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DESIGNING A SUSTAINABLE PHARMACEUTICAL INDUSTRY: THE ROLE OF CHEMICAL ENGINEERS

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4.1 INTRODUCTION

Pharmaceutical processing in general involves difficult and complex tasks, but is absolutely critical to improving and maintaining patient health and saving lives. In order to continue to create the life-saving medicines that society needs, it is necessary to discover and develop molecules that are very often complex (e.g, enantiomers with several chiral centers, high molecular weight, and high degree of functionality). Producing this type of molecule as a drug substance frequently requires complex chemistries and extensive purification processes. Bulk chemicals typically require between 1 and 2 chemical transformations, while pharmaceutical active ingredients usually require 6 or more. In addition to the technical complexities, the pharmaceutical industry needs to accommodate a high level of attrition, uncertainties in demand forecasts, and the relatively short length of the patent period, among other challenges. For every 5000 compounds evaluated in preclinical testing, only about 5 progress far enough to enter clinical trials and on average only 1 might actually gain approval by the US FDA for marketing [1]. Given an average of 12 years required to discover, develop, and deliver a new drug candidate to market, process development must be optimized in a relatively short amount of time under constraints where innovation and investment are difficult.

Given these historical challenges and complexities an enhanced approach to develop sustainable pharmaceutical processes is needed. A new approach will require innovation based on sustainability principles in order to improve and enhance the efficiency of our manufacturing processes. It must also have the potential to lower costs, which could in turn lower prices to widen global access to medicines in the marketplace.

Doing this effectively requires innovation, and of all the professions, engineering is in the best position to leverage innovative approaches [2]. The role of engineers in general, and chemical engineers in particular, is crucial to delivering more sustainable pharmaceutical processes.

4.2 A WORD ON SUSTAINABILITY

Since the 1980s sustainability was identified by the United Nations as the solution that would address the environmental issues that have affected the world. In a widely accepted definition, sustainability implies meeting the needs of today without compromising the ability of future generations to meet their own needs. This is translated into a triple-bottom line approach where environmental, economic, and social aspects are in balance. In other words, sustainable systems or process are the ones that

- minimize environmental impacts,
- are economically viable, and
- are socially responsible [3, 4].

However, implementing sustainability on an operational basis may be difficult due to the intrinsic interrelated, interdependent

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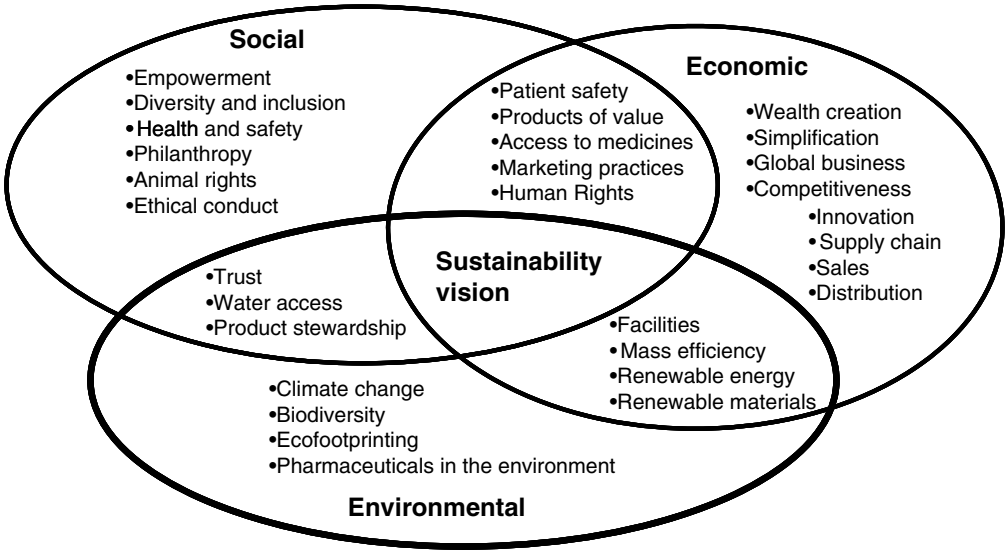

FIGURE 4.1 A triple-bottom approach to Sustainability, with some sustainability opportunities and issues for the pharmaceutical industry.

nature of the concept. For instance, just measuring the sustainability of pharmaceutical processes may is a very complex task more akin to a multivariable optimization. Chemical engineers have indeed proposed these approaches for measuring sustainability of processes [5–7]. In addition, sustainability is a dynamic system—it can only be measured with a long-term horizon and with extended boundaries (i.e., a life cycle approach). There have been many attempts to measure the sustainability or "greenness" of pharmaceutical synthesis through a series of "green metrics." Some approaches have focused on waste, such as the E-factor, the amount of waste generated in order to produce 1 kg of product. [8, 9] Approaches have focused on mass efficiency (or its inverse, mass intensity) trying to highlight the process optimization and innovation side of the equation through prevention instead of waste minimization approaches [10–12]. More evolved approaches try to include life cycle and process systems engineering in a more holistic view of the impacts. Figure 4.1 shows a triple-bottom approach to sustainability, with some sustainability opportunities and issues for the pharmaceutical industry.

At the end of the day, in order to design sustainable pharmaceutical processes, there is need to integrate sustainability criteria inherently in process development and optimization. Doing so is an essential part of anticipating, minimizing and solving problems that might arise in actual production, as well as embedding sustainable processes in manufacturing.

4.3 GREEN CHEMISTRY AND GREEN ENGINEERING PRINCIPLES

Following the publication of the green chemistry principles [13, 14], an initial attempt to capture principles of green engineering was made [15] with the publication of 12 proposed green engineering principles. These principles were aligned with the previous green chemistry principles, although one drawback is that the two lists were not integrated but were published separately. So in 2003, about 60 chemists and engineers from industry, government, and academia met in San Destin, Florida to discuss principles of green engineering. This group intended to appeal to the large engineering audience (beyond chemical industry), in addition to potentially broadening the scope of previous work to incorporate principles of sustainability [16]. These sets of principles are in general accepted by most people and have proven very powerful in disseminating the intent and guidelines of green chemistry and engineering. Green engineering and chemistry approaches are synergistic and need to be applied in parallel to realize the most potential benefit. However, these principles can be simplified [17]. So that when designing novel chemistry routes, selecting reactors or separations, designing chemical processes, building plants, and so on one should strive to

- maximize resource efficiency,
- eliminate and minimize EHS hazards, and
- design systems holistically and use life cycle thinking.

But is this simplified approach sufficient? The most commonly cited principles have been mapped to this simpler set of three [18], which seem to cover all the guidelines that have been postulated, as shown in Table 4.1.

With regard to pharmaceutical processes, there are efforts current efforts underway to integrate green chemistry and

TABLE 4.1 Mapping the Three Main Green Chemistry and Engineering Principles

Principles	Maximize Resource Efficiency	Eliminate and Minimize Hazards and Pollution	Design Systems Holistically and Using Life Cycle Thinking
Green chemistry (Anastas and Warner)	• Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product • The use of auxiliary substances (e.g. solvents and separation agents) should be made unnecessary whenever possible and, innocuous when used • Energy requirements should recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure • Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible • Catalytic reagents (as selective as possible) are superior to stoichiometric reagents	• It is better to prevent waste than to treat or clean up waste after it is formed • Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment • Chemical products should be designed to preserve efficacy of function while reducing toxicity • Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products • Analytical methodologies need to be further developed to allow for real-time in-process monitoring and control prior to the formation of hazardous substances • Substances and the form of a substance used in a chemical process should chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires	• A raw material feedstock should be renewable rather than depleting whenever technically and economically practical
• Green chemistry (Winterton)	• Identify and quantify by-products • Report conversions, selectivities, and productivities • Establish full mass balances for a process • Anticipate heat and mass transfer limitations • Quantify and minimize use of utilities	• Measure catalyst and solvent losses in aqueous effluent • Investigate basic thermochemistry • Recognize where safety and waste minimization are incompatible • Monitor, report, and minimize laboratory waste emitted	• Consult a chemical or process engineer • Consider effect of overall process on choice of chemistry • Help develop and apply sustainability measures • Recognize where safety and waste minimization are incompatible
Green engineering (Anastas and Zimmerman)	• Separation and purification operations should be designed to minimize energy consumption and materials use • Products, processes, and systems should be designed to maximize mass, energy, space, and time efficiency • Products, processes, and systems should be "output pulled" rather than "input pushed" through the use of energy and materials	• Designers need to strive to ensure that all material and energy inputs and outputs are as inherently nonhazardous as possible • It is better to prevent waste than to treat or clean up waste after it is formed	• Embedded entropy and complexity must be viewed as an investment when making design choices on recycle, reuse, or beneficial disposition • Targeted durability, not immortality, should be a design goal • Design for unnecessary capacity or capability (e.g., "one size fits all") solutions should be considered a design flaw

(*continued*)

TABLE 4.1 (*Continued*)

Principles	Maximize Resource Efficiency	Eliminate and Minimize Hazards and Pollution	Design Systems Holistically and Using Life Cycle Thinking
	• Design of products, processes, and systems must include integration and interconnectivity with available energy and materials flows		• Material diversity in multicomponent products should be minimized to promote disassembly and value retention • Products, processes, and systems should be designed for performance in a commercial "afterlife" • Material and energy inputs should be renewable rather than depleting
Green engineering (San Destin Declaration)	• Minimize depletion of natural resources • Strive to prevent waste • Conserve and improve natural ecosystems while protecting human health and well being	• Ensure that all material and energy inputs and outputs are as inherently safe and benign as possible • Strive to prevent waste • Conserve and improve natural ecosystems while protecting human health and well being	• Engineer processes and products holistically, use systems analysis, and integrate environmental impact assessment tools • Use life cycle thinking in all engineering activities • Develop and apply engineering solutions, while being cognizant of local geography, aspirations, and cultures • Create engineering solutions beyond current or dominant technologies; improve, innovate, and invent (technologies) to achieve sustainability • Actively engage communities and stakeholders in development of engineering solutions

green engineering principles. In 2005, the American Chemical Society (ACS), the Green Chemistry Institute (GCI), and several major pharmaceutical companies came together to form the ACS GCI Pharmaceutical Roundtable. The strategic priorities of the Roundtable are to inform and influence the green processing research needs of the industry, to identify innovations that will be required, to educate both pharmaceutical leaders as well as others in the benefits of this approach and to provide green processing expertise to global pharmaceutical operations.

Applying these three generic principles to process development strategies will allow us to design sustainable pharmaceutical processes. In other words, processes that are better, cheaper, faster, cleaner and are sustainable by design in that they

- optimize the use of material and energy resources;
- eliminate or minimize environment, health and safety hazards; and
- minimize life cycle impacts.

4.4 CHEMICAL ENGINEERS—DESIGNING SUSTAINABLE PHARMACEUTICAL PROCESSES

4.4.1 Resource Efficiency

Following the three general green principles above, let us start with one of the main challenges for chemical engineers in designing sustainable pharmaceutical processes: maximizing the use of material and energy resources.

This challenge has also been recognized by the ACS GCI PR, and as a result it has chosen process mass intensity (PMI) as a measure to drive efficiency improvements in pharmaceutical syntheses. The ACS GCI Pharmaceutical Roundtable members have used this common process mass intensity metric (total mass of materials per mass of product) to compare data from each company on an equitable basis.

This benchmarking, has allowed the group to drive innovation and improvements in terms of material utilization. For instance, during the 2008 benchmarking exercise of the ACS GCI PR it was found that the median mass intensity of the processes under different stages of development across all the stages was about 120 kg material/kg API according to the data provided by the seven-member companies at that time, with a maximum of 887 kg material/kg API and a minimum of 23 kg material/kg API. This benchmarking also found that most of the material requirements are solvent (about half) followed by water (about 30%), reactants (about 9%), and other materials as the balance [19]. This is generally aligned with other studies performed previously by GSK, both in the process and in the life cycle boundaries [20].

In general there is opportunity to improve the resource utilization during the development cycle, with the median moving from 185 kg material/kg API during preclinical to about 45 kg material/kg API (Figure 4.2) in the commercial phase. It is during this period of optimization that chemical engineers have the opportunity to collaborate with chemists and R&D scientists in improving the "sustainability profile" of pharmaceutical processes. Creating processes that are more material and energy efficient, are inherently safer, and that minimize the life cycle impacts on the environment.

This is part of the rationale that pharmaceutical companies have followed when they have set mass efficiency and energy reduction metrics to drive improvements. GlaxoSmithKline has set a target to double the average mass efficiency of processes for new products introduced between 2006 and 2010, roughly halving resource consumption and waste generation and aggressive targets for reduction of energy consumption and its impact on climate change [21]. Furthermore, more aggressive mass efficiency targets have been set beyond 2010 for R&D and manufacturing. In order to drive the changes required to achieve more sustainable processes, GlaxoSmithKline has established a Sustainable Processing Team drawn from discovery, development, and with strong links to manufacturing units to apply sustainability strategies developed within R&D and manufacturing [22]. The manufacturing unit also has established a Sustainable Manufacturing Center of Excellence to leverage innovative technologies and processes, to drive step change improvement in support of the ambition to deliver a sustainable and cost-effective active pharmaceutical ingredient supply base. In addition to sustainable processing initiatives, a Climate Change Program has been started and a central fund established to finance energy saving projects. In 2008, 171 projects were completed that are expected to result in a saving of more than 550,800 GJ of energy per year (more than 40,000 tons of carbon dioxide equivalents).

Recognizing the importance of the role that chemical engineers play in this area, GSK's Sustainable Processing Team has set up engineering working groups to improve and optimize processes by focusing primarily on green engineering and solvent optimization and recovery. The aim of these working groups is to interact and collaborate with the R&D chemists to achieve the design of more sustainable pharmaceutical processes.

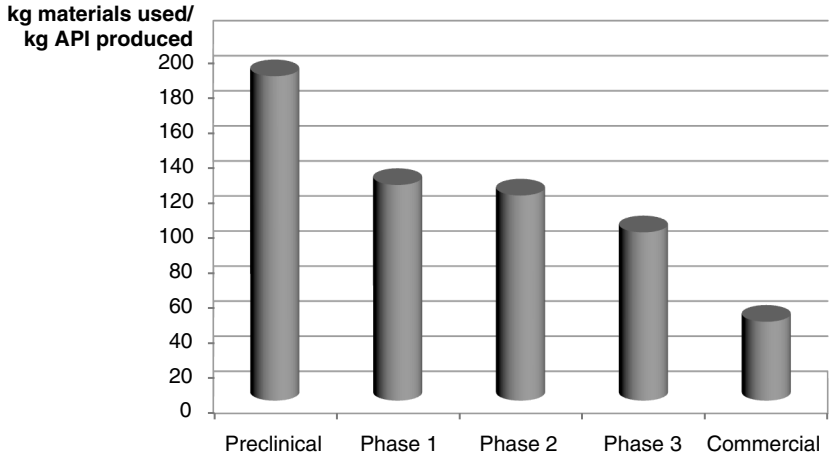

FIGURE 4.2 2008 process mass intensity benchmark of the ACS Green Chemistry Institute Pharmaceutical Roundtable. Medians by development phase are shown. Processes included in each phase: preclinical: 7; phase I: 5; phase II: 13; phase III: 16; commercial: 5. (Ref. 12.)

GSK has not been the only pharmaceutical company to leverage mass efficiency or mass intensity metrics to optimize processes. Merck has used PMI to drive improvements during the development phase with a primary focus on engineering. For Merck, this has meant optimizing the unit operations and processes with the assumption that the best chemistry is in place. Using this approach in a coupling reaction, the engineering group was able to reduce the PMI from 107 to 40 kg/kg API (more than doubling the mass efficiency, improve the cycle time and crystallization robustness, and replacing dimethyl chloride with either *iso*-propyl or ethyl acetate). This was accomplished by utilizing techniques of unit operation screening, solvent screening, polymorph screening, and process synthesis—without modifying the chemistry [23].

4.4.2 Beyond Resource Efficiency—Health, Safety, and Life Cycle Impacts

In the last section we saw good examples of how to drive improvements in terms of improving resource efficiency, but to complete the sustainability picture, one needs to integrate health and safety hazard and risk considerations, as well as life cycle impacts. The additional challenge that comes with this improve impacts that reach beyond manufacturing.

The importance of minimizing health and safety risks has been largely integrated into the work of developing pharmaceutical processes. However, much of these considerations have been made by the use of controls after a process is designed (e.g., globe boxes for charging potent materials, explosion suppression systems). The sustainability challenge at this point is to ensure that health and safety considerations are inherent to the process design as a built-in feature, not as a bolt on control. Chemical engineers have the remit to eliminate the need for materials of concern, designing systems where the remaining materials are contained by design and are inherently safer process through improved heat and mass transfer, among others.

The minimization of life cycle impacts has become one of the areas of work for chemical engineers, given our ethical responsibilities and the growing awareness and expectations of stakeholders. Ten years ago terms such as "carbon footprinting" or "ecofootprinting" were relegated to academic settings, and now are mainstream. Minimizing life cycle impacts however is intimately linked to resource efficiency and health and safety aspects. A pharmaceutical process with enhanced mass and energy efficiency will have a reduced environmental footprint given the reduction of natural resources consumption (mass and energy), and reduction of waste generated. When health and safety aspects are addressed in the design stage, it reduces the life cycle costs associated with health and safety controls, waste disposal, and reduces risks associated with improper control systems.

Life cycle assessment is also the framework that would allow us to address the wider aspects of sustainability, given the need to design process that addresses impacts that extend beyond our factory boundaries and over a longer term horizon. A process with a minimized environmental footprint is an obvious environmental benefit but it also provides societal and economic benefits that allows for providing medicines to patients globally at a lower price, with the potential business benefit of allowing the discovery company to be competitive after patent expiration. The sooner we can reduce our costs through process improvements the sooner the economic, social, and environmental goals can be realized. Using the life cycle assessment can highlight where in the process improvements can be focused to get the most impact on reducing energy, raw materials use, or emissions. For instance, a 10% reduction in solvent use may save more energy and reduce the environmental footprint than a 10% reduction in raw materials or improvement in yield. However, it can be challenging to acquire the information needed to assess the resource and energy consumption and emissions generated for all phases over the life of a product from cradle to grave, including extraction of raw materials, production, transport, use, and disposal.

Using life cycle thinking or taking a cradle-to-grave approach to design addresses the entire life of the product. For instance, the following questions are addressed:

- Are the raw materials from renewable or nonrenewable resources?
- How will the product or wastes be disposed?
- Can packaging be minimized?
- How can the product be designed to degrade at the end of life or for ease of recycling or reuse?
- How can it be designed to decrease impacts during the use of the product? (e.g., Can a propellant be removed from a spray?)

Are options (raw materials, unit operations, disposal, etc.) selected based on the life cycle impacts? There have been some attempts to facilitate the integration of health, safety and life cycle aspects as part of the chemical engineering design work within the pharmaceutical industry. One framework for integrating health, safety, and life cycle considerations into pharmaceutical technologies or processes has been proposed [24, 25]. This framework integrates considerations regarding efficiency, energy, health and safety, and environmental impacts (including life cycle impacts) to compare and select unit operations or processes from a "green" standpoint. For example, Table 4.2 shows the high-level comparative assessment performed between different options for solvent recovery and/or disposal within a particular pharmaceutical process. This framework has been utilized to develop GlaxoSmithKline's *Green Technology Review* and *Green Technology Guide* (Figure 4.3).

TABLE 4.2 Comparison of Technologies for Solvent Recovery or Disposal

	Environment	Safety	Efficiency	Energy
Pressure Swing Distillation, Vacuum	**Yellow**	**Yellow**	**Yellow**	**Yellow**
Pressure Swing Distillation, Atmospheric	**Yellow**	**Yellow**	**Yellow**	**Yellow**
Atmospheric Distillation plus Vapour Permeation	**Yellow**	**Yellow**	**Yellow**	**Green**
Incineration	**Red**	**Yellow**	**Red**	**Red**

Color Key:

Green alternatives with significant advantages

Red alternatives with significant disadvantages

Yellow alternatives that do not exhibit significant advantages or disadvantages

* For the Environment category, mass indicators and life cycle indicators were considered. For the Energy category, energy requirements and life cycle energy were considered.

The safety column includes both health and safety considerations. For the environment category, mass indicators and life cycle indicators were considered. For the energy category, energy requirements and life cycle energy were considered.

However, there is much work that needs to be done in this regard, especially as related to the full integration of life cycle impacts within the decision-making processes of pharmaceutical companies.

4.4.3 Improving the Sustainability Profile

To realize sustainability aspirations, it is necessary to fully leverage the skill set of chemical engineers with an integrated sustainability mindset.

It all starts with innovation.

For the pharmaceutical industry, there are a series of key areas that chemical engineers need to integrate actively in designing more sustainable pharmaceutical processes. Some of these have been identified by the ACS GCI PR Green Engineering Subteam as a preliminary list, and include process intensification, continuous processing, bioprocessing, mass and energy integration, scale-up aspects, separation technologies, solvent selection, nanotechnology, life cycle assessment, and the integration of chemistry and engineering.

These areas represent different levels of development and different levels of innovation needed. Some of these areas such as process intensification, continuous processes, or bioprocessing are indeed not new, but need to be adapted and adopted into pharmaceutical processes. Some of them

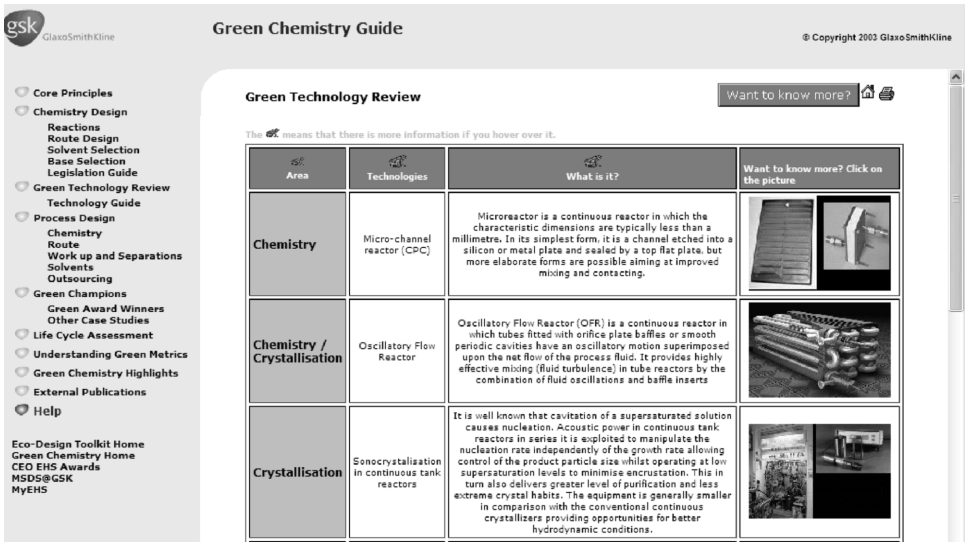

FIGURE 4.3 GlaxoSmithKline's *Green Technology Review* screenshot.

have not been explored in much detail, such as nanotechnology, some of them have been under development for sometime, such as separation technologies, solvent selection, and separations. Furthermore, areas such as life cycle assessment and the integration of chemistry and engineering will require implementation of different approaches in design, scale-up, and operation of manufacturing processes.

There are already examples of advances in these areas. Continuous microreactors from Corning [26] that have been utilized for API and intermediate production, continuous secondary processing alternatives explored by several companies, and bioprocesses currently established or being explored in our pharmaceutical plants [27, 28], process intensification has been demonstrated for some processes [29], life cycle assessment evaluations and tools of pharmaceutical processes [30, 31], to mention a few. However, a more widespread uptake is needed so these areas become best chemical engineering practices within the pharmaceutical industry.

In addition, these areas need to be addressed in a systematic, interrelated fashion and not in isolation. One can envision perhaps the possibility of an enzymatic process running continuously; or a heavily intensified process that utilizes hybrid reaction/separation unit operations to enhance mass and energy transfer. The extent to which these type of processes can be made operational will depend on how well innovation can be developed and applied.

4.5 FUTURE OUTLOOK

The challenge for chemical engineers will be to continue to advance the state-of-the-art of chemical engineering as it applies to the pharmaceutical industry in order to design more sustainable processes.

The aim would be to reduce both costs and environmental impact—both resource consumption and waste generation—while enhancing the social advantages. The first challenge is to improve the efficiency of the industry's processes while reducing health and safety hazards and risks and addressing life cycle impacts from a design perspective.

This will require that chemical engineers develop and utilize skill sets that perhaps have not been identified and intensively applied to pharmaceuticals.

One of the skills that will be needed is the mastery of continuous processes and process intensification applied to pharmaceuticals. Better scientific process understanding will be needed to fully leverage the opportunity that continuous flow manufacturing could represent for the pharmaceutical industry.

Another opportunity is the further development and extension of bioprocesses. One specific challenge may be that we could be dependent on the use of genetically modified microorganisms, which will require a increased dialogue with regulators and the public to ensure that the right controls are in place and that the public understands the risks and the benefits associated with genetically modified microorganisms. The development of new bioprocesses is also an exciting endeavor that will bring a particular need for process system engineers to develop quantitative decision-making tools and rapid simulation that will include both process design and sustainability principles.

Advances in process systems engineering will be dependent on development of better and more sophisticated tools (including property prediction packages and the development of a database for bio-based molecules).

Finally, to routinely assess sustainability of processes will require more robust and transparent life cycle inventory databases of pharmaceutical materials; as well as better modeling and understanding of the social and economic aspects of sustainability and their relationships.

The pharmaceutical industry is committed to discovering medicines that allow people around the world to live longer, healthier, and more productive lives. In pursuing a sustainable approach to process development and manufacturing, the industry may be in a better position to delivering on this promise.

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