Assessing and Mitigating the Environmental Impact of Human Pharmaceuticals

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*Toxicology and Safety Considerations in the Development of Devices and Drugs*
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Jim Laurenson
US Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)
Environmental Assessment Team
Silver Spring, MD 20993-0002
james.laurenson@fda.hhs.gov
Overview

• Background
• Environmental Assessment
• Mitigation

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Background

Protect the public health by ensuring the safety, efficacy, and security of human drugs

Benefit vs. Risk...
...before and after approval

- Reviews of drug applications before marketing
- Surveillance of unexpected health risks post-market
- Monitoring of drug information/advertising to ensure truthful, balanced information
Background

1. Fast track designation
2. Accelerated approval
3. Priority review designation
4. Breakthrough therapy designation

In FY 2017, new applications and requests increased compared to five year averages:

- ~650 orphan designation requests – ~60% increase
- 48 NMEs and original BLAs – 14% increase
- 106 non-NME NDAs – 28% increase
- 231 efficacy supplements – 43% increase
Background

Number of FDA Orphan Drug Approvals

*2017 figure as of 9/15/2017
Background

2017, a year of FDA “firsts” in rare disease

- **tisagenlecleucel** – First gene therapy approval in the United States
- **avelumab** – First FDA-approved treatment for metastatic merkel cell carcinoma
- **lesipasvir + sofosbuvir** – First HCV Direct-Acting Antivirals approved for use in adolescents
- **cerliponase alfa** – First FDA-approved treatment for a form of Batten disease
- **edaravone** – First new treatment for patients with ALS in over 2 decades
- **ibrutinib** – First FDA-approved therapy for the treatment of chronic graft-versus-host disease (GVHD)
- **benznidazole** – First treatment approved in the United States for the treatment of Chagas disease
Background

Safety Risks

YOU'RE AT NCAC-SOT...

PARENTS, DO YOU KNOW WHERE YOUR PRESCRIPTION DRUGS ARE?
Background

Safety Risks

• At least **71,000 young children/year** enter emergency rooms due to unsupervised exposure to medicines

• Approx **1,700 pediatric hospitalizations/year** due to unsupervised exposures to opioids alone

• At least **6 pediatric deaths/year** occurred prior to 2015 due to opioids on the “flush list”

• Overdose deaths from prescription and illicit opioids doubled from **21,089 in 2010** to **42,249 in 2016**
Background

Publications on Pharmaceuticals and Personal Care Products in the Environment (EPA 2013)
Environmental Assessment

In a Nutshell

http://youtu.be/OYbRIJLBzn4
Environmental Assessment

The Entire Tree
Environmental Assessment

The Law

- Implement the 1970 National Environmental Policy Act (NEPA), 42 U.S.C. §4321 et seq
- Assess environmental impact of federal actions, such as drug approvals
Environmental Assessment

Regulations and Guidance

Council on Environmental Quality (CEQ) Rules and Guidance
- 40 CFR 1500-1508, + recent “20 questions” update notice
- Programmatic reviews
- Categorical exclusion review
- Cumulative impact

- Provides detailed information on a variety of topics related to preparing and filing exclusions and EAs

Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity (2016)
- Guidance on how to identify/assess drugs with E, A, or T activity
- Recommends contacting CDER early to determine need for EA
Environmental Assessment

Process

Proposed Agency Action, e.g., New Drug Application

Meets Criteria for Limited Risk, e.g., effluent < 1 ppb?

Yes

Extraordinary Circumstances?

Yes

Environmental Assessment (EA)

No

Categorical Exclusion

Environmental Impact Statement (EIS)

Significant Impact?

Yes

Finding of No Significant Impact (FONSI)

No
# Environmental Assessment

## Assays

<table>
<thead>
<tr>
<th>Physical/Chemical Characterization</th>
<th>Environmental Depletion</th>
<th>Environmental Effects Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water solubility</td>
<td>Hydrolysis</td>
<td>Acute toxicity</td>
</tr>
<tr>
<td>Dissociation constants</td>
<td>Aerobic biodegradation</td>
<td>Chronic toxicity</td>
</tr>
<tr>
<td>Octanol/water partition coefficients</td>
<td>Soil biodegradation</td>
<td>• Aquatic invertebrates</td>
</tr>
<tr>
<td>Vapor pressure/Henry's Law constants</td>
<td>WWTP degradation</td>
<td>• Fishes</td>
</tr>
<tr>
<td>Soil or sediment/water partition coefficients</td>
<td>Photolysis</td>
<td>Algal growth &amp; repro</td>
</tr>
<tr>
<td>Fish bioconcentration</td>
<td>Metabolism</td>
<td>Earthworm toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimum inhibitory concentrations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Microbial respiration inhibition</td>
</tr>
</tbody>
</table>
Environmental Assessment

Example Cumulative Ecological Assessments

Ethynyl Estradiol and Other Human Pharmaceutical Estrogens in the Aquatic Environment: A Review of Recent Risk Assessment Data
James P. Laurensen, Raanan A. Bloom, Stephen Page, and Nakissa Sadrich

Summary of EE2 Screening-Level Risk Quotients (RQs) Under Mean-Flow Assumptions for Predicted Exposure Conc (PEC) Based on a Predicted No-effects Conc (PNEC) of 0.1 ng/L

<table>
<thead>
<tr>
<th>Measurement</th>
<th>PEC (ng/L)</th>
<th>RQ&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>0.00064</td>
<td>0.0064</td>
</tr>
<tr>
<td>90th percentile</td>
<td>0.0075</td>
<td>0.075</td>
</tr>
<tr>
<td>99th percentile (approx.)</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.46</td>
<td>4.6</td>
</tr>
</tbody>
</table>
Environmental Assessment

Example of Uncommon Pathway: Water Reuse

• Reused water with contaminants in cooling tower drift (EPA 2012)
• While volatiles drift up and dissipate...
• ...non-volatiles are in air near plant and deposit to surrounding land and water
• Toxicity benchmarks being developed to compare to concentrations
Environmental Assessment

Weight of Evidence (WoE) Approaches

Weight of evidence (WoE):
“a process in which all of the evidence considered relevant for a risk assessment is evaluated and weighted.” (WHO, 2009)

Use and examples of WoE approaches in scientific assessments:
• Weight of Evidence in Ecological Assessment. EPA, 2016.
• Guidance on the use of the weight of evidence approach in scientific assessments. EFSA, 2017.

1. Assemble evidence
• Pharm/Tox: In vivo, in vitro, in silico
  • Physicochemical properties
  • Environmental fate
  • Exposure data

2. Assess/weight evidence
• Assess relevance, reliability, consistency
  • Select WoE method

3. Integrate evidence
• Consistency/concordance with other evidence
  • Summarize results in table/graph
  • Apply WoE method

4. Draw conclusion
• Report results
• Address uncertainties and data gaps
Environmental Assessment
Related Activities

• Intra- and inter-agency and international coordination
  – NEPA Intra-agency Workgroup
  – Federal Inter-agency Workgroup on Pharmaceuticals in Water
  – US Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
  – Other countries, international bodies

• Research
  – American Association of Pharmaceutical Scientists (AAPS) Journal running theme Issue: PPCPs in the environment (2014-present)
  – Ethinyl estradiol and other human pharmaceutical estrogens in the aquatic environment (2014)
  – Risks Associated with the environmental release of pharmaceuticals on the FDA "flush list“ (2017)
  – Using in vitro and in silico data to identify pharmaceuticals with potential (anti-)estrogenic activity in aquatic vertebrates at environmentally relevant concentrations (Pinto et al., 2019)
Environmental Assessment

Related Activities

Risks of “Flush List”

• W/highly conservative assumptions, including entire API mass is flushed, no dilution or degradation
  - most “flush list” APIs present a negligible eco-risk
  - a few need additional eco-tox data, though based on other data, also likely negligible eco-risk

• Using similar conservative assumptions for human-health risks, all present negligible risk through ingestion of water and fish
Environmental Assessment

Related Activities

*Risks of “Flush List” cont’d*

• Assessment of potential to yield subtle effects in fish

\[
ER = \frac{H_{TPC}}{(PEC_{sw-2}) \cdot P_{b:w}}
\]

• where:
  - \( ER \) = effect ratio
  - \( H_{TPC} \) = the human therapeutic plasma concentration
  - \( PEC_{sw-2} \) = predicted concentrations in U.S. surface waters, with metabolism
  - \( P_{b:w} \) = the plasma (blood):water partitioning coefficient for fish, based on either \( LogD_{7.4} \) or \( LogK_{ow} \)

• An \( ER < 1 \) suggests presence of an API at concentrations in fish plasm known to yield therapeutic effects in humans
# Environmental Assessment

## Related Activities

*Risks of “Flush List” cont’d*

<table>
<thead>
<tr>
<th>API</th>
<th>$P_{EC_{sw-2}}$ (ng/L)</th>
<th>$H_{PC}$ (mg/L)</th>
<th>$P_{b/w,LogD}$</th>
<th>$ER - LogD_{7.4}$</th>
<th>$P_{b/w,LogK_{ow}}$</th>
<th>$ER - LogK_{ow}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>26</td>
<td>0.0005</td>
<td>46</td>
<td>0.42</td>
<td>42</td>
<td>0.46</td>
</tr>
<tr>
<td>Diazepam</td>
<td>11</td>
<td>0.1</td>
<td>18</td>
<td>509</td>
<td>18</td>
<td>518</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>7</td>
<td>0.003</td>
<td>21</td>
<td>21</td>
<td>91</td>
<td>4.7</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>120</td>
<td>0.01</td>
<td>0.18</td>
<td>475</td>
<td>2.86</td>
<td>29</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>47</td>
<td>0.005</td>
<td>0.20</td>
<td>539</td>
<td>0.78</td>
<td>136</td>
</tr>
<tr>
<td>Meperidine</td>
<td>2</td>
<td>0.1</td>
<td>3.1</td>
<td>16,091</td>
<td>6.8</td>
<td>7,302</td>
</tr>
<tr>
<td>Methadone</td>
<td>55</td>
<td>0.05</td>
<td>15</td>
<td>62</td>
<td>153</td>
<td>5.9</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>3</td>
<td>0.01</td>
<td>0.20</td>
<td>16,333</td>
<td>9.58</td>
<td>348</td>
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<tr>
<td>Morphine</td>
<td>824</td>
<td>0.01</td>
<td>0.11</td>
<td>115</td>
<td>0.27</td>
<td>45</td>
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<tr>
<td>Naloxone</td>
<td>3</td>
<td>0.01</td>
<td>1.4</td>
<td>2,324</td>
<td>1.5</td>
<td>2,210</td>
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<tr>
<td>Naltrexone</td>
<td>3</td>
<td>0.003</td>
<td>0.96</td>
<td>1,044</td>
<td>2.72</td>
<td>368</td>
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<tr>
<td>Oxycodone</td>
<td>113</td>
<td>0.005</td>
<td>0.28</td>
<td>158</td>
<td>2.18</td>
<td>20</td>
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<tr>
<td>Oxymorphone</td>
<td>149</td>
<td>0.0003</td>
<td>0.36</td>
<td>5.0</td>
<td>0.60</td>
<td>3.0</td>
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<tr>
<td>Tapentadol</td>
<td>90</td>
<td>0.05</td>
<td>0.37</td>
<td>1,486</td>
<td>29.55</td>
<td>19</td>
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<tr>
<td>Sodium Oxybate</td>
<td>2,391</td>
<td>50</td>
<td>0.0005</td>
<td>40,680,888</td>
<td>0.0406</td>
<td>514,506</td>
</tr>
</tbody>
</table>
Environmental Assessment

Related Activities

An Approach for Using In Vitro and In Silico Data to Identify Pharmaceuticals with Potential (Anti-)Estrogenic Activity in Aquatic Vertebrates at Environmentally Relevant Concentrations

Caroline Lucia Pinto, a,b,* Raanan A. Bloom, b and James P. Laurenson b

- Can be expanded to other endocrine-relevant mechanisms of action (androgen and progesterone receptors, thyroid and steroidogenesis pathway interactions).

- Might help determine need for EA data for drug applications and support prioritization
Mitigation

Many Options

- Mitigation measures and alternative actions in EAs, etc.
- Policies, recommendations, e.g.:
  - Label directions
  - Education
  - Drug take-back and other disposal
- Personal waste requirements, e.g., hospital collection
- Cost/risk incentives, e.g., limits on initial # of doses
- “Greener” alternatives, e.g., improved bioavailability, risk scores
- Personalized medicine and improved diagnostics for
  - the right drug
  - at the right amount
  - for the right reason
- Improved wastewater treatment

Daughton & Ruhoy, 2012
Mitigation

Drug Take-back/Disposal

https://youtu.be/4ZyP_lyXWHI
Mitigation

Drug Take-back/Disposal

fda.gov/drugdisposal
Mitigation
Packaging and Inserts

17 PATIENT COUNSELING INFORMATION

- Advise patients to read the FDA-approved patient labeling (Medication Guide). Remind patients to be mindful that menstrual changes could reflect pregnancy and to discuss contraception options with healthcare providers.
- If pregnancy occurs, see Contraindications (14.4).
- Advise patients on contraceptive options, not to stop taking this medication until taking advice from healthcare providers.

- Instruct patients to dispose of unused medication via a take-back option if available or to store in a locked cabinet; otherwise follow FDA instructions for disposing of medication in the household trash, and not to flush down the toilet.
  www.fda.gov/drugdisposal, and not to flush down the toilet.

- Advise adequate intake of calcium and vitamin D to reduce the incidence of osteoporosis. 

- Advise patients to seek immediate medical attention for suicidal ideation and behavior.
  • Promptly seek medical attention [see Warnings and Precautions (5.4)].

- Counsel patients on signs and symptoms of liver injury [see Warnings and Precautions (5.3) and (5.4)].
Mitigation

Green Alternatives

How to Read the Table

THE SUBSTANCE can be found under several different drug groups. For example, trazodone can be found under “A Alimentary Tract and Metabolism” as well as “D Dermatologicals”. Substances indicated in bold are included in “Klofta Ligan 2014”, Stockholm County Council’s “Wise List” of recommended drugs for common diseases (including recommendations for specialized care).

THE PBT INDEX is a measure of environmental hazard and can assume all values from 0–9 (the total of P, B, and the T-value). The higher the value of a substance, the greater its danger to the environment.

A (*) AFTER THE PBT INDEX indicates that the assessment is uncertain due to lack of data.

Two substances may have the same risk values but different PBT values, but the risk assessment can also be different even if the PBT values are the same.

When assessing a medication’s environmental impact, consideration should be given to both environmental risk and environmental hazard since bioaccumulation and persistence are not included in the risk assessment.

RISK refers to toxic risk to the aquatic environment; the calculation based on Swedish conditions and is given as insignificant, low, moderate, or high. "Cannot be evaluated" means that the manufacturer has stated that the documentary basis for assessment of risk is insufficient. Information about environmental risks can be obtained from www.foss.se. For risk "exempt", see p.6

P (Persistence) can assume the value 0 or 3

B (Bioaccumulation) can assume the value 0 or 3

T (Toxicity) can assume the value 0–3

VOLUME IN DDD: The sales by prescriptions and to hospitals in DDD (Defined Daily Doses) of the substance in Stockholm County Council during one year.

Indicates DDD for C (combination drugs, 1 tablet = 1 DDD)
E (drugs for external use, 1 gram = 1 DDD)
DDD indicated for pharmaceuticals.
Mitigation
Improved Wastewater Treatment

Figure 5. Population Served by POTWs for Select Years between 1940 and 2012 and Projected (if All Needs Are Met) by Treatment Level.

Source: U.S. Public Health Service and EPA Clean Watersheds Needs Surveys

From: Clean Watersheds Needs Survey (CWNS) 2012 Report to Congress
Thank you!

Contact us at
CDER.EA.Team@fda.hhs.gov