chronic exposure to Ps and mixtures cannot be ruled out with current knowledge

10 improvement areas across the life-cycle



1. Improved understanding of risks
2. Designing “greener” substances

3. Ensuring robustness, consistency and transparency of ERA

4. Promoting “greener” manufacturing processes

5. Ensuring environmental risks are adequately taken into account and translated into mitigation actions

6. Ensuring environmental risks and impacts observed post-marketing are identified and reported
7. Promoting sustainable use

8. Ensuring appropriate collection and disposal of waste PPs
9. Promoting more effective WW treatment
10. Better management of sludge, manure and wastewater for reuse

Design

1. Improved understanding of the risks from pharmaceuticals to the environment

Rationale

- Knowledge gaps: occurrence, chronic exposure at low doses, metabolites and transformation products, mixtures in environmentally realistic settings, link release of antimicrobials – spread of AMR – impacts on human & animal health, etc.

Means?

- EU and public-private funding opportunities for research?

AMR: Antimicrobial resistance

2. Designing "greener" substances

Rationale

- Potential benefits vs. consequences for quality, effects and side effects
- Little implementation and research in a competitive environment

Means?

- EU and public-private funding opportunities?
- Share at EU level resources and concrete examples?

Authorisation

3. Ensuring the scientific robustness, consistency and transparency of risk assessments

Rationale

- ERA = key legislative instrument
- Representativeness of environmental expertise in scientific committees involved in risk-benefits analysis (for HMPs)?
- Limited access to environmental datasets to environmental authorities and general public
- Limited capacity of current ERA to capture all significant risks (PBT, endocrine, excipients and transformation products, etc.)
- Relevance of separate ERAs for each pharmaceutical using same API?

Means?

- Strengthen environmental expertise in scientific committees at national and EU level?
- Standardise reporting and improve access to relevant environmental endpoints (e.g. PAR)?
- Expand the scope of ERA to better consider risks related to PBT, endocrine-properties, metabolites, excipients?
- Share information on fate and effect of each API, to be used in ERA Phase 2?

ERA: Environmental risk assessment
PBT: Persistent, Bioaccumulative, Toxic
PAR: Public assessment report

Manufacturing

4. Promoting "greener" manufacturing processes

Rationale

- Hotspots of contamination downstream of pharmaceutical manufacturing facilities
- No specific API limits set for effluent discharges and no transparency about releases
- Impact of EU consumption of pharmaceuticals at global scale
- Voluntary initiatives from the industry to reduce emissions in the EU and/or along the global supply chain
- Insufficient EU instruments to regulate emissions (e.g. IED, REACh, GMP)

Means?

- Set emission levels for APIs and excipients for manufacturing facilities?
- Promote good environmental manufacturing practices relevant to pharmaceuticals?
- Promote consideration of environmental standards in supply chains?

API: Active pharmaceutical ingredient
IED: Industrial Emission Directive
GMP: Good Manufacturing practice

Marketing

5. Ensuring environmental risks are adequately taken into account and translated into mitigation actions

Rationale

- Little influence of ERA outcomes for HMPs
- Little implementation and follow-up of Risk mitigation measures (RMM)?
- Several incomplete ERA dossiers (limited knowledge; “post-marketing commitments”)
- No update of ERA dossiers at post-marketing stage
- Access to OTC with significant risks
- Scarce reporting of adverse effects at environmental concentrations

Means?

- Conduct a catching-up procedure for a selection of pharmaceuticals?
- Revise ERAs based on new information?
- Consider ERA results in risk-benefits analysis for HMPs?
- Link ERA outcomes to OTC status?
- Better identify responsibilities for the enforcement of RMM

ERA: Environmental risk assessment
OTC: Over the counter
RMM: Risk Mitigation Measure

Use

6. Ensuring environmental risks and impacts observed post-marketing are identified and reported

Rationale

- Informal surveillance of environmental issues compared to pharmacovigilance
  - For VMPs: Mandatory reporting but debated implementation
  - For HMPs: Environmental surveillance under Member States responsibility.
- No EU-wide targeted monitoring of PP in surface and ground water except for substances under the watch lists
- Limited collaboration between health/ veterinary and environmental competent authorities

Means?

- Strengthen surveillance of environmental issues at post-marketing stage?
- Further include PPs representing a risk in watch lists for surface and groundwater?
- Develop mechanisms for better collaboration and information exchange between competent authorities?

PSURs: Periodic Safety Update Reports

Use

7. Promoting sustainable use of pharmaceuticals

Rationale

- A number of unsustainable practices reported in the literature:
  - 'Over-use' through auto-medication or 'over-prescriptions',
  - Misuse,
  - Treatment's discontinuation,
  - Consumption of OTCs with significant environmental risks
- Key role of doctors, veterinarians and pharmacists, which are in direct contact with patients
- Lack of awareness of professionals and general public

Possible Means?

- Increase consideration of environmental aspects during medical/veterinary education, training of professionals?
- Increase consideration in procurement decisions?
- Organise public campaigns?
- Tailor packaging size for delivery?
- Regulate further OTC status?
- Etc.

OTC: Over the counter

Collection and disposal

8. Ensuring appropriate collection and disposal of waste pharmaceutical products

Rationale

Case of unused PP:

- Requirement from all EU Member States to provide collection systems.
- Insufficient results (heterogeneous implementation, limited collection points, lack of awareness of general public on their contribution to PiE)

Case of waste contaminated by PP (e.g. effluents):

- No legislative requirement with regard to treatment and monitoring for most PPs
- Pilot initiatives, locally, for source segregation in hospitals

Means?

- Sharing lessons learnt from current implementation: success stories and difficulties for better enforcement and incentive
- Reviewing classification of hazardous substances (CLP) or List of waste?
- Etc.

Collection and disposal

9. Promoting more effective treatment of wastewater

Rationale

- No EU-wide regulation for the monitoring and removal of PPs in WWTPs effluents
- Regular detection of significant PP concentrations in effluents from WWTPs
- Benefits of advanced water treatments compared to conventional treatments at removing PP
- Need for further optimisation and higher efficiency (recalcitrant pollutants, spread of AMR)
- Limited development despite EU funding opportunities (e.g. RTD H2020, JPI, EIP, CF, ESIF)

Means?

- Monitor PPs and AMR microorganisms in hotspots' effluents (large WWTP)?
- Increase clarity and access to EU funds?
- Promote innovative mechanisms for investment at national level (water pricing, extended producers'responsibility)?
- Etc.

Collection and disposal

10. Better management of sludge, manure and wastewater for reuse

Rationale

- Presence of PPs including antimicrobials and AMR microorganisms in manure, sludge and reclaimed water
- Concerns with regard to possible bioaccumulation in the trophic chain and development and spread of AMR
- Not tackled currently in EU policy instruments of potential relevance (IED, Sludge Directive, Fertilizer Regulation, etc.)
- Reuse forbidden in some Member States because of precautionary principles

Means?

- Set concentration limits of Ps (and AMR microorganisms?) in sludge, manure, and WW for reuse?
- Revise Good agricultural practices and best available techniques for handling of manure in order to mitigate possible contaminations?
- Better links with Circular Economy package?
- Etc.

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Health Care Without Harm

Health Care Without Harm Europe