Innovations that Decrease Exposure and Risk by Reducing the Quantity of Drugs Entering the Environment

Green Chemistry & Drug Therapy

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Pharmaceutical Life Cycle

Topics covered in talk

• Research and Development
  – Drug Design/Discovery
    • Drug molecule (Drug Substance/Active Pharmaceutical Ingredient (API))
  – Drug Formulation (Product) Design/Development
    • Pill, Capsule, IV, etc.
  – Drug manufacturing (synthesis) process development
    – Safety, Metabolism, Clinical, Environmental Investigation
    – Drug Registration
• Manufacturing – Drug Substance (API) & Drug Product
• Drug distribution and reverse distribution
• Sales/Prescription
• Patient use
• Disposal/Metabolism/Excretion
• Environmental fate and effects
1. Personalized Medicine
   - **Concept:** Drug/dose selection tailored to the genetics of a subpopulation of the patients with a medical condition
     - **Objective:** increase efficacy & decrease side effects
     - **Environmental implications:** less of an individual drug is used, less loading to the environment so lower environmental concentration, less risk potential
   - **Status:** Progress (Herceptin®) & Promise
     - Human genome mapped
     - **Scientific challenges:**
       - Genetic/molecular markers of disease
       - Diagnostic tools for identifying subpopulations
       - Therapeutic options
2. Biologics

- **Concept**: Biological medicines (monoclonal antibodies, vaccines, gene therapies, therapeutic proteins) target disease with great specificity
  - **Environmental implications**: Natural molecules, do not persist

- **Status**: Substantial innovation
  - 633 biotechnology medicines in development in 2008\(^{(4)}\)
  - 15 biologics included in the 34 new medicines FDA approved in 2009\(^{(5)}\)
Example of Personalized Medicine & Biologics
Breast Cancer Treatment with Herceptin®

1. **Personalized Medicine**
   - Approximately 30% of breast cancer cases are characterized by over-expression of a cell surface protein called human epidermal growth factor receptor 2 (HER2).
   - For these patients, standard therapy is not effective, but an antibody drug called Herceptin® (trastuzumab) does work.
     - Substantially reduces tumor recurrence in combination with chemotherapy.
   - Molecular diagnostic tests for HER2 identify the 30 percent of patients that will benefit from receiving Herceptin®.
     - Drug prescribed to that 30% of patients rather than to a larger percentage.

2. **Biologics**
   - Herceptin® is protein based and will rapidly degrade in the environment.
Wait a minute?!?

- Human Estrogen is also a natural molecule, and estrogen is present in surface waters receiving effluent. How do we know biological drugs, as natural molecules, will not persist?

- Biodegradation
  - Factors impacting degradation/rates: food, complexity of chemical structure, prior experience, genetic/enzymatic tools, concentration, environmental factors

- Estrogen does biodegrade
  - Rates, Pseudo-Persistence

Proteins (Amino Acids)
DNA (Nucleic Acids)

Biodegradation products (ultimate biodeg = CO₂ and water)
What is **Green Chemistry**?

“…the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products.”

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The Twelve Principles of Green Chemistry

1. Prevent waste: Design chemical syntheses to prevent waste, leaving no waste to treat or clean up.

2. Design safer chemicals and products: Design chemical products to be fully effective, yet have little or no toxicity.

3. Design less hazardous chemical syntheses: Design syntheses to use and generate substances with little or no toxicity to humans and the environment.

4. Use renewable feedstocks: Use raw materials and feedstocks that are renewable rather than depleting. Renewable feedstocks are often made from agricultural products or are the wastes of other processes; depleting feedstocks are made from fossil fuels (petroleum, natural gas, or coal) or are mined.

5. Use catalysts, not stoichiometric reagents: Minimize waste by using catalytic reactions. Catalysts are used in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and work only once.

6. Avoid chemical derivatives: Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.

The Twelve Principles of Green Chemistry

7. Maximise atom economy: Design syntheses so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms.

8. Use safer solvents and reaction conditions: Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals.

9. Increase energy efficiency: Run chemical reactions at ambient temperature and pressure whenever possible.

✓ 10. Design chemicals and products to degrade after use: Design chemical products to break down to innocuous substances after use so that they do not accumulate in the environment.

11. Analyze in real time to prevent pollution: Include in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of byproducts.

12. Minimize the potential for accidents: Design chemicals and their forms (solid, liquid, or gas) to minimize the potential for chemical accidents including explosions, fires, and releases to the environment.

Design for Degradation (Green Chemistry Principle # 10)

- **Concept:** Drug designed to degrade after use, innocuous products
- **Status:** Challenging scientific problem, limited investment
  - Drugs must have a chemical structure that results in:
    - Bioactivity = binding with a target in the body
    - Acceptable safety profile
    - Stability in synthesis, formulation, storage, use
  - **BUT,** then we want the drug to switch to unstable, which is also a function of structure
  - **Dilemma:** Currently lack the scientific knowledge to achieve BOTH the necessary drug properties and instability following efficacy

- **Opportunities:**
  - Develop a structure/environmental toxicity screen to inform drug discovery early, when 1,000’s of molecules are evaluated
  - Approach to designing potentially problematic drugs with a molecular switch to turn on “instability” once in the environment
Drug Formulation

1. **Concept**: Improve bioavailability and/or target a location
   - Increase efficacy, reduce side effects, minimize use & environmental load
   - Approaches to affinity and bioavailability:
     - Nanotechnology*
     - Conjugates/prodrugs (ex, rifamycins)
     - Drug Particle Size Optimization
   
   * Nanotechnology - environmental toxicity an emerging area of concern and research\(^\text{14}\)

   - **Status**: Current applications; innovation, especially nanotechnology

2. **Concept**: Use a less stable drug, for example, by encapsulating drug in a biodegradable polymer – functional in body but unstable in the environment

   - **Status**: idea stage
Formulation Example
Bisphosphonate Prodrugs\textsuperscript{16}

• Osteomyelitis – a bone infection
  – Treatment often requires surgery and prolonged antibiotic therapy
  – New class of prodrugs developed: rifamycins are linked to a bisphosphonate with high affinity for bone tissue
  – Antibiotics are delivered directly to infection site, where they are concentrated to exert therapeutic activity
1. **Greener Drug Synthesis - Manufacturing**

- **Concept**: (Re)Design drug synthesis to minimize material/energy/water use and waste generation
  - Foundation = 12 principles of green chemistry

- ACS Green Chemistry Institute, Pharmaceutical Roundtable
  - Innovation example: since 2007, award almost $1 million in academic grants to discover greener reactions important to pharmaceutical industry\(^\text{17}\)

- Pharmaceutical companies have won 9 US EPA Presidential Green Chemistry Challenge Awards

- Example from US EPA Presidential Green Chemistry Challenge Awards:
  - Roche Colorado, antiviral Cytovene®: Eliminated ~ 2.5 million lbs of hazardous liquid waste and > 55,000 pounds of hazardous solid waste each year \(^\text{18}\)
Green Chemistry in Process Development

- Exemplified by the Pregabalin (Lyrica®) Process Development Program
- Pregabalin treats Neuropathic Pain
- Launched in the US in September 2005
Efficient synthesis of racemic Pregabalin

- Racemic means equal amounts of left- and right-handed enantiomers of a chiral molecule

Final Step is separation of the enantiomers

Wrong enantiomer difficult to recycle

Pregabalin (Lyrica®) Launch Process

25-29 % overall

> 99.5 % ee
Biocatalytic Kinetic Resolution Route

- All 4 reactions are conducted in water
- Resolution at first step (wrong enantiomer can be recycled)
- Enzymatic Step scaled up to 10,000 Kg scale
Pregabalin enzymatic process – environmental benefits

- Between 2007 and 2020 the new synthesis will eliminate:
  - 185,000 tonnes of solvent, >90 % reduction
  - 4,800 tonnes of mandelic acid, a 100 % reduction
  - 2,000 tonnes of Raney nickel catalyst, a 90 % reduction
  - 15,000 tonnes of starting material, >50 % reduction

- Latest Process uses > 7 times fewer inputs than the product launch route

- Energy usage reduced by 83%

- Solvent and Energy savings are the equivalent to saving 413,550 tonnes of CO₂ emissions
  - Equivalent to taking 69,000 US cars off the road for a year!
Pregabalin Summary

- Launched in the US in September 2005
- Sales in 2009 $ 2.84 billion
- Enzymatic chemistry scaled to 10 tonnes
- All 4 reactions performed in water
- Process switched to the enzymatic route in 3Q2006
- By switching very early in the product lifetime, gain close to maximum benefits to the environment.
- In 2006 Pfizer received the AstraZeneca Award for Excellence in Green Chemistry and Engineering for its work on Pregabalin.
1. **Greener Drug Synthesis – Manufacturing (Cont.)**

- Examples of Success are Powerful and Important.

- Extent to which green process chemistry manufacturing initiatives (drug synthesis) have minimized the release of active drug to wastewater and the environment not clear
  - Active drug only present in final step(s) of the synthesis
  - Final process step may be carried out in an organic solvent – no wastewater
2. **Drug Product Formulation**  
(incorporating the drug substance into a pill, capsule, etc.)

- US Geological Survey publication June 2010, US pharmaceutical formulation facility (PFF) discharges
  
  - “findings suggest that current manufacturing practices at these PFFs can result in pharmaceuticals concentrations from 10 to 1000 times higher than those typically found in WWTP effluents”

- **Status**: New findings from effluents of 2 WWTP receiving wastewater from PFF
  - How representative of US pharmaceutical formulation facilities (PFF)?
  - Possible source: equipment (blenders, etc.) cleaning operations using water/cleaning agents

- **Opportunity**:
  - Apply green chemistry principles to drug formulation manufacturing operations
Concept: Remove drugs during Treatment

- Challenges:
  - Over 16,000 domestic WWTP (Wastewater Treatment Plants)
  - Diversity of chemicals, different susceptibilities to treatment
  - Knowledge gaps:
    - What are the specific risks from drugs in water to humans/wildlife?
    - What operations are most effective for removing drugs?
    - What is the cost/benefit of advanced technology (environ. trade-off)?

- Opportunities:
  - Innovations to improve effectiveness
    - US EPA’s Sustainable Water Infrastructure Initiative
    - Academic, government, and industry research initiatives

- Maximizing waste prevention (green chemistry principle # 1) preferable to relying on treatment
Moving Forward - 1

- Drug therapy and drug formulation innovations can benefit patients and the environment

- Green Chemistry is:
  - An economical26 and proven solution for greener drug substance manufacturing
  - A tool for greening drug product manufacturing
  - A research opportunity for greener drug design

- Scholarship and innovation needs:
  - Rapid and early feedback on the environmental properties of drug candidates (next slide)
  - Designing and formulating more unstable drugs when environmental risks are significant
  - Evaluating risks of emerging contaminants
  - Waste/drinking water treatment options for removing contaminants of concern
There are principles for designing effective drugs\textsuperscript{27}

BUT there are no design rules for avoiding or addressing (formulation, etc.) drugs that may be environmentally toxic during the early phases of research when a drug structure is finalized.

- Fate and effect studies during the drug development cycle are designed to identify environmental risks
  - A regulatory requirement and a good step, but these studies occur late in the R&D process long after the drug, and typically formulation, are determined

- We need an environmental toxicity screen suitable for the drug discovery stage, when many 1,000’s of compounds are screened rapidly for drug candidates
  - Exploration of alternative structures with more favorable properties
  - Incorporation of a molecular instability switch
  - Development of formulations to minimize drug use or enable use of a less stable drug
References / Sources - 1

6. Herceptin® example, Personalized medicine example: http://www.ageofpersonalizedmedicine.org/
15. Image: Drug Targeting. Modified and used with permission of B. Cue.
17. Source: B. Cue, 2010 ACS meeting presentation, Boston, MA.
19. Image: ACS Green Chemistry Institute logo. Used with ACS permission. From ACS GCI website
28. Pregabalin (Lyrica®) slides provided and approved for use by Dr. Peter Dunn, Pfizer
Rich Williams

Experience with pharmaceuticals includes:

- 17 years of environmental science and green chemistry leadership roles in Pfizer* Global R&D, achieving most senior research position (senior research fellow)
- Founding chair of Society of Environmental Toxicology and Chemistry (SETAC) Pharmaceuticals Advisory Group
- Co-founded and chaired the Pfizer Groton Green Chemistry team for 4 years, co-authoring a US Presidential Green Chemistry award winning nomination
- Chair, SETAC Pellston Workshop Steering Committee, addressed the adequacy of the existing science to identify risks and the environmental impacts of pharmaceuticals as contaminants
- Chair, Pfizer Pharmaceuticals in the Environment Leadership Team
- Member, Pfizer Nanotechnology Safety Practice Network
- Chair, Environmental Risk Assessment Team, Pharmaceutical Research and Manufacturers of America (PhRMA)
- Editor. Human pharmaceuticals: assessing the impacts on aquatic systems. SETAC Press; 2005:368p
- Consultant for the evaluation of chemicals and development of greener chemicals and products
- Organizing committee and opening speaker, Human Health Risk Assessment for Pharmaceuticals in the Environment, Society of Toxicology, Seattle, March 2008
- Member of a team that established a publicly available environmental classification system for pharmaceuticals in Sweden
- Program Committee and keynote speaker for a drug registration EA conference: DIA/HESI/SAPS Workshop on Environmental Assessment of Human Medicines, Stockholm, May 22-23, 2006

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*, Opinions expressed in this talk are those of Richard Williams, not those of Pfizer, and are not based on Pfizer proprietary information.