# 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**)

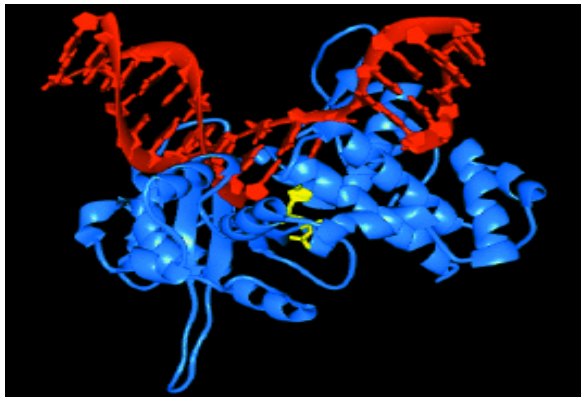
- Research and Development
  - **Drug Design/Discovery**
    - Drug molecule (Drug Substance/Active Pharmaceutical Ingredient (API))
  - **Drug Formulation (Product) Design/Development**
    - Pill, Capsule, IV, etc.
  - **Drug manufacturing (synthesis) process development**
  - Safety, Metabolism, Clinical, 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**

# Drug Therapy



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

# Drug Therapy





## 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[6]

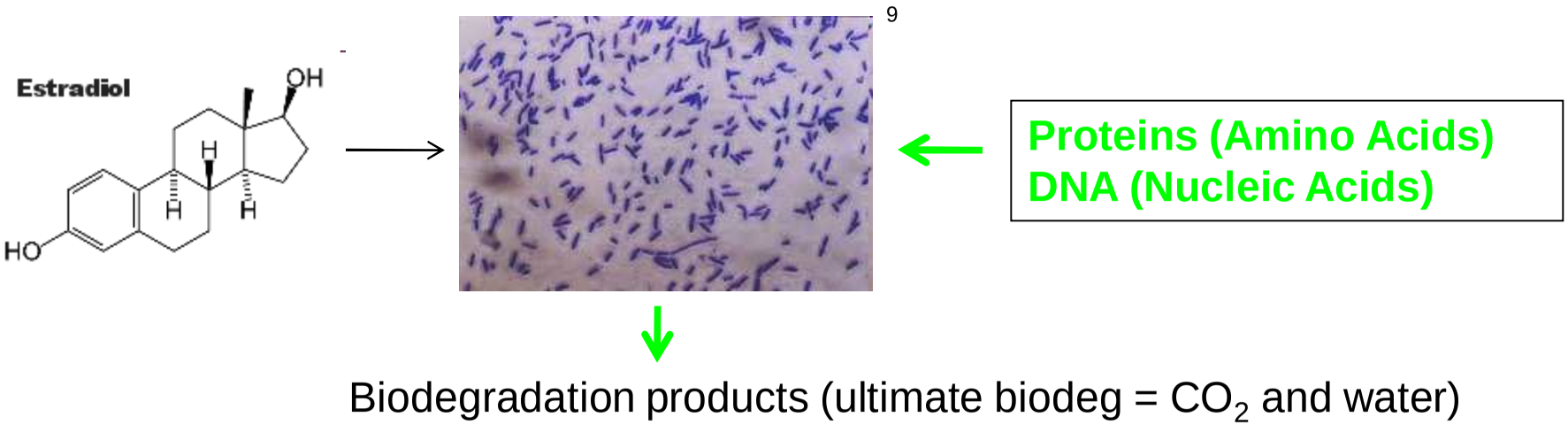
- Approximately 30% of breast cancer cases are characterized by over-expression of a cell surface protein called human epidermal growth factor receptor 2 (HER2)
- For these patients, standard therapy is not effective, but an antibody drug called Herceptin® (trastuzumab) does work
  - Substantially reduces 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[7]

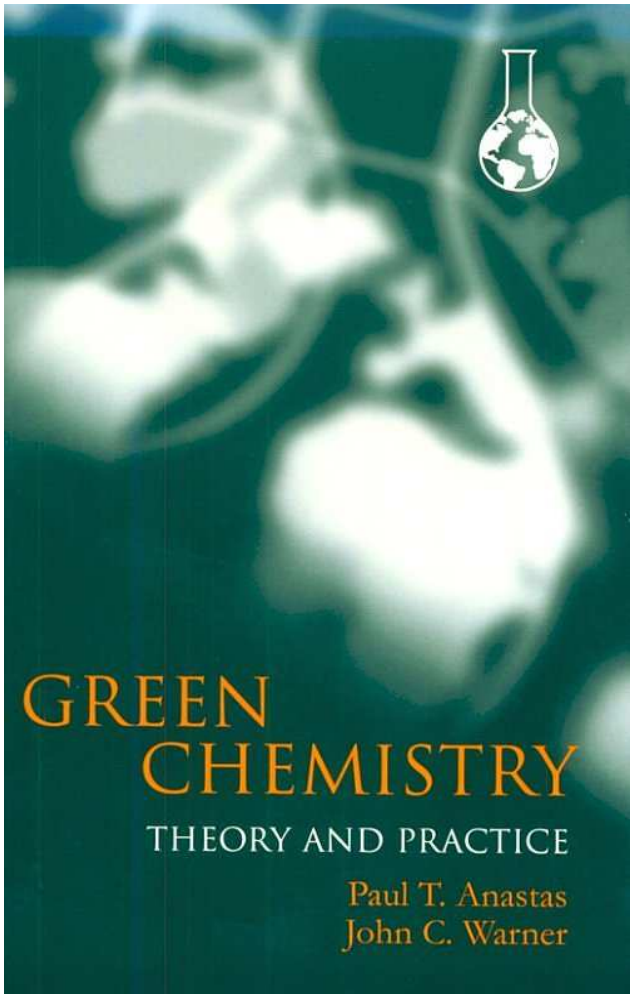
# Wait a minute?!?

- 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[8]
  - Rates, Pseudo-Persistence

# 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."[10]

# 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.

Paul T. Anastas and John C. Warner, *Green Chemistry: Theory and Practice* (New York, NY: Oxford University Press Inc., 1998).

# The Twelve Principles of Green Chemistry

7. **Maximize 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

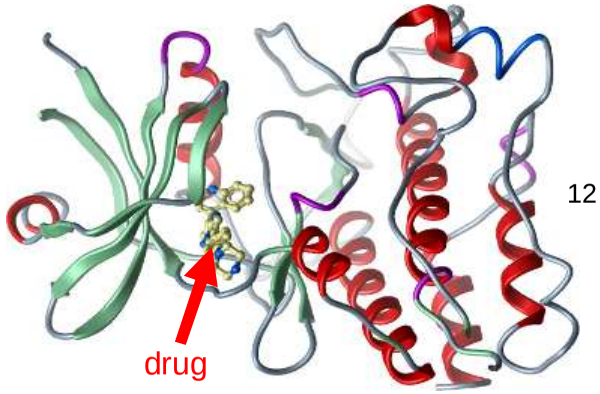
Paul T. Anastas and John C. Warner, *Green Chemistry: Theory and Practice* (New York, NY: Oxford University Press Inc., 1998).

# Drug Discovery

## Design for Degradation (Green Chemistry Principle # 10)

- Concept: Drug designed to degrade after use, innocuous products
- Status: Challenging scientific problem, limited investment[13]
  - 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

Drug Receptor – a protein

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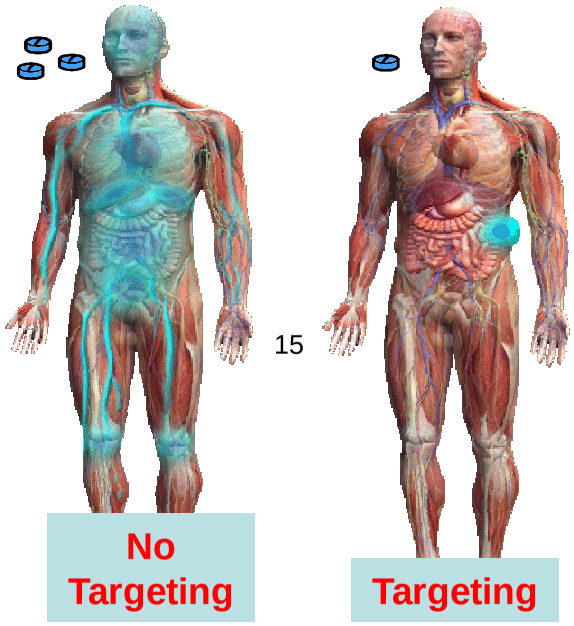
- BUT, then we want the drug to switch to unstable, which is also a function of structure
- Dilemma: Currently lack the scientific knowledge to achieve BOTH the necessary drug properties and instability following efficacy

- 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

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* Nanotechnology - environmental toxicity an emerging area of concern and research[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[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

# Green Chemistry



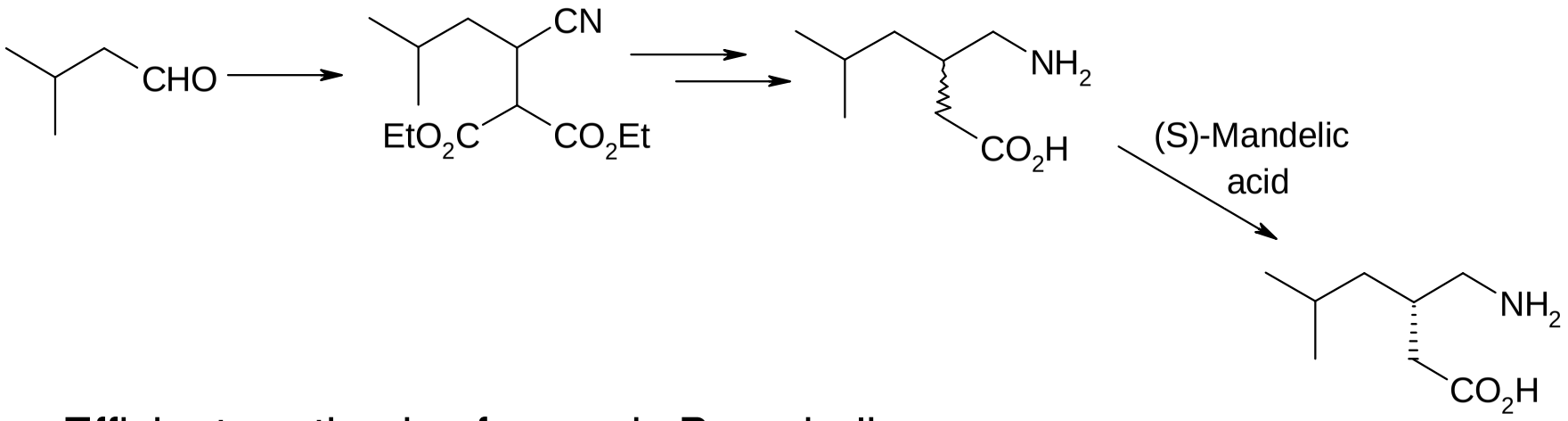
## 1. Greener Drug Synthesis - Manufacturing

- 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[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 [18]

# Green Chemistry in Process Development[28]

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

# Pregabalin (Lyrica®) Launch Process[28]

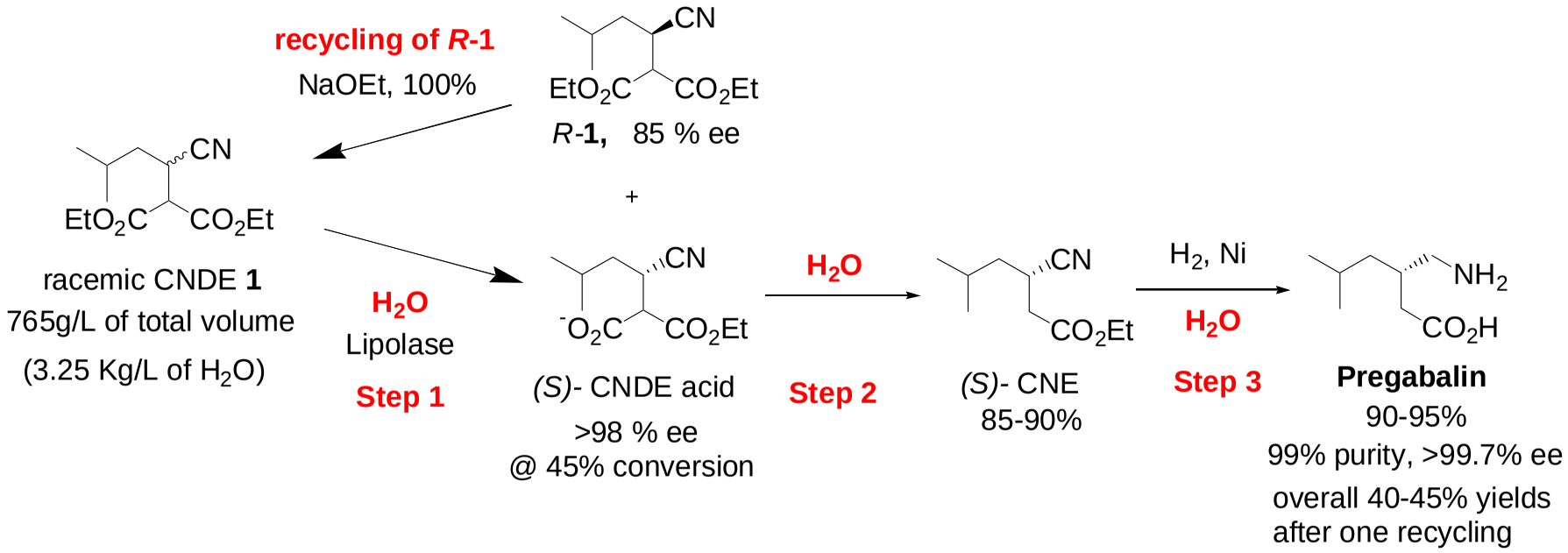



25-29 % overall

> 99.5 % ee

- 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

# Biocatalytic Kinetic Resolution Route[28]




- 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[28]

- 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 $CO_2$ emissions
  - Equivalent to taking 69,000 US cars off the road for a year!

# Pregabalin Summary[28]


- 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.
- Chemistry published Martinez et al. (*OPRD*, 2008, *12*, 392).
- In 2006 Pfizer received the AstraZeneca Award for Excellence in Green Chemistry and Engineering for its work on Pregabalin.

# Green Chemistry



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

# Manufacturing


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 [21]
  - "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

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# Wastewater & Drinking Water Treatment

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Concept: Remove drugs during Treatment

- Challenges:
  - Over 16,000 domestic WWTP (Wastewater Treatment Plants)[24]
  - 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 [25]
    - 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 economical[26] 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

# Moving Forward – 2
## Drug Design Principles

- There are principles for designing effective drugs[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

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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 (P*h*RMA)
- 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.