Greening The Pharmaceutical Industry To Afford Good Laboratory Practice

Presented By

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I am so glade to be here in this International Conference of GLP , GCP & GMP.



Who am I

1. Professor & Head of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Cairo University.
2. Trainer in Faculty and Leadership Development Center, Cairo University.
3. Reviewer for Higher Education Institutions, conducted by the National Authority of Quality Assurance and Accreditation of Education, Egypt.
4. Evaluator at Project administration, Ministry of Higher Education, Egypt.
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Other Posts:

1. Director of Career Center, Faculty of Pharmacy, Cairo University.
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Green
Chemistry

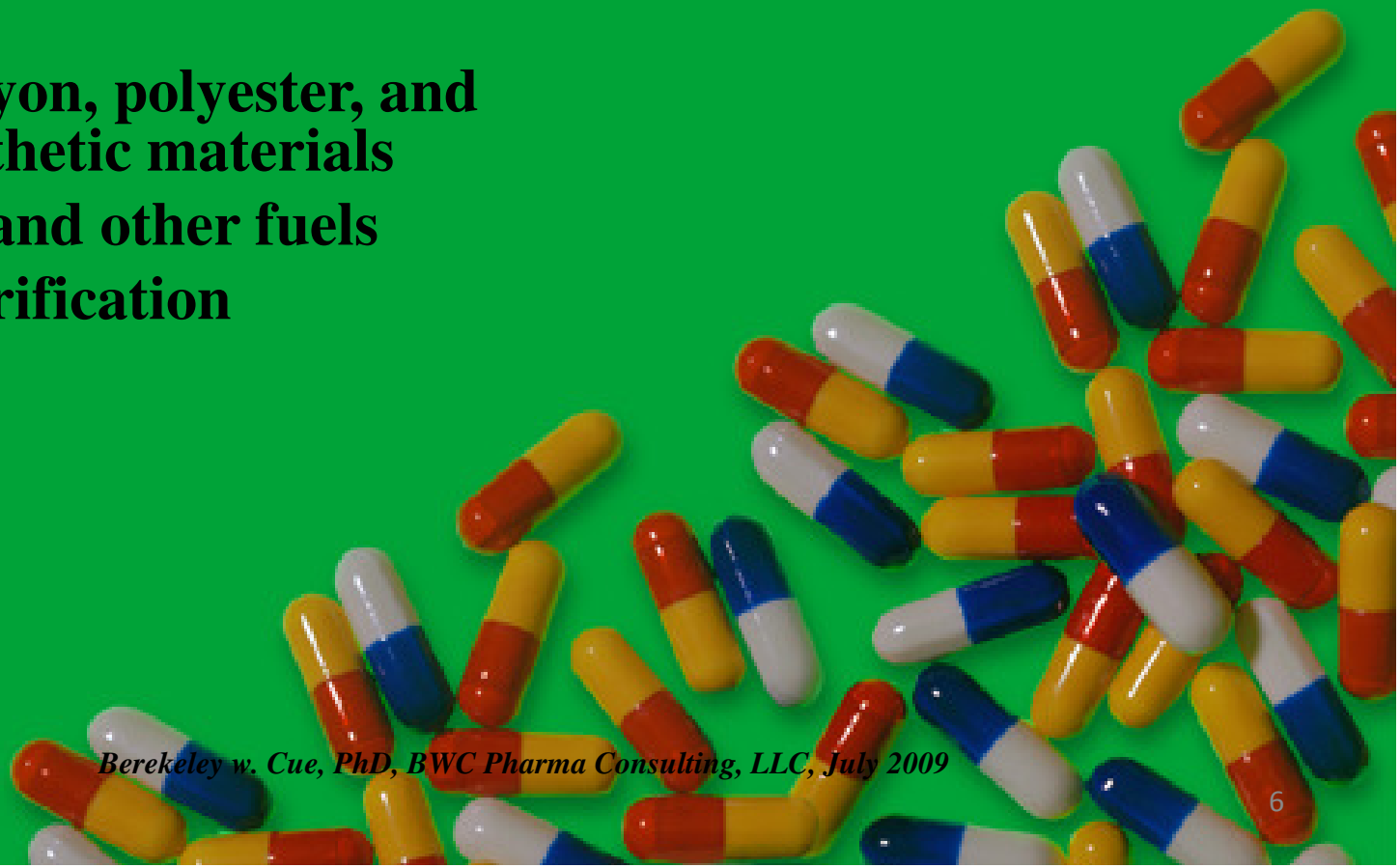
First, let's consider chemistry's benefits….

The chemical industries produce many products that improve our lives and upon which we depend.

Berekeley w. Cue, PhD, BWC Pharma Consulting, LLC, July 2009

Benefits of chemical industries

- **Antibiotics and other medicines**
- **Fertilizers, pesticides**
- **Plastics**
- **Nylon, rayon, polyester, and other synthetic materials**
- **Gasoline and other fuels**
- **Water purification**



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"Better Things for Better Living Through Chemistry"
DuPont

- **Ibuprophen**
- **Lipitor**
- **Celebrex**
- **Vioxx**
- **Rogaine**
- **Prozac**
- **Viagra**
- **Prilosec**

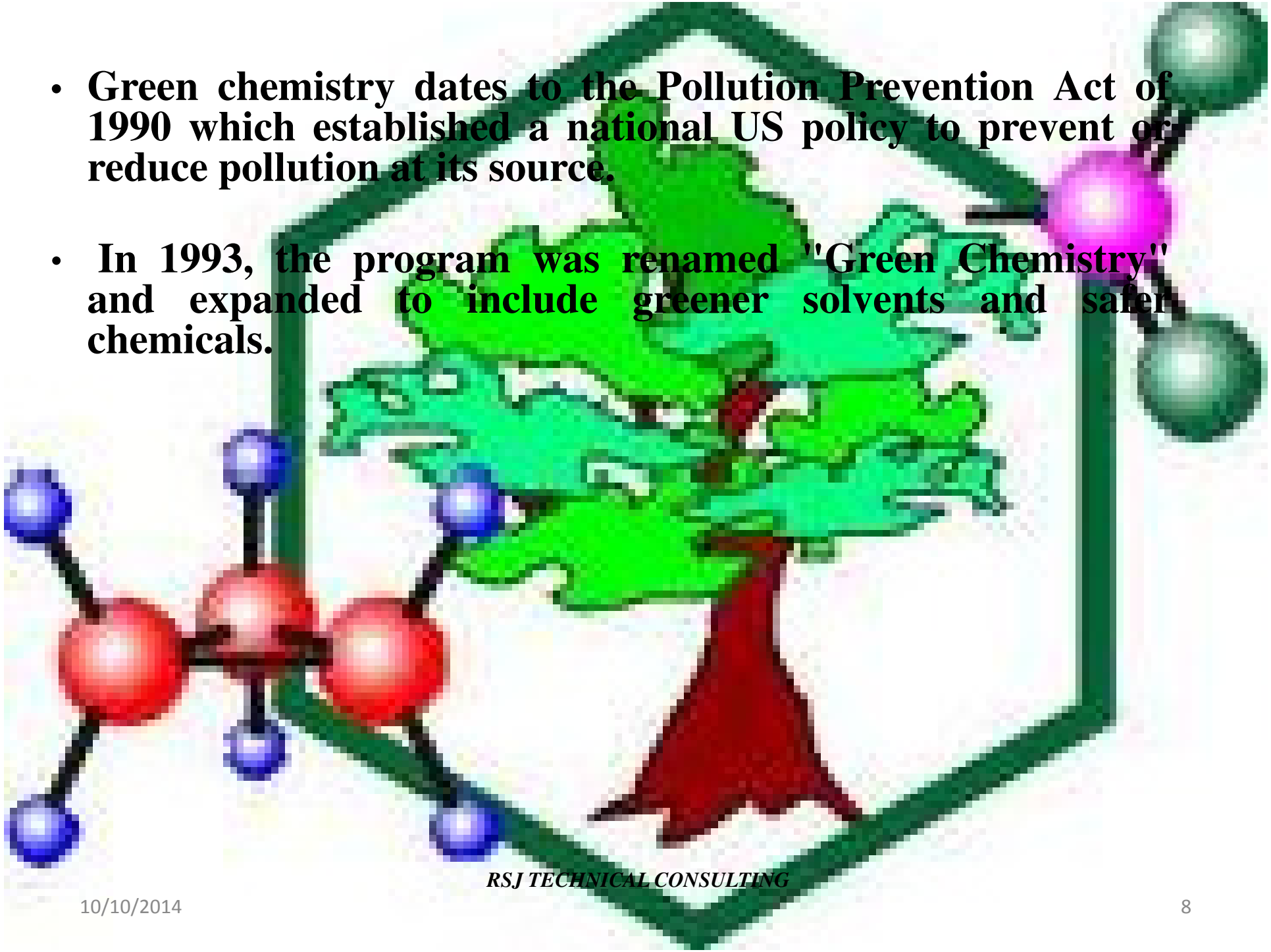
- **Nylon**
- **Dacron**
- **Polystyrene**
- **Acrylics**
- **Teflon**
- **Rayon**

- **DNA**
- **Recombinant Technology**
- **PCR**

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- **Green chemistry dates to the Pollution Prevention Act of 1990 which established a national US policy to prevent or reduce pollution at its source.**

- **In 1993, the program was renamed "Green Chemistry" and expanded to include greener solvents and safer chemicals.**



The 12 Principles of Green Chemistry

1- Prevention of wastes

It is better to prevent waste than to treat or clean up waste after it has been created.

2-Less Hazardous Chemical Synthesis

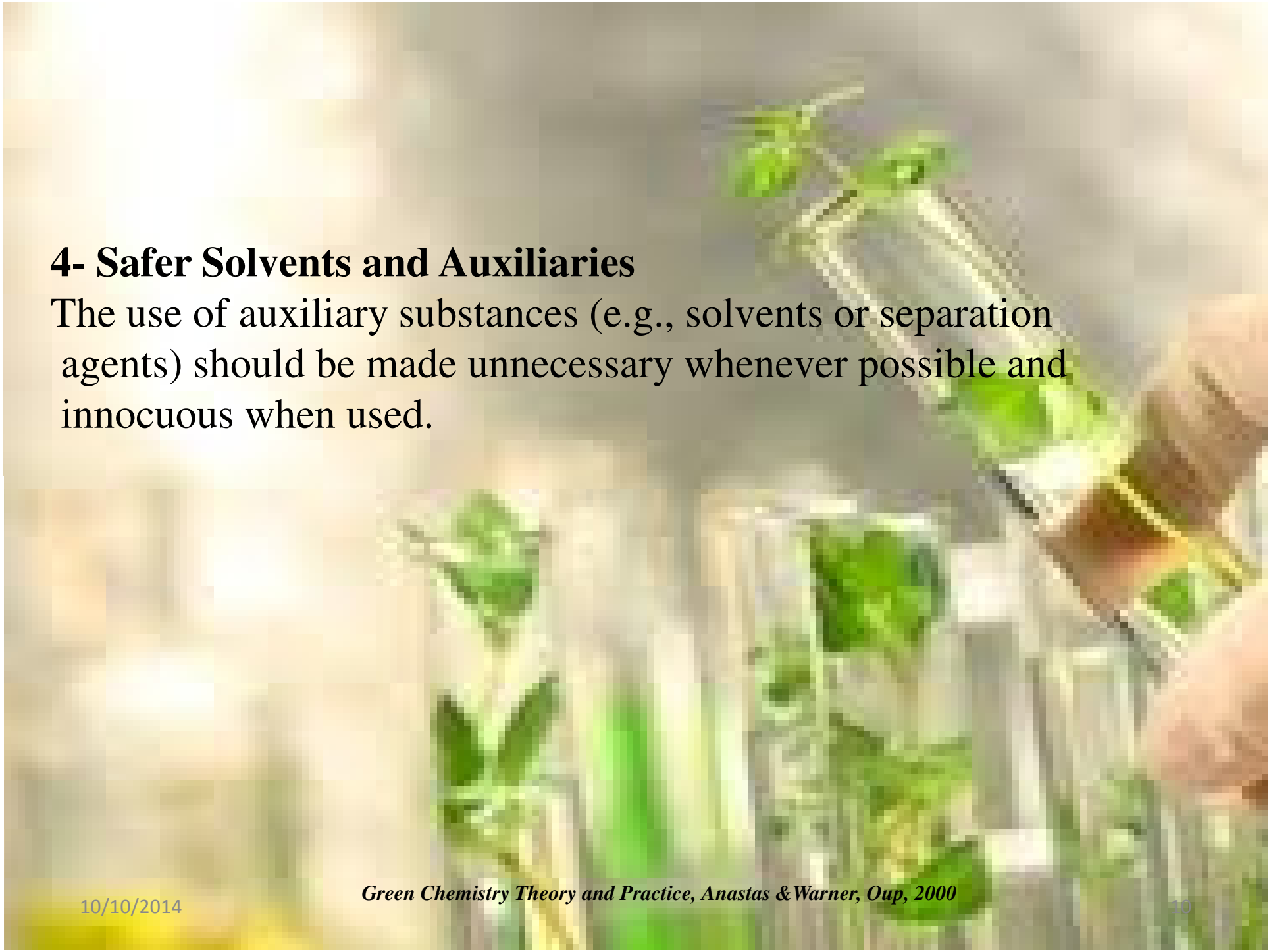
Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to people or the environment.

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3-Designing Safer Chemicals

Chemical products should be designed to effect their desired function while minimising their toxicity.

Green Chemistry Theory and Practice, Anastas & Warner, Oup, 2000



4- Safer Solvents and Auxiliaries

The use of auxiliary substances (e.g., solvents or separation agents) should be made unnecessary whenever possible and innocuous when used.

Green Chemistry Theory and Practice, Anastas &Warner, Oup, 2000

Pfizer Medicinal Chemistry Solvent Selection Guide

Preferred	Usable	Undesirable
Water	Cyclohexane	Pentane
Acetone	Heptane	Hexane(s)
Ethanol	Toluene	Di-isopropyl ether
2-Propanol	Methylcyclohexane	Diethyl ether
1-Propanol	TBME	Dichloromethane
Ethyl Acetate	Isooctane	Dichloroethane
Isopropyl acetate	Acetonitrile	Chloroform
Methanol	2-MeTHF	NMP
MEK	THF	DMF
1-Butanol	Xylenes	Pyridine
t-Butanol	DMSO	DMAc
	Acetic Acid	Dioxane
	Ethylene Glycol	Dimethoxyethane
		Benzene
		Carbon tetrachloride

5- Design for Energy Efficiency

Energy requirements of chemical processes should be recognised for their environmental and economic impacts and should be minimised. If possible, synthetic methods should be conducted at ambient temperature and pressure.

Energy sparing chemistry begins to use **Microwave Chemistry** in order to increase energy efficiency.

Green Chemistry Theory and Practice, Anastas & Warner, Oup, 2000

Recently, microwave chemistry is the science of applying microwave irradiation to chemical reactions. Microwaves act as high frequency electric fields and will generally heat any material such as polar molecules in a solvent or conducting ions in a solid.

6- Use of Renewable Feedstocks

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

7- Reduce Derivatives

Unnecessary derivatization (use of blocking groups protection/de-protection, and temporary modification of physical/chemical processes) should be minimised or avoided if possible, because such steps require additional reagents and can generate waste.

8- Catalysis

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

Green Chemistry Theory and Practice, Anastas & Warner, Oup, 2000

9- Design for Degradation

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

10- Real-time Analysis for Pollution Prevention

Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

11- Atom Economy

Synthetic methods should be designed to maximise the incorporation of all materials used in the process into the final product.

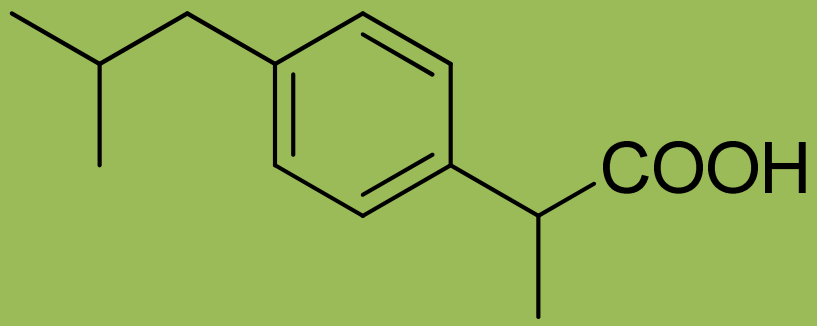
12- Inherently Safer Chemistry for Accident Prevention

Substances and the form of a substance used in a chemical process should be chosen to minimise the potential for chemical accidents, including releases, explosions, and fires.

Green Chemistry Theory and Practice, Anastas & Warner, Oup, 2000


Applications

A Greener Synthesis of Ibuprofen Which Creates Less Waste and Fewer Byproducts

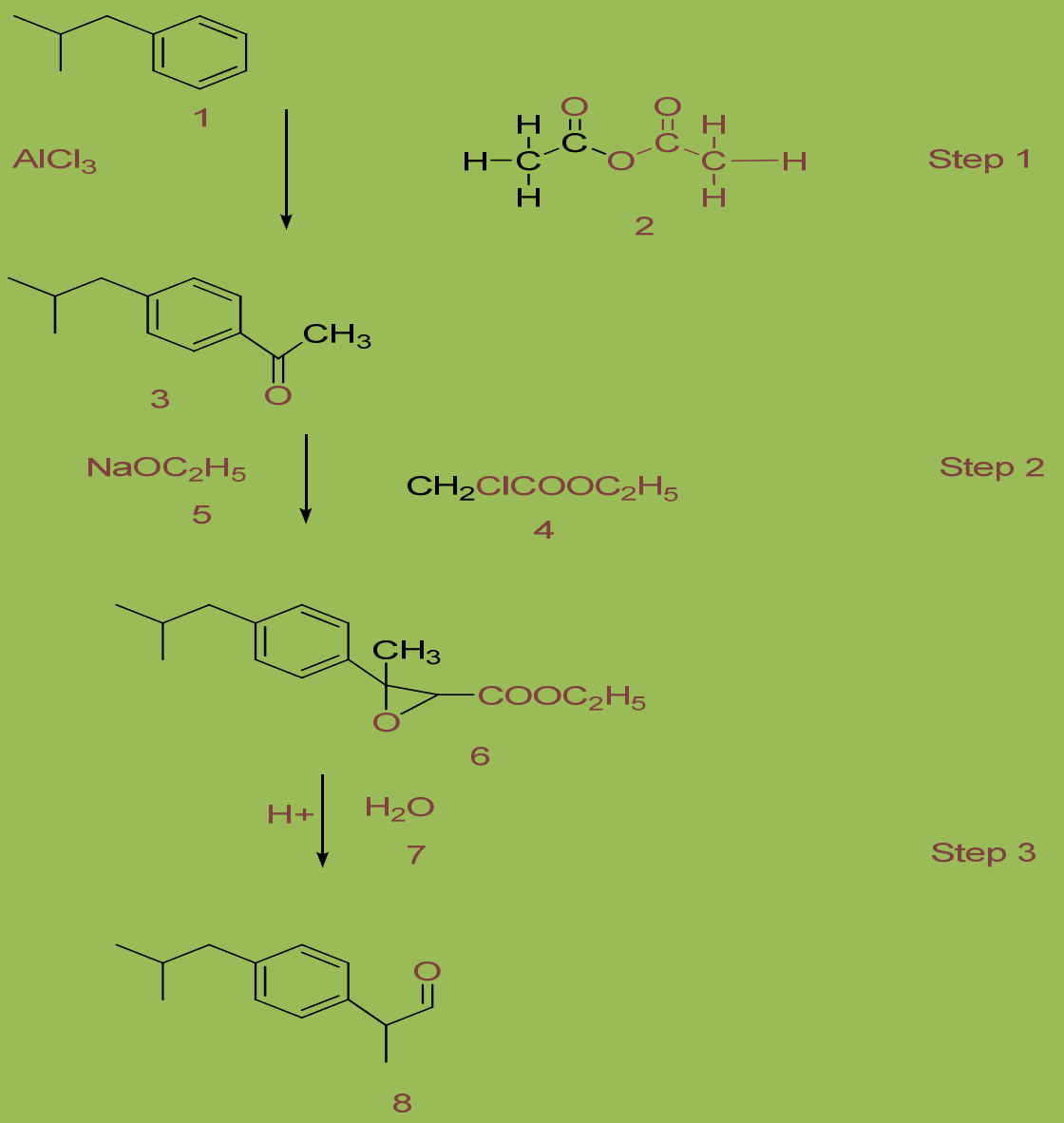


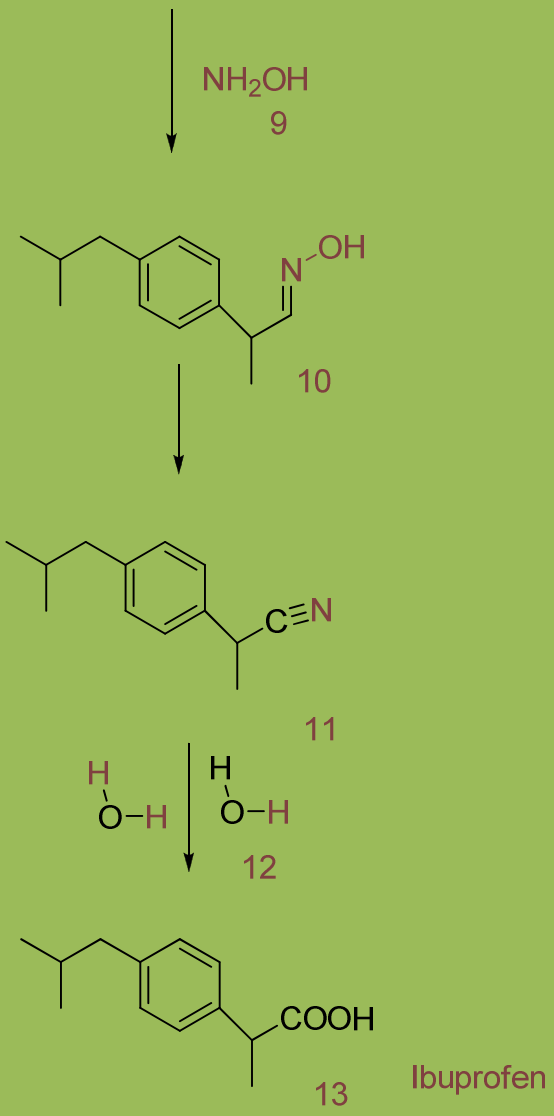
www.epa.gov/greenchemistry

The traditional industrial synthesis of ibuprofen was developed and patented by the Boots Company of England. This synthesis is a six-step process and results in large quantities of unwanted waste chemical byproducts that must be disposed of or otherwise managed. Much of the waste that is generated is a result of many of the atoms of the reactants not being incorporated into the desired product (ibuprofen) but into unwanted byproducts (poor atom economy/atom utilization).

The BHC Company has developed and implemented a new greener industrial synthesis of ibuprofen that is only three steps. In this process, most of the atoms of the reactants are incorporated into the desired product (ibuprofen). This results in only small amounts of unwanted byproducts (very good atom economy/atom utilization) thus lessening the need for disposal and mediation of waste products.

Trost, Barry M. The Atom Economy—A Search for Synthetic Efficiency. Science 1991, 254, 1471–1477.


1
AlCl3
2
Step 1
CH3
3
O
NaOC2H5
5
CH2ClCOOC2H5
4
Step 2
CH3
COOC2H5
O
6
H+
H2O
7
Step 3
O
8

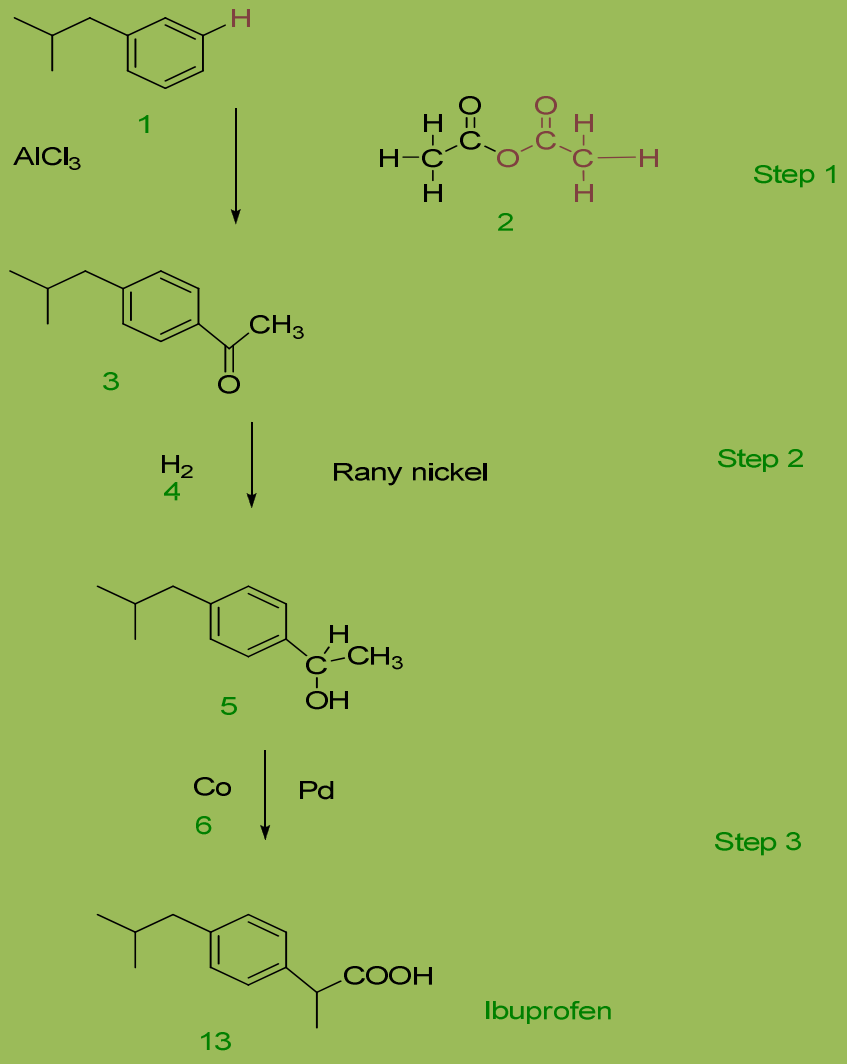


SCHEME 1. The Boots Company Synthesis of Ibuprofen—The Brown Synthesis

Table 1 shows a calculation of the atom economy of the overall reaction.

Reagent		**Used in ibuprofen**		**Unused in ibuprofen**	
Formula	**M_r**	**Formula**	**M_r**	**Formula**	**M_r**
$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
$C_7H_6O_3$	102	C_2H_3	27	$C_2H_3O_3$	75
$C_4H_7ClO_2$	122.5	CH	0	$C_3H_6ClO_2$	109.5
C_2H_5ONa	68		0	C_2H_5ONa	68
H_3O	19		0	H_3O	19
NH_3O	33			NH_3O	33
H_4O_2	36	HO_2	33	H_3	3
Total		**Ibuprofen**		**Waste products**	
$C_{20}H_{42}NO_{10}ClNa$	514.5	$C_{13}H_{18}O_2$	206	$C_7H_{24}NO_8ClNa$	308.5

Green Chemistry: The BHC Company Synthesis of Ibuprofen—A Greener Synthesis of Ibuprofen.



SCHEME 2. The BHC Company Synthesis of Ibuprofen— The Green Synthesis

Table 2 shows a calculation of the overall atom economy; it is 77% almost double that of the Boots' synthesis .

Reagent		**Used in ibuprofen**		**Unused in ibuprofen**	
Formula	**M_r**	**Formula**	**M_r**	**Formula**	**M_r**
$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
$C_7H_6O_3$	102	C_2H_3O	43	$C_2H_3O_2$	59
H_2	2	H_2	2		0
CO	28	CO	0		0
Total		**Ibuprofen**		**Waste products**	
$C_{15}H_{22}O_4$	266	$C_{13}H_{18}O_2$	206	$C_2H_4O_2$	60

Conclusion

Good Laboratory Practice (GLP)

- **embodies a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, reported and archived.**
- **also, is concerned with preclinical development including research laboratory: discovery & development of new drugs/therapy.**

Ridley, R., Handbook: good laboratory practice (GLP): quality practices for regulated non clinical research and development, Second edition, 2009, World Health Organization

Green Chemistry

- **embodies a set of principles that provides both a strategy for developing safer products and the normative standards for distinguishing desirable outcomes from less desirable ones.**
- **affords a framework within which laboratory studies include greener solvents and safer chemicals to prevent or reduce pollution at its source.**
- **also, is concerned with research laboratory for preclinical development : discovery & development of new drugs/therapy.**

Green Chemistry Theory and Practice, Anastas &Warner, Oup, 2000



Indeed, greening the pharmaceutical industry

afford Good Laboratory Practice.

Recommendations

There are six key tools for designing greener chemicals/processes:

- **Alternative feedstocks/starting materials (raw materials).**
- **Alternative reagents (substances in which other substances are dissolved).**
- **Alternative solvents (substances in which other substances are dissolved).**

Anatas, at the EPA, and Warner, at the University of Massachusetts-Boston

- **Alternative product/target molecule (molecule on which research is focused).**

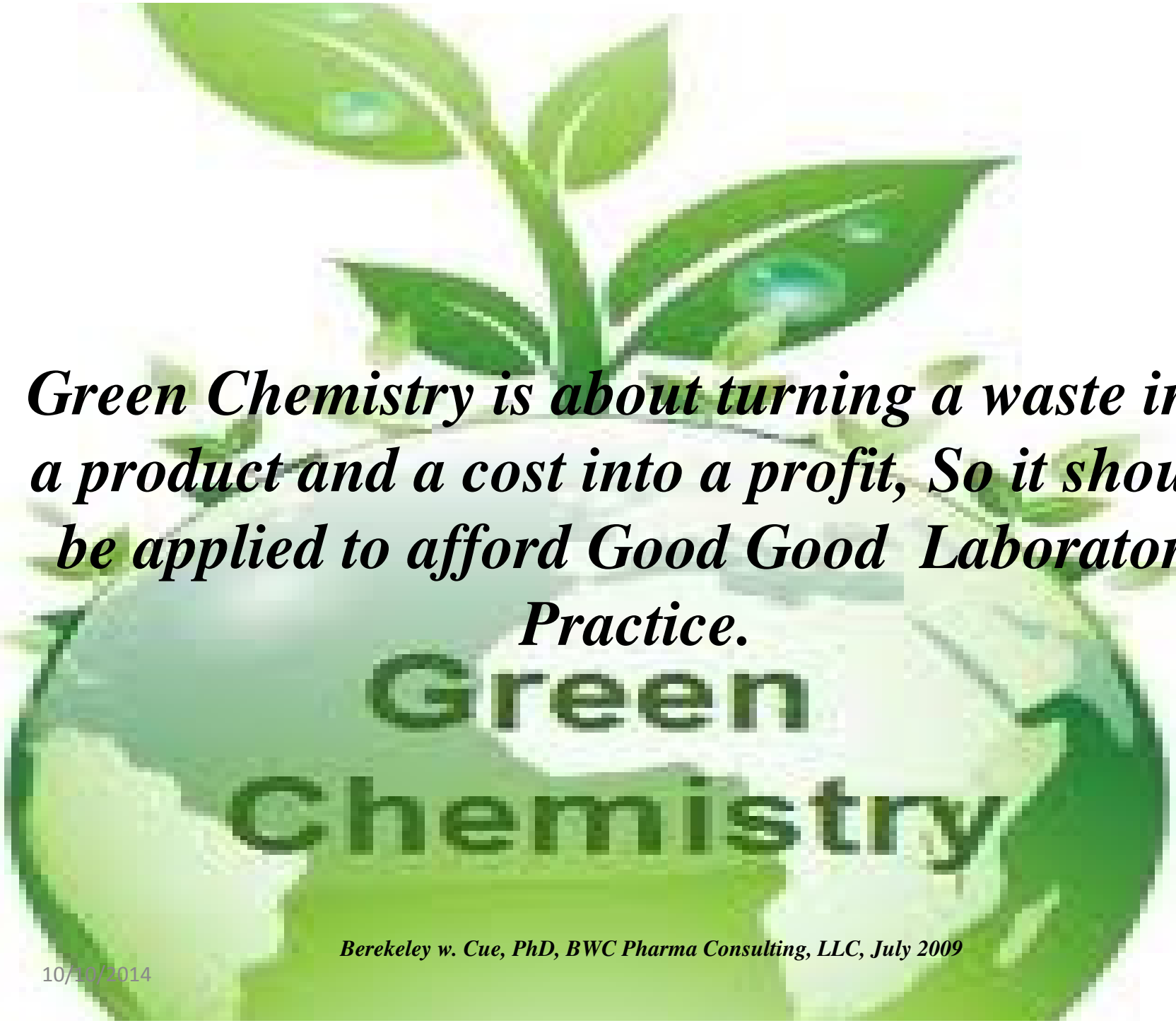
- **Alternative catalysts (reusable reagents that are not consumed during the chemical reaction).**

- **Finally, quality control (real – time measurements).**

Anatas, at the EPA, and Warner, at the University of Massachusetts-Boston

•***Chemists Must place a Major Focus on the Environmental Consequences of Greening Pharmaceutical Products and the Processes by which these Products are Made. We Must Consider Our Chemical Ecological Footprint.***

Anatas, at the EPA, and Warner, at the University of Massachusetts-Boston



Green Chemistry is about turning a waste into a product and a cost into a profit, So it should be applied to afford Good Good Laboratory Practice.

Berekeley w. Cue, PhD, BWC Pharma Consulting, LLC, July 2009


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Thanks
to you all!