Green Chemistry for Pharma API Industry

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Green Chemistry: Is it New?

All about reducing:

- Waste
- Materials
- Hazards
- Risks
- Energy
- Cost
Societal Image on Chemistry

- Chemistry was once viewed as a field of innovation resulting in health and food production breakthroughs and many such things for modern convenience.
- Chemistry is now viewed many as Fouling the planet.
- The US congress declares that pollution should be prevented or reduced at the source. Wherever pollution cannot be prevented be treated in an environmentally safe manner (The pollution prevention act of 1990).
Utilization of PTS-Amide - a by-product from Sacharin production

Exploited by Poona Synthetics Pvt. Ltd. in 1969
**Production of Diazepam**

Shorter and efficient synthesis, reduces the use of resources

**Original process of HOFFMAN-LA-ROCHE:**  
(USP. 3109843, dated 5-11-1963)

Chemical reactions and structures are depicted in the diagram.

**NCL Process:**

Chemical reactions and structures are depicted in the diagram.

Commercialized by Cipla in 1973
Green Chemistry (Ibuprofen)

(Anti Inflammatory, Anti Rheumatic)

BOOTS Process (GB 971 700:2.2.1961):

\[
\begin{align*}
\text{(A)} & \xrightarrow{\text{CH}_3\text{COCl, AlCl}_3} \text{(B)} \\
\text{(B)} & \xrightarrow{\text{Cl CH}_2\text{CO}_2\text{Et, NaOEt, EtOH}} \text{EtCOOEt} \\
\text{EtCOOEt} & \xrightarrow{\text{1. NaOH, 2. H}} \text{CHO} \\
\text{CHO} & \xrightarrow{\text{Cr}_2\text{O}_3} \text{NH}_2\text{OH/1/2 H}_2\text{SO}_4 \\
\text{NH}_2\text{OH/1/2 H}_2\text{SO}_4 & \xrightarrow{\text{NaOH}} \text{CO}_2\text{H}
\end{align*}
\]

Ibuprofen
Green Chemistry (Ibuprofen)

(Anti Inflammatory, Anti Rheumatic)

CHEMINOR’S Method:

\[
\begin{align*}
(B) & \quad \text{H}_2, \text{Raney-Ni} \quad \rightarrow \quad (C) \\
& \quad \text{SOCl}_2 \quad \rightarrow \quad \text{Ibuprofen}
\end{align*}
\]
G.D. Searle Project

A case study for eliminating toxic substances

N-(4-Cyanophenyl)-3(S)-aminopyrrolidone

(Avras first project: initiated in 1996)

UREA DERIVATIVES

(Anti Thrombotic Agents)
Filed June 1995
Synthesis of (3S)-3-amino-1-(4-cyanophenyl)-2-oxopyrrolidine

AVRA’s first approach:

\[
\begin{align*}
\text{NaN}_3 & \quad \text{DMF} \\
\text{H}_2, \text{Pd/C} & \\
\text{HCl} & \\
\end{align*}
\]
Process for the preparation of Aminopyrrolidines

G. D. SEARLE’s approach:

\[
\text{NC-CH}_2\text{NH}_2 + (\text{N-Boc L-Methionine}) \rightarrow \text{NC-CONH-NHBoc}
\]

Base

\[
\text{Me-S-Me + 2Me}_2\text{S} \rightarrow \text{Dimethyl sulhide (toxic gas)}
\]

\[
\text{ALANINE UREA DERVS. (ANTITHROMBIOTIC AGENTS)}
\]
Refinement of the Process – For Production Quantities
Dynamic Resolution

\[
\text{Hydrolysis}
\]

\[
\begin{align*}
\text{Racemic} & \quad \text{OH} \quad \text{COOH} \quad \text{(R)-M.A} \\
& \quad \text{NC} \quad \text{N} \quad \text{O} \quad \text{N} \quad \text{H}_2 \\
\end{align*}
\]

\[
\text{(S) (R)-M.A. salt throws out}
\]

\[
\begin{align*}
\text{(R) (R)-M.A. salt in solution} & \\
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{CHO} \\
\end{align*}
\]

\[
\begin{align*}
\text{Hydrolysis} & \quad \text{H}^+ \\
\end{align*}
\]
Some well published incidents from the past

- The Cuyahoga river fire in the Ohio became so polluted with chemicals, it caught fire in June 1969, resulted in the Clean Water Act.

- A plant accident in Bhopal released Methyl isocyanate, nearly 4000 people died (2-3 December, 1984).

- These became rallying points for Environmental laws

- Ministry of Environment and forests (India):
  In 1976, Mrs. Gandhi added article 48A to the constitution concerning environment. This has resulted in the creation of Ministry of Environment and Forests in 1985.
The need for Green Chemistry

• In 1997 US Industries reported that 23.85 billion pounds of hazardous substances were treated, recycled, used for energy production, disposed of or released to the environment.

• Green Chemistry is mainly utilized in the design and manufacturing of pharmaceutical substances on a waste to product ratio, the pharma industry is one of the least environmentally acceptable, generating **25 to 100 kilos of waste for every 1 kilo of active pharmaceutical ingredient**.

• **80% of the waste is mostly solvents.** Although solvents play a critical role, large volumes are often used to purify the compounds.
Paul Anastas in 1991 while working at the Office of Pollution and Toxic Substances at the U.S. Environment Protection Agency (EPA) coined the term “GREEN CHEMISTRY”

Green Chemistry is the development of chemical and engineering methods for pollution prevention. The emphasis on the term “Green” is towards increasing the level of conscientiousness for the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances.

Since 1992 the NSF has awarded substantial funding and awards for projects that sought to develop new and cleaner technologies.

**Main advantages:**
- Reduce waste, eliminate costly reagents
- Reduce the use of energy and resources
- Recycle chemicals
- Use less hazardous products
Twelve Principles of Green Chemistry

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

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

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

- **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.

- **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.

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

Cont…
Twelve Principles of Green Chemistry

- **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.

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

- **Increase energy efficiency**: Run chemical reactions at ambient temperature and pressure wherever possible.

- **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.

- **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.

- **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.

USA Presidential Green Chemistry Awards

Announced in 1995 by the Clinton administration and the first award was presented in 1996.

**The criteria include:**
- Greener reaction conditions for an old synthesis
- A green synthesis for an old chemical
- The synthesis of a new compound that is less toxic

**Examples:**
- Barry Trost's concept of atom economy
- A new synthesis of Ibuprofen
- The use of \( \text{CO}_2 \) as a blowing agent
- \( \text{H}_2\text{O}_2 \) as an oxidizing agent
- Development of new insecticides that are more specific to target organisms

In 2007 US House of Representatives allocated nearly $200 million over three years for Green Chemistry Research and Development.
Green Chemistry (Ibuprofen)

Boots-Hoechst-Celanese Industrial Process
(Presently BASF corporation)
(U.S. Presidential Green Chemistry challenge award - 1997)

Number of synthetic steps cut to half.

The percentage of raw materials, reagents used that end up in the final product - hovered between 80% and 99%.

Acetic acid is recycled. It reduced clean-up costs.
• The key improvement in the Sertraline synthesis was reducing a three-step sequence in the original process to a single step. Overall, the process changes reduce the solvent requirement to 6,000 gal from 60,000 gal per ton of Sertraline, according to Pfizer.

• On an annual basis, the changes eliminate 440 metric tons of titanium dioxide-methylamine hydrochloride salt waste, 150 metric tons of 35% hydrochloric acid waste, and 100 metric tons of 50% sodium hydroxide waste.

• The first three reaction steps are carried out without isolating the intermediates. The team chose to use the more environmentally benign ethanol as the only solvent, which eliminates the need to use, distill, and recover the other solvents.
Roche Colorado Corporation has successfully applied the principles of green chemistry to manufacture Cytovene®️, a potent antiviral agent.

- The new process reduced the number of chemical reagents and intermediates from 22 to 11, eliminated the only two hazardous solid waste streams, eliminated 11 different chemical from the hazardous liquid waste streams, and efficiently recycled and reused four of the five ingredients not incorporated into the final product.

- This technology was awarded the Presidential Green Chemistry Challenge Award in the U.S. in 2000. Roche Colorado developed an environmentally friendly way to synthesize Cytovene®️.

- Their process eliminates nearly 2.5 million pounds of hazardous liquid waste and over 55,000 pounds of hazardous solid waste each year. This process also increases the overall yield more than 25 percent and doubles the production throughput.
Taxol is isolated from the bark of a Yew tree (Taxus beccata) and is used widely for the treatment of Uterus and breast cancers. As its requirements went up, production of Taxol was achieved by condensing 10-Deacetylbaccatin (isolated from needles of T-beccata) and semisynthetically produced to give Taxol. BMS succeeded the production of Taxol from Deacetylbaccatin by plant cell fermentation technology, which has improved the sustainability of Taxol supply while reducing the substantial waste.

Eliminated 10 solvents, 6 drying steps and 6 intermediates.
(Eliminated 71,000 pounds of hazardous chemicals)
USA Presidential Green Chemistry Awards

Atorvastatin (Lipitor): Early Synthesis.

a. Diastereoselective aldol reaction (1991)

b. Chiral pool approach

- Discovered by Park-Davis in 1987 and acquired by Pfizer in 2000
- Patent expired in November 2011
Codex Inc. directed evolution of three biocatalysts to produce the key intermediates, Ethyl (R)-4-cyano-3-hydroxybutyrate starting from ethyl 4-chloroacetoacetate

Other examples include the production of Sertraline (Pfizer 2002), Roche (2000) for Cytovene (anti viral) for improving the yield from 16 to 55% and eliminating chromium waste etc.
Artemisinin - Improved drug production

The project has supported by Institute of One World Health

(ACS. Chem. Biol. 2008, 64-76)
Many countries signed international treaties to reduce pollution levels.

EX. 1. Montreal protocol to protect the ozone layer.
It is an international treaty designed to protect the Ozone layer by phasing out the production of numerous substances that are responsible for Ozone deletion.

2. Global treaty on persistent organic pollutants.
(Stockholm convention organised by UNEP regarded as Global Public Health Treaty came into force in 2004. Humans and other organisms are exposed to POPs around the world, in many cases for extended periods of time, resulting in both acute and chronic toxicity effected on human and wildlife.

Rio declaration on environment and development (June 1992).
Since the beginning, the awards 18 years ago till 2013 EPA received 1,490 nominations and presidential awards to 88 technologies. It has resulted in the reduction of 825 million pounds of hazardous chemicals and solvents, saved 21 billion gallons of water and eliminated 7.9 billion pounds of CO2 releases to the air.

A research report from 2011 concluded that Green Chemistry will save industry $ 65.5 billion by 2020.
Green Process: Ex. Sugar Industry

Photosynthesis

Juice

Sugar (Human consumption)

CO₂ Generates

Molasses

Fermentation

Ethyl alcohol

CO₂

Chemicals from renewable resource (Acetic acid, Ethyl acetate etc.)

Bagasse

Boiler feed

Bio-fuel

Salicylic acid from Phenol

Leaf and other plant cuttings

Electricity generation

Soil (Organic manure)

Sugarcane production 2008 (tons)

• Brazil - 514,079,729
• India - 355,520,000
• China - 106,316,000
To the Public:
They have a responsibility to serve the public interest and safety and to further advance the knowledge of science. They should actively concerned with the health and safety of co-workers, consumers and the community.

To the Environment:
They have a responsibility to understand the health, safety and environmental impacts of their work to recognize the constraints of limited resources and to develop sustainable products and processes that to protect health, safety and prosperity of future generations.