Green and sustainable pharmacy practice – Guidance for practitioners

6 July 2020
Facilitator

Gonçalo Sousa Pinto,
Lead for Practice Development and Transformation
FIP
Announcements

Webinar house rules

1. This webinar is being recorded and live-streamed via Facebook.
2. The recording will be available on our website www.fip.org.
3. You may ask questions using the questions box.
4. You are welcome to provide feedback to webinars@fip.org.
5. We invite you to become a member of FIP at www.fip.org/membership_registration
Introduction
Programme of today’s webinar

Overview

1. Introduction - Gonçalo Sousa Pinto – 5 min

2. Jaakko Teppo will provide a theoretical introduction (25 min) about how APIs make their way to the environment and which kinds of molecules are the most problematic and why – highlighting the case of antimicrobial resistance (AMR).

3. Eeva Teräsväri will then discuss the classification of APIs and present different solution models from across production and distribution chain (25 min).

4. Panel discussion and questions from the audience – 30 min

5. Wrap-up and take-home messages – 5 min

©FIP: All the information in this video are confidential and cannot be copied, downloaded or reproduced without the formal approval of FIP (International Pharmaceutical Federation).
Learning objectives

After this webinar the participants should:

1. Understand the mechanisms of how active pharmaceutical ingredients (APIs) end in the environment
2. Understand what kind of problems APIs cause for the environment
3. Get ideas and models of how pharmacists can prevent these problems
Green and sustainable pharmacy practice
Guidance for practitioners
Part I

Jaakko Teppo
PhD (Pharm)
Jaakko Teppo

Researcher and member of the Generation Green working group

University of Helsinki, Division of Pharmaceutical Chemistry and Technology
PART 1

• Active pharmaceutical ingredients (APIs) and their properties
• Flow of APIs in the nature
• Residuals in the environment
• Metabolic processes of APIs
• Wastewater management (not discussed during the presentation)
• Where are APIs found
• Effects in nature (some examples presented, others for self-learning)
• Ecotoxicity measures
Active pharmaceutical ingredients (APIs)

• Type of exposure, chronic/acute
• Biotransformation
  Degradation in the nature (sun)
• Interactions
• Interactions between molecules
• Concentration in the food chain
• ~ 3000 molecules + other ingredients
• Analytical sensitivity
APIs in the environment – flow

Figure 1: Main emission pathways of human and veterinary pharmaceuticals entering the environment.

https://www.umweltbundesamt.de/sites/default/files/medien/378/publikationen/pharmaceuticals_in_the_environment_0.pdf
APIs in the environment - flow
APIs in the environment, flow
RESIDUALS IN THE ENVIRONMENT

- Biologically active transformation products of APIs
- Biologically active transformation products of additives

Problematic APIs:
- Antibiotics
- Analgesics
- Lipid-lowering drugs
- Betablockers
- Sytostatics
- Hormones
- Lipophilic, stable molecules
- Molecules which can accumulate in food chains
Metabolism of APIs – what happens in the body

https://upload.wikimedia.org/wikipedia/commons/thumb/7/79/Acetaminophen_metabolism.png/220px-Acetaminophen_metabolism.png

https://upload.wikimedia.org/wikipedia/commons/thumb/9/97/Xenobiotic_metabolism.png/350px-Xenobiotic_metabolism.png
Biotransformation has effects in analytical work, are you measuring API or metabolites?

Drug Metab Dispos 1997, 275-280

Fig. 4 – The fluctuation of carbamazepine load in the influent and effluent of STP K along with the influent flow rate.

https://upload.wikimedia.org/wikipedia/commons/thumb/6/6c/Beta_D-Glucuronic_acid.svg/200px-Beta_D-Glucuronic_acid.svg.png
Wastewater management
What happens to APIs when treated in waste water plant

- **Mechanisms**
  - Adhesion to the sludge
  - Biotransformation or biodegradation

- **Oxidation, nitrification, etc.**
  - Sometimes some byproducts

- **Not all APIs react in the same way – huge differences**
  - Calculation of speed and effectiveness of the process
  - Metabolites should be considered
Why is it difficult to remove all APIs from the waste water?

Huge chemical variability between APIs
Where are APIs detected

Figure 3: Global occurrence of pharmaceuticals: Pharmaceuticals have been found in the environment in all UN regional groups (WW 2014).

https://www.umweltbundesamt.de/sites/default/files/medien/378/publikationen/pharmaceuticals_in_the_environment_0.pdf
<table>
<thead>
<tr>
<th>Pharmaceutical</th>
<th>Therapy Group</th>
<th>Number of countries worldwide in which pharmaceuticals have been found in the aquatic environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>Analgesics</td>
<td>50</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Antiepileptic drugs</td>
<td>48</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Analgesics</td>
<td>47</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>Antibiotics</td>
<td>47</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Analgesics</td>
<td>45</td>
</tr>
<tr>
<td>Estrone</td>
<td>Estrogens</td>
<td>35</td>
</tr>
<tr>
<td>17-β-Estradiol</td>
<td>Estrogens</td>
<td>34</td>
</tr>
<tr>
<td>17-α-Ethinylestradiol</td>
<td>Estrogens</td>
<td>31</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Antibiotics</td>
<td>29</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Analgesics</td>
<td>29</td>
</tr>
<tr>
<td>Clofibric acid</td>
<td>Lipid-lowering drugs</td>
<td>23</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Antibiotics</td>
<td>20</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Antibiotics</td>
<td>16</td>
</tr>
<tr>
<td>Estriol</td>
<td>Estrogens</td>
<td>15</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>Antibiotics</td>
<td>15</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>Analgesics</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 1: Several globally marketed pharmaceuticals have been found in the aquatic environment of all UN regional groups (IWW 2014).
What happens to the APIs in the environment?

Adsorption of sulfonamides on lake sediments

Zhongxing ZHONG1,2, Jian XU1,2, Yuan ZHANG1,2, Lei LI1,2, Changsheng GUO1,2, Yan HE3,4, Wenhong FAN5,6, Beijing ZHANG7

Front Environ Sci Eng 2013, 518-525

Uptake of pharmaceuticals, hormones and parabens into vegetables grown in soil fertilized with municipal biosolids

Lyne Sablevin7, Peter Duren7, Sheldon Roote-Gelot7, Michael Payne7, David R. Lapen7, Edward Topp7,8

Sci Environ Technol 2012, 233-236

BIOAVAILABILITY OF PHARMACEUTICALS IN WATERS CLOSE TO WASTEWATER TREATMENT PLANTS: USE OF FISH BILE FOR EXPOSURE ASSESSMENT

Maria Laiti1, Jenny-Maria Brosnahan1, Helmut Sined1, Leif Kronberg1, and Anna Orland1

(1Division of Environmental Science and Technology, Department of Biological and Environmental Science, University of Sydakylä, Aavali, Finland)
(2Division of Water Chemistry, Aalto University, Turku, Finland)
(3Center for Fish and Wildlife Health, University of Bern, Bern, Switzerland)

Environ Toxicol Chem 2012, 1831-1837

Irrigation of Root Vegetables with Treated Wastewater: Evaluating Uptake of Pharmaceuticals and the Associated Human Health Risks

Tomer Makhl1, Yehoshua Maoz1, Gali Tadmor1, Moshe Shenker1, and Benny Chefer2,3,4,5

Environ Sci Technol 2014, 9325-9333
A pharmacognostic example

**Natural Products**

Occurrence of the Synthetic Analgesic Tramadol in an African Medicinal Plant

Ahène Boumendjel, Germain Sooing Tailwe, Elisabeth Ngo Bum, Tanguy Chabrol, Chantal Beney, Valérie Strüger, Romain Haudecoeur, Laurence Marcourt, Sousa Challal, Emerson Ferreira Queiroz, Florence Sounad, Marc Le Borgne, Thierry Lomberget, Antoine Depaquis, Catherine Lavand, Richard Robius, Jean-Luc Wolfender, Bruno Bonaz, and Michel De Waard

Angew Chem Int Ed 2013, 11780-11784

**Anthropogenic Contamination**

Tramadol—A True Natural Product

Souvik Kusari, Simplice Joel N. Tatamso, Sebastian Zühlke, Ferdinand M. Talontsi, Simenon Fogue Konan, and Michael Spitteler

Angew Chem Int Ed 2014, 12073-12076

https://commons.wikimedia.org/wiki/File:Nauclea_latifolia_.jpg

https://upload.wikimedia.org/wikipedia/commons/thumb/7/74/Tramadol_as_a_racemic_mixture.svg/270px-Tramadol_as_a_racemic_mixture.svg.png
## APIs effects in the environment

### Main problem is the biological activity of API

<table>
<thead>
<tr>
<th>Pharmaceutical</th>
<th>Fluoxetine</th>
<th>Oxazepam</th>
<th>Ivermectin</th>
<th>Enrofloxacin, Ciprofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic group</td>
<td>Antidepressant</td>
<td>Antidepressant</td>
<td>Antiparasitic</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Non-target organism</td>
<td>Leopard Frog (Rana pipiens)</td>
<td>European perch (Perca fluviatilis)</td>
<td>Dung fly and beetles (Cynococcus (Anabaena flosaquae), Duckweed (Lemna minor))</td>
<td>Growth inhibition</td>
</tr>
<tr>
<td>Effects</td>
<td>Delayed tadpole development</td>
<td>Altered behaviour and feeding rate</td>
<td>Mortality of eggs and larvae</td>
<td>Growth inhibition</td>
</tr>
<tr>
<td>Study type</td>
<td>Laboratory</td>
<td>Laboratory</td>
<td>Laboratory and field</td>
<td>Laboratory</td>
</tr>
<tr>
<td>Reference</td>
<td>Foster et al. 2010</td>
<td>Brodin et al. 2013</td>
<td>Liebig et al. 2010</td>
<td>Ebert et al. 2011</td>
</tr>
</tbody>
</table>

### APIs effects in the environment

<table>
<thead>
<tr>
<th>Pharmaceutical</th>
<th>Diclofenac</th>
<th>17α-Ethynylestradiol</th>
<th>Diclofenac</th>
<th>Sulfinamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic group</td>
<td>Analgesics</td>
<td>Synthetic estrogen</td>
<td>Analgesics</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>Non-target organism</td>
<td>Vulture (Gyps bengalensis)</td>
<td>Fathead minnow (Pimelophalus promelas)</td>
<td>Rainbow trout (Onchorhynchus mykiss)</td>
<td>Maize (Zea mays), Willow (Salix fragilis)</td>
</tr>
<tr>
<td>Effects</td>
<td>Population collapse due to renal failure</td>
<td>Population collapse due to feminization of male fish</td>
<td>Strong reactions of liver, kidney, and gills</td>
<td>Adverse effects on root growth, Death of maize at high conc.</td>
</tr>
<tr>
<td>Study type</td>
<td>Wildlife</td>
<td>Whole-lake experiment</td>
<td>Laboratory</td>
<td>Greenhouse</td>
</tr>
</tbody>
</table>

[https://www.umweltbundesamt.de/sites/default/files/medien/378/publikationen/pharmaceuticals_in_the_environment_0.pdf](https://www.umweltbundesamt.de/sites/default/files/medien/378/publikationen/pharmaceuticals_in_the_environment_0.pdf)
Antimicrobial resistance (AMR)

~200 antibiotic production facilities - mainly India & China

An estimated 30,000 – 70,000 tonnes of waste with antimicrobial activity is generated by the antibiotics industry

>95% of antibiotic manufacturing waste is in liquid form. It needs treatment before release to the environment

Environments polluted with untreated waste can create reservoirs of antibiotic resistance

Additional cost to prevent untreated waste release into the environment is ~$0.50 per kilogram of active ingredient
Pharmaceutical Pollution: A hidden cause of AMR

The way that antimicrobials are produced, the by-products which result, and particularly the impact of effluent from factories on AMR, is an issue which has too often been neglected in discussions about AMR.

There is growing evidence of API manufacturers that do not adequately treat waste products, with the result that high concentrations of antibiotic active ingredients are disposed into the local environment creating ‘reservoirs’ of antibiotic resistant bacteria.

(AMR Review, May 2016)
Outsourcing the problem?

Pharmaceutical pollution in India is bitter pill for Nordea

Concern over environmental damage caused by outsourcing of drug manufacturing

BUT:

Emerg Infect Dis 2008, 70-72
Intersex fish

Figure 2.—Microscopic appearance of testicular oocytes in smallmouth bass. (A) Oocytes observed within testes of male smallmouth bass were primarily previtellogenic, chromatin nucleolus stage (arrow). Bar = 50 μm. (B) Immature oocytes (arrows) are most often observed around the central area (a) in close proximity to blood vessels and nerves (b). Bar = 100 μm. H&E stain used.
Effects near the wastewater management units

Roach
(*Rutilus rutilus*)

http://www.luontoportti.com/suomi/images/14241.jpg

**FIGURE 2.** Incidence of intersexuality in samples of male roach from various rivers. The proportion of intersex roach (containing oocytes in their testes and/or with female reproductive ducts) in rivers (F–M), lakes or canals (B–E) in England and southern Ireland and in a laboratory control population (A). Sites B–E received no sewage treatment works (STW) effluent, whereas rivers F–M received varying amounts of STW effluent from more than one STW. Rivers F–J were sampled both upstream and downstream of major STWs (the two sites on these rivers were several kilometers apart and separated by one or more physical barriers). The inset diagram illustrates the general trends in the data when results from control, upstream, and downstream sites were pooled. The asterisks denote significance from the field control sites (B–E) at the following significance levels: *, $p = 0.05$; **, $p = 0.01$; ***, $p = 0.001$.**
Not only due to contraceptives

https://upload.wikimedia.org/wikipedia/commons/thumb/4/46/Metformin.svg/220px-Metformin.svg.png

Chemosphere 2015, 38-45
Mussels suffering

Physiological effects of diclofenac, ibuprofen and propranolol on Baltic Sea blue mussels

Hanna Ericson, Gunnar Thorsén, Linda Kumblad

Aquat Toxicol 2010, 223-231

http://images.csmonitor.com/csm/2013/07/mussel.jpg?alias=standard_600x400
Oxazepam effecting fish behavior

European perch (Perca fluviatilis)

http://www.luontoportti.com/suomi/images/14044.jpg

Fig. 2. Feeding rate of perch after oxazepam treatments. Feeding rate is expressed as the latency to capture the first zooplankton, the 10th zooplankton, and the 20th zooplankton. Error bars represent ±1 SE (n = 25 in all treatments); statistically significant differences between the control and treatments are indicated (*P < 0.05 or ***P < 0.001).

Fig. 1. Fish behavioral response to two concentrations (low: 1.8 µg liter⁻¹; high: 910 µg liter⁻¹) of dissolved oxazepam compared to control treatment (0 µg liter⁻¹). (A) Activity, measured as number of swimming bouts (>2.5 cm) during 10 min. (B) Boldness, measured as the inverse of latency to enter a novel area during the total trial time (900 s). (C) Sociality, measured as the cumulative time (in seconds) spent close to a group of conspecifics. Error bars represent ±1 SE (n = 25 in all treatments); statistically significant differences between the pre- and posttreatments are indicated (*P < 0.05 or ***P < 0.001).
Usage of illicit drugs

Sci Total Environ 2012, 432-439
Diclofenac and Indian vultures

Avian scavengers and the threat from veterinary pharmaceuticals

https://upload.wikimedia.org/wikipedia/commons/thumb/0/00/Diclofenac.svg/200px-Diclofenac.svg.png

How to measure the ecotoxicity

- USA 1980s part of the dossier
- REACH in Europe for chemicals - not for APIs
- Environmental Classification of Pharmaceuticals at [www.fass.se](http://www.fass.se) - Guidance for pharmaceutical companies, Sweden and Norway
How is the evaluation done

1. APIs

PNEC (predicted no-effect concentration)

PEC (predicted environmental concentration)

If the relation >1, => risk. If >10, a big risk

If the relation is <1, small risk to environment, very small <0,1

Real risk is also based on the national usage figure

2. Products

No existing system
Green and sustainable pharmacy practice
Guidance for practitioners
Part II

Eeva Teräsmi
MS in pharm, pharmacy owner, FIP vicepresident
Speaker

Ms Eeva Teräsalmi
FIP Vice President (Finland)
Global problem - global solutions

• UN: Environment program since 1972

• UN: Sustainable development goals
  Proposition to add AMR -indicator
UN and WHO: Green procurement in health care sector


Medicines:
During man-made and natural catastrophs – drug donations and disposal

Stockholm County Council Environmental Classification of Pharmaceuticals: The Stockholm County Council introduced environmental classification of pharmaceuticals and described their environmental hazards and risks. This is helpful in substituting more environmentally friendly components during production. This environmental classification and EU legislation on medical products provide guidelines for manufacturers to follow Good Manufacturing Practices and environmental standards. http://www.janusinfo.se/, www.fass.se

The Viennese Database for Disinfectants (WIDES Database) is a user-friendly database established by the City of Vienna Climate Protection Programme, ÖkoKauf Wien, to assist hospitals and other health care settings to assess effectiveness, safety and environmental factors when procuring disinfectants. http://www.wien.gv.at/english/environment/protection/oekokauf/disinfectants/7.
CLASSIFICATION SYSTEMS

• Based on APIs risk to environment x consumption

• Environmental Classification of Pharmaceuticals at www.fass.se – Guidance for pharmaceutical companies, Sweden and Norway

• Classification is needed if we want to
  - inform customers
  - influence purchasing processes and tenders
  - create a mark for packages/eco-friendly medicine
  - change the pricing mechanisms

• Should be based on the whole life-cycle of one product – these systems do not exist

• FDA, EU- environmental risk analysis only for new molecules, there are about 2000 APIs in the market which are unclassified
EU: Strategic Approach to Pharmaceuticals in the Environment 2019

- For both human- and veterinary medicines from production to waste
- Raise awareness and promote prudent use!
- Improve training and risk assessment
- Gathering monitoring data
- “Green design”
- Reduce emissions from manufacturing
- Reduce waste
- Improve wastewater treatment
- AMR-European One Health Action
Green Pharmacy Practice
Taking responsibility for the environmental impact of medicines

• FIP/WHO: Guidelines on Good Pharmacy Practice 2009
WHAT PHARMACISTS CAN DO?

- Drug development and research: Green chemistry - principles
- Industry: small emissions and effective processes, classification of medicines role of GMP?
- Wholesalers: effective logistics and procurement processes
- Hospital pharmacies: Drug committee work and procurement, education and collection of waste at point, risk management of own actions
- Open care pharmacy: Adherence to the medical therapies, information to customers, medical waste, risk management of own actions
- Regulation: classification of medicines, drug prices, GMP etc
- Education: Future pharmacists should be aware of the problem and of the solutions
Benign by design – green chemistry and green formulations

Re-Designing of existing pharmaceuticals for environmental bioregradability: A tiered approach with β-blocker propranolol as an example
Tusha: Rastogi, Christoph Leder, and Klaus Kümmerer

Environ Sci Technol 2015, 11756-11763
RATIONAL MEDICINE USAGE

- Rational prescribing and usage are main factors to prevent the problem!!!
- Drug waste management is expensive. The amount of drug waste should be minimized.
- Consumers should be informed about the impacts of medical wastage.
- In Finland the cost of medical waste is ~100 million euros/year!
DRUG WASTE

- Legislative actions about waste management are necessary
- Classification of medical waste as hazardous waste
- Incineration (>930 °C) is the only way to dispose medical waste safely
- Take up-programs should be organised (based on national legislation)
- In many countries pharmacies are running take-back programs
- In hospitals treatment on the spot -work
Effective wastewater management
Treatment at the source

Medical Wastewater Treatment In COVID Times

By Zhenzhen Xu 17 April, 2020

Coronavirus can be found in faeces/urine so medical wastewater must be treated properly. CWR's Xu expands on China's efforts in Wuhan & beyond.

Table shows that the most important issues for a community pharmacy are to improve medication compliance so that all medicines dispensed are actually used by the consumer. Also participating in the medical waste collection programmes is essential.

It is important to be able to measure the success of different actions taken. One can measure the amount of waste collected, the amount of electricity used, the consumption of paper etc.
PHARMACEUTICAL EDUCATION

It is of importance that the future pharmacists should be aware of sustainable solutions and practice. These topics should be included and integrated on all pharmacy curriculums.

More information:
Sivén M et al: Generation Green – A holistics approach to implementation of green principles and practices in education programmes in pharmaceutical and medical sciences at the University of Helsinki. Sustain chem Pharm 16:100262, 2020
Any questions?

*Please use the Q&A tool*
Wrap up & Conclusions
Episode 22

Key considerations for developing COVID-19 treatments: Learning from the past and planning for the future

In partnership with: BPS Pharmacy Practice Research Special Interest Group

Moderator
Victoria García Cardenas
Senior Lecturer
University of Technology Sydney (Australia)

Speaker
Syed Shahzad Hasan
Senior Research Fellow/Senior Lecturer
University of Huddersfield (UK)

Speaker
Dalia Dawoud
Associate Editor, Research in Social and Administrative Pharmacy (UK)

Date
7 July

Time
15:00 CEST
The FIP CEO Interviews...

7 July, 12:00 CEST

Catherine Duggan
Chief Executive Officer, International Pharmaceutical Federation (FIP)
The Netherlands

Carmen Peña
Immediate Past President, FIP
Doctor in Pharmacy, Complutense University of Madrid
Spain
Thank you for attending!

Please provide feedback through the survey you will see at the end of the event