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Commentary: an industrial perspective on green chemistry

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Chemistry is an integral part of the pharmaceutical business. Green chemistry is understood to be a superior, innovative chemistry, that is, cost-effective and has minimum impact to the environment. Over the past decade, the pharmaceutical industry has been moving toward the application of green chemistry principles by introducing new production and analytical technologies, using greener solvents and emphasizing enzymatic chemistry.

The prelude to green chemistry may have been an environmental movement. In the latter half of the 20th century, an exponentially increasing number of environmental regulations were enacted around the developed countries. In the U.S., the Clean Air Act (CAA) of 1970, the Clean Water Act (CWA) of 1972, the Resource Conservation and Recovery Act (RCRA) of 1976 and their amendments have set the fundamental regulations covering the air, water and hazardous waste pollutants, respectively. In 2001, the US Environmental Protection Agency promulgated Pharmaceutical MACT standards that regulate 187 hazardous air pollutants (HAPs), including methylene chloride, methanol, methyl-*t*-butyl ether, toluene and acetonitrile among others, which are solvents commonly used in the pharmaceutical industry. The resulting compliance burden associated with these regulations was such that pharmaceutical companies started to *re*-evaluate the synthesis of high volume products that use significant quantities of hazardous solvents. Today, many HAPs including methylene chloride and chloroform are no longer commonly used in the synthesis of new drug substances and substantial justification is needed in order to do so.

As the regulatory climate has become more stringent, the chemical syntheses have become more complex and product quality concerns demand more pure final products. If conventional chemical methods were only used, raw material use and waste generation would continually increase. The industry had to look to unconventional and greener methods to produce pharmaceutical actives.

Beyond the environmental reasons, other drivers promote the increased application of green chemistry in the pharmaceutical industry. In most green chemistry applications, the mass intensity is reduced. This corresponds to a lower cost since fewer amounts of raw materials are used to make the same product. The less amount of raw materials used creates a domino effect in terms of benefits, i.e., reduced time to handle the material, simpler operation, less waste generation, less waste treatment and disposal, etc.

Green Chemistry Drivers

- Reduced Cost
  - ➢ Raw Materials
  - ➢ Operation
  - ➢ Waste Disposal
- Increased Process Efficiency
  - ➢ Quality
  - ➢ Yield
  - ➢ Process time
- Reduced Energy Use (and greenhouse gases)
- Environmental Improvement
  - ➢ Reduces potential concerns about 'Pharmaceuticals in the Environment'
- Reduced Liability
- Improved Health and Safety
- Enhanced Corporate Image
- Added Intellectual Property

Green chemistry can also increase process efficiency by producing a higher quality product and/or yield and reducing process time. In pharmaceutical industry, the quality of products cannot be compromised. A synthesis that has a lower mass intensity but reduces the quality would not be classified as a green chemistry application.

There are other drivers that may not be as apparent, but are as important. One of the other drivers is reduced energy use and its equivalent greenhouse gases. The mass intensity has been reported to be proportional to energy intensity. The reduced waste generation, already mentioned earlier, further reduces environmental liability, since waste generators are responsible for the waste from cradle-to-grave. Green chemistry can improve the health and safety of employees by using inherently safer materials. Finally, all these improvements impact the environment in a positive way and, therefore, enhance the corporate image.

Nevertheless, the drivers alone are not enough to sustain the green chemistry application. We need more scientists and engineers who will take actions toward this endeavor. One of the keys for its success is educating the future generation. It is important that new graduates who enter the pharmaceutical industry be knowledgeable of the concept of green chemistry and not just chemistry. Some universities are ahead of the curve and offer green chemistry focused courses, but more is still needed to encourage students to learn and to apply green chemistry.

Another key factor for success is access to greener solvents. Based on an industry survey, over 50% of materials used in pharmaceutical processes are organic solvents. Some of these solvents are recovered and reused, but the vast majority is incinerated as a mean of disposal. This has a large impact on cost

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and the environment. Although there might not be an ideal green solvent for all types of syntheses, it would certainly help if newer solvents are ‘proven’ to be less hazardous to health and environment than the solvents in the current market. Documentation such as ecotoxicity data, USP/ICH residual solvent concentration, occupational exposure limits, etc. would provide the evidence to consider a solvent to be green. Furthermore, the solvent needs to be available in bulk quantity at competitive price and have a sustainable supply, unlike the recent shortage of acetonitrile.

If having drivers is the first step toward green chemistry, the pharmaceutical industry has many. The second step is resources—human and materials. The next step can be said to be psychological. Green chemistry is a change of mindset, of how chemists approach and develop a chemical synthesis. It goes beyond the comfort zone of using tried and tested reagents, solvents and technologies. It is innovative and perhaps even bold. No one said that green chemistry is easy. However, with passion to strive for continuous improvement, the pharmaceutical industry can turn the challenges into green opportunities.