SUSTAINABLE CHEMICAL MANUFACTURING FOR 21ST CENTURY PHARMACEUTICALS

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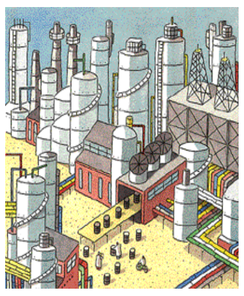
Introduction[1,2]
The pharmaceutical industry develops, produces and provides medicines that allow patients to live longer and healthier. However, there is a significant number of challenges that industry needs to solve for a more sustainable future. Active Pharmaceutical Ingredients (APIs) manufacturing is characterized by its low resource efficiency . Their molecular complexity requires the consumption of large amount of non green solvents, the use of stoichiometric quantities rather than catalytic and their manufacturing utilizes non-recoverable precious metals. Thus, there is a need for change, with research under way aimed at improving current processes and developing new syntheses and applying Green Chemistry good practices in pharmaceutical manufacturing.

Life Cycle of Drugs

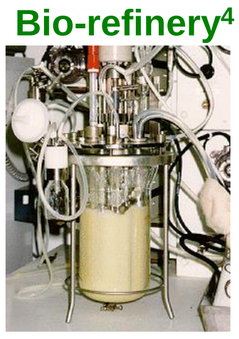

Petroleum feedstock

Petroleum Refinery[3]



Fuels
Solvents
Bulk chemicals
Plastics
Fine Chemicals
Oils

Bio-refinery[4]



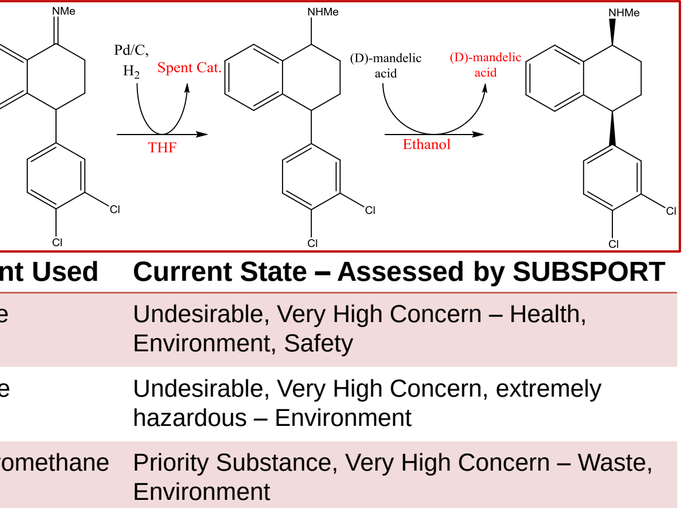
Biomass

Raw Materials

- Most APIs are based on organic compounds from non-renewable fossil materials
- Limited use of renewables as raw materials
- Scarce metals

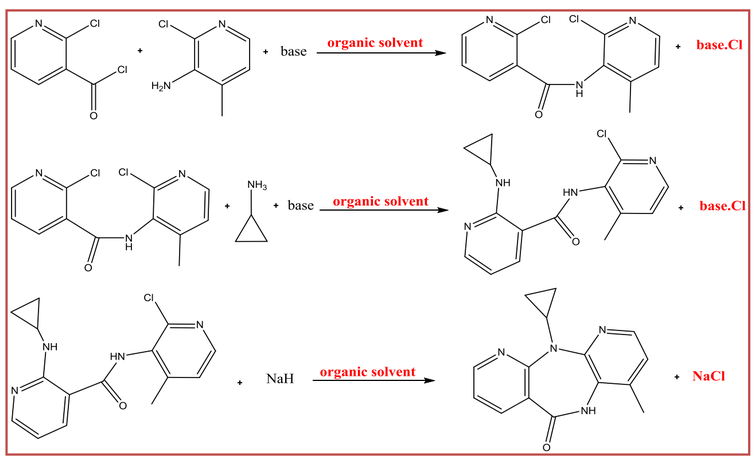
Elemental Sustainability

Periodic Table highlights the critical elements based on non-reserves and current rate of consumption



Case Study 1
NEVIRAPINE[5] – AntiHIV1 API

- Highly selective non-nucleoside inhibitor of HIV-1 Reverse Transcryptase
- Example of non-green practice



- **Industrial manufacturing suffers from:**
  - Large use of hazardous solvents

Solvent Used	Current State – Assessed by SUBSPORT
Cyclohexane	Undesirable, extremely hazardous – Health
1,4-dioxane	Undesirable, extremely hazardous – Safety, Health
Hexane	Undesirable, Very High Concern – Health, Environment, Safety
Toluene	Undesirable, Very High Concern, extremely hazardous – Environment
Dimethylformamide	Undesirable, Very High Concern, extremely hazardous – Health
Dichloromethane	Priority Substance, Very High Concern – Waste, Environment
Ethyl Acetate	Acceptable, Some concern of its waste
Tetrahydrofuran	Waste, Safety
Xylene	Priority Substance, High Concern – Environment

  - Use of hazardous reagents (e.g. NaH)
  - Low Mass Efficiency
  - By-products for disposal

APIs Manufacture

• Hazardous reagents
• Usage of scarce metals that are not recycled - recovered
• Large energy consumption
• Multi-step processes
• **Large consumption of SOLVENTS**

LARGE VOLUMES OF HAZARDOUS WASTE

70-80% contributors of APIs waste

Formulating
- Waste
- Energy cost
- Washing solvents

Patient
- Waste product
- Uncontrolled disposal

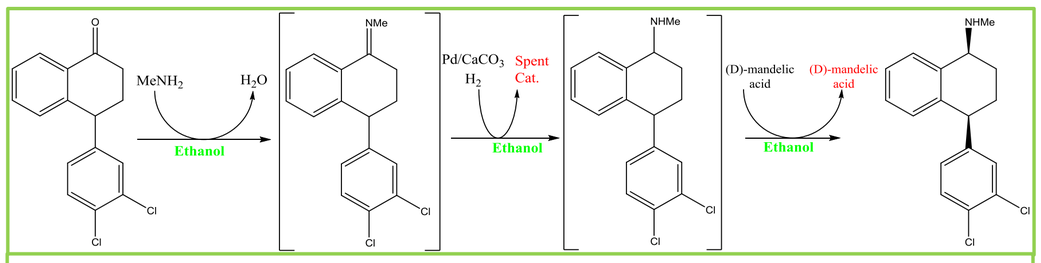
End of Life
- Bioaccumulation
- Persistence

Case Study 2: Improved Synthesis
SERTRALINE[6] – Antidepressant API

- Inhibitor of synaptosomal serotonin uptake
- Important API for treatment of depression and dependency- and other anxiety-related disorders

Bad Points:
- Use of hazardous solvents
- Hazardous reagents
- By-products disposal

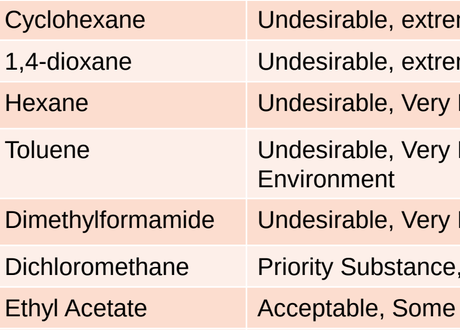
Solvent Used	Current State – Assessed by SUBSPORT
Hexane	Undesirable, Very High Concern – Health, Environment, Safety
Toluene	Undesirable, Very High Concern, extremely hazardous – Environment
Dichloromethane	Priority Substance, Very High Concern – Waste, Environment
Tetrahydrofuran	Waste, Safety



Good Points:
- Reduce number of solvents to one
- Employment of a benign solvent – ethanol
- Less hazardous reagents and waste

A practical way forward[7]

We developed a strong and unified set of metrics for researchers and the Pharmaceutical Industry.
This sustainable toolbox gives a holistic approach of assessing the environmental impacts of the Pharmaceutical processes through the use of Green Chemistry Metrics.



$$Reaction\ Mass\ Efficiency = \frac{mass\ of\ product(s)}{mass\ of\ all\ reagents}$$

Takes into account:
- **Yield**
- **Atom Economy**
- **Reagents excess**

Benefits

For Industry:
Lower cost manufacturing
For Patients:
New greener and safer products
Lower cost drugs
For Environment:
Less hazardous waste
Usage of more sustainable feedstock

Acknowledgement
We thank the Innovative Medicines Initiative (IMI) for funding the CHEM21 project and all the CHEM21 members for their valuable support.

Conclusion[2]
APIs manufacturing can be improved in terms of resource efficiency, sustainability and lower environmental impact through the substitution of hazardous solvents and reagents with safer and greener alternatives, the switch from stoichiometric to catalytic reactions, and the minimisation of use of the scarce metals and other auxiliary substances. However, improved methodologies need to be assessed through a unified sustainability metrics toolkit in order to be implemented in the pharmaceutical industry. CHEM21 (Chemical Manufacturing Methods for the 21st century Pharmaceutical Industry) is a new pan-European project where Pharmaceuticals and Universities are working together, committed to deliver a sustainable pharmaceutical manufacturing. Under this consortium an objective green metrics toolkit was developed in order to provide a holistic approach of assessment.

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