Organic Process Research & Development

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pubs.acs.org/OPRD

Key Green Engineering Research Areas for Sustainable Manufacturing: A Perspective from Pharmaceutical and Fine Chemicals Manufacturers

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ABSTRACT: In 2005, the American Chemical Society (ACS) Green Chemistry Institute (GCI) and global pharmaceutical companies established the ACS GCI Pharmaceutical Roundtable to encourage the integration of green chemistry and engineering into the pharmaceutical industry. The Roundtable developed a list of key research areas in green chemistry in 2007, which has served as a guide for focusing green chemistry research. Following that publication, the Roundtable companies have identified a list of the key green engineering research areas that is intended to be the required companion of the first list. This publication summarizes the process used to identify and agree on the top key green engineering research areas and describes these areas, highlighting their research challenges and opportunities for improvements from the perspective of the pharmaceutical industry.

1. INTRODUCTION

The pharmaceutical industry is devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives and is committed to bringing key medicines to the patient with minimal environmental impact. The concept of Green Engineering is not new in pharmaceutical manufacturing. In recent years, the pharmaceutical industry has paid significant attention to productivity improvement, waste reduction as well as quality improvement and control in both the research and development (R&D) and manufacturing areas. This is driven not only by the consideration of cost reduction but also by the awareness of increasing sustainability of the manufacturing process.

In 2005, the American Chemical Society (ACS), Green Chemistry Institute (GCI), and several global pharmaceutical corporations founded the ACS GCI Pharmaceutical Roundtable (hereafter referred to as the Roundtable). The activities of the Roundtable reflect the joint belief that the pursuit of green chemistry and engineering is imperative for a sustainable business and environment. Therefore, the mission of the Roundtable is to catalyze the implementation of green chemistry and engineering into the business of drug discovery, development, and production. To achieve this mission, the Roundtable identified four strategic priorities:

1. **Informing and influencing the research agenda** in the high value-added areas of green chemistry and engineering.

Special Issue: Sustainable Process Chemistry

Received: December 10, 2010
Published: February 22, 2011

Figure 1. Process used to identify and agree on the key green engineering areas.

Table 1. Key green engineering research areas: results of the brainstorming and prioritization exercises

Rank	Main Key Areas	Sub-areas/aspects	Votes
1	Continuous Processing	Primary, Secondary, Semi-continuous, etc.	12
2	Bioprocesses	Biotechnology, Fermentations, Biocatalysis, GMOs,	11
3	Separation and Reaction Technologies	Membranes, crystallizations, etc.	11
4	Solvent Selection, Recycle and Optimization	Property modeling, volume optimization, recycling technologies, in process recycle, regulatory aspects etc.	10
5	Process Intensification	Technology, process, hybrid systems, etc	9
6	Integration of Life Cycle Assessment (LCA)	Life cycle thinking, Total Cost Assessment, carbon / eco-footprinting, Social LCA, streamlined tools	4
7	Integration of Chemistry and Engineering	Business strategy, links with education, etc.	4
8	Scale up aspects	Mass and energy transfer, Kinetics, and others	3
9	Process Energy Intensity	Baseline for pharmaceuticals, estimation, energy optimization	1
10	Mass and Energy Integration	Process integration, Process Synthesis, Combined Heat and Power, etc	0

2. **Developing tools for innovation.** To identify, design, and provide tools that promote innovation in green chemistry and engineering.
3. **Educating leaders**. To educate leaders and scientists in the merits of applying green chemistry and engineering in the pharmaceutical industry.
4. **Collaborating globally.** To provide green chemistry and engineering expertise worldwide to pharmaceutical corporations and fine chemical companies.

In 2007 the Roundtable developed a list of key Green Chemistry research areas[1] that was published as a perspective article to provide an assessment of the current state of the art in those areas, and to highlight opportunities for future improvement.

As a natural follow up to the 2007 work, the Roundtable has decided to develop and publish key green engineering research areas from the perspective of pharmaceutical and fine chemical manufacturers. In this paper, the process for defining these key areas and research needs is reported, and their research challenges and opportunities for improvements from the pharmaceutical industry perspective are defined.

2. PROCESS FOR IDENTIFYING AND AGREEING ON THE KEY GREEN ENGINEERING AREAS

The process started with gathering ideas from engineering, chemistry, and biotechnology representatives from the member companies collaborating in an initial brainstorming exercise. During this exercise, the ideas generated were grouped in specific areas that would help focus research and requirements (Figure 1).

The expert group felt that all the ideas generated were high quality and worthy of research support, and that the grouped list provided focused guidance of the industry needs while also giving additional context. The list of research areas was refined and then prioritized by a blinded process of each member company voting for their top five areas of interest.

The output of the brainstorming exercise and prioritization is shown in Table 1. One of the key messages was that there was a lot of commonality in the individual company votes. This allowed the Roundtable to quickly identify not only the 10 Key Green Engineering Research Areas but also the top five priorities from the Roundtable members' perspective. There were additional areas identified that did not obtain any votes during prioritization (e.g., mass and energy integration).

Once the results from the brainstorming and the initial vote were known, the member companies sought external feedback from academics and other industrial areas via presentations and discussions in conferences such as the annual meeting of the American Institute of Chemical Engineers (AIChE)[2] and the American Chemical Society's Green Chemistry and Green Engineering annual conference.[3] In general, the feedback received has been very positive.

3. THE TOP 10 GREEN ENGINEERING RESEARCH AREAS

For each of the key research areas shown in Table 1, a short overview containing the description, research challenges and opportunities, its relevance, and recommendations are given. Although all of the areas are covered in this publication, it was decided that the primary focus will be on the top five research areas.

3.1. Continuous Processing. Currently pharmaceutical manufacture is dominated by batch processing. Pharmaceutical manufacturing typically involves several consecutive but segmented unit operations/processes which produce drug substance (or

API - active pharmaceutical ingredient) and the formulated drug product, respectively. Assurance of product quality and uniformity is dominated by techniques involving sampling and measuring at discrete points (although increase in the use of inline/real-time techniques through application of Process Analytical Technologies, PAT, has been seen in recent years). Because of the high-quality attributes of the products, manufacturing is carried out under a rigorous regulatory framework with the highest quality standards.

Pharmaceutical and fine chemical manufacture can be characterized as an industry traditionally operating in flexible multipurpose batch plants both for API and formulated drug product. In response to a changing marketplace and business environment the pharmaceutical industry is undergoing significant changes. With increased cost-pressures, companies are looking at opportunities to lower operating costs. By some estimates, cost of goods of APIs represent on average 30% of revenues, based on sampling a number of pharmaceutical manufacturers. This translates to significant potential cost savings if more efficient methods can be adopted.[4,5] In other industries, such as confectionary or petroleum, where margins have been historically lean, continuous processing is often utilized. Continuous Processing (CP) is one aspect of process intensification in which the goal is to reduce costs, reduce the size of process equipment, improve product quality, reduce energy consumption, solvent utilization, and waste generated. A CP approach is constrained only by the limits of chemistry and physics, whereas batch processing is often constrained by equipment limits. When applied to pharmaceutical manufacturing and fine chemicals, the rationale for continuous processing includes several advantages:

Economics. Lower cost of production can be obtained via reduced inventory, footprint, waste and emissions, and energy consumption. One example is the potentially lower cost of goods when running supercritical chemistry in supercritical solvents such as carbon dioxide and near-critical water, although uptake of this technique by pharma outside chromatography has so far been negligible.[6] Continuous reactors can be better suited for cryogenic reactions since the heat removal efficiency is greatly increased over a batch reactor.

Quality. Operation under continuous steady state offers improved product quality and consistency versus batch operations which are run dynamically. This quality increase can be obtained by improved mass and heat transfer and the ability to operate more intensely at higher temperatures. In addition, process deviations can be less detrimental since there is less risk to product due to lower holdup, resulting in less product rework requirements (less raw materials, waste, and energy use). More precise control of variables such as temperature, pressure, and heat transfer can improve yields and selectivity and reduce process variance. This "steady-state" operation can be superior when compared to possible batch-to-batch variability. Also, integrating PAT can provide opportunity for real-time release of product. Finally, during development and scale up, the orders of scale up to production mode can be reduced when compared to a batch operation. One example of improved consistency and safety as compared to batch is the scale-up of a continuous enolization, oxidation, and quench process to produce 6-hydroxybuspirone.[7] The flow process utilized static mixers and a custom trickle bed reactor assembly to generate over 100 kg of API. The authors reported faster processing times as a result of higher operating temperatures, more consistent reactions via steady-state operation, and increased safety due to significantly lower inventories of flammable solvent in the presence of oxygen, when compared to the batch operation.

Safety. Process safety is enhanced via smaller reactor volumes and holdup volumes of potentially hazardous reagents or solvents within the process. Smaller flow containment facilities (i.e., walk-in hoods) provide a reduced potential for exposure of high-potency and/or cytotoxics via processing when compared to the batch configuration. Continuous processing can enable the minimization of risks with hazardous chemistry that otherwise would have to be abandoned or heavily modified to run in batch mode. One example of safety drivers favoring continuous processing is the reduced potential for explosion of flammable atmosphere in batch processing: Kopach et al. observed that headspace components in a batch reactor can lead to explosive conditions which is a barrier to commercial scale up. Running in a tubular reactor eliminates this headspace, allows higher temperatures to decrease reaction time, and lowers the amount of hazardous compounds present.[8] Another continuous flow application with a safety driver is continuous nitration. New nitration chemistry processes run continuously are frequently cited as offering safety benefits from significantly reduced inventories of hazardous reaction media (in the reactor volume) and thus offer significantly reduced risk of operation.[9−11]

Environmental. Batch processes are inherently wasteful with frequent nonvalue-added operations. One relatively recent aspect of continuous technology is microreactor technology, which exhibits unprecedented reaction control. Microreactors combine the advantages of continuous processing with the complexity of the pharmaceuticals synthesis.[12−14] One example of an application is the utilization of rapid mixing and heat transfer when running a highly concentrated reaction stream, which minimizes waste. Another advantage of continuous processing is the potential for solvent reductions since the reaction can be run neat in a flow reactor or at least more concentrated. Thus, significant reduction can be realized in Process Mass Intensity (PMI). Solvent usage and emissions can also be reduced due to the lower frequency of cleaning compared to cleaning in batch operation. This would occur from the CP steady-state operations which should require occasional shutdown and cleaning.

3.1.1. Research Challenges and Opportunities for Pharmaceutical Continuous Processes. Design and development of fully integrated continuous processes requires detailed understanding of the process so that the resultant knowledge can be used to run at steady state, providing consistent, high-quality product. Although many process unit operations are compatible with continuous mode, new approaches to chemical synthesis and reaction technology for production of APIs need to be developed, expanded, and optimized to enable continuous regime at scale.[15,16]

For drug product production, additional research and development is required for understanding the fundamental engineering of operations such as blending, granulation, and drying. Although it is assumed that the benefits of continuous operation may be more fully realized with the design of new production facilities, there is a need to develop process intensification approaches that can be applied to convert batch multipurpose facilities into continuous.

There are significant challenges to continuous processing related to startups and shutdowns caused by operational issues and equipment failures (e.g., clogging), and additional research is needed to address those issues. In general much more

Table 2. Annual production and business volumes of major bioderived products, 2005−2007[a]

product	annual production (kton)	annual market size (B$)
bioethanol	>50,000	>10
amino acids (except chemically produced D,L-methionine)	>3000	3.7 (41% L-glutamic acid, 41% L-lysine.HCl, 8% L-threonine, 10% others)
citric acid	1,800	1.6
lactic acid	250	>0.5
ascorbic acid (vitamin C)	107	0.5
anti-infective antibiotics	>100	55 (160 products: 36% β-lactams, 19% antivirals, 12% quinolones, 11% macrolides, 22% other)
industrial enzymes	>100	2.3 (34% detergents, 27% foods, feeds 16%, textiles 10%, other 13%)
gluconic acid	60	0.13
xanthan	30	0.4
pharmacological agents	<10	>50 (statins, cyclosporines, etc.)
riboflavin (vitamin B2)	5	0.13
biopharmaceuticals	<1	63 (200 products: 21% EPO, 11% MAbs, 10% interferon, 9% human insulin, 50% other)

[a] From refs 19 and 20.

development work is required to extend continuous to biologics/biopharmaceutical processing.

3.2. Bioprocesses. There is increased interest in industrial biotechnology fueled in great part by global issues such as climate change, petroleum depletion, energy and food supply, biodiversity, etc. The applications range from high value-low volume products such as biopharmaceuticals to low value-large volume products (such as bioplastics and biofuels). Some of the enablers and drivers include the current developments in technology (molecular and synthetic biology, enzyme and cell evolution, high-throughput experimentation tools, model-driven design and development), new manufacturing concepts (integrated biorefineries,[17,18]), governmental mandates (biofuels) as well as opportunities from regulatory (FDA: process analytical technology, quality by design) and intellectual property perspective (patent expiry resulting in novel processes for (bio)generics—also termed biosimilars). In addition, next-generation concepts, such as usage of cell-free synthesis, transgenic plants/animals as alternative production platforms may provide further improvements in the future.

As a result, biotechnology products are strengthening their market positions, with annual sales of over $187 billion. Table 2 contains a short list of materials produced through bioprocesses, the volumes produced in 2005−2007, and estimated market sizes.[19,20] Over 90% of the revenues are in the (bio)pharma markets, but processing volumes are much higher in the biofuel, biochemical, food, and feed segments.

Bioprocesses and biotransformations have for some time been known to contribute to highly stereo-, chemo-, and regioselective routes that can sometimes reduce the number of steps in a synthesis, lower the energy needs, and produce less green house gases (GHG) emissions[21−23] and hazardous waste. Numerous industrial biotransformations are in operation worldwide.[24] Most of these known biotransformations are used to produce intermediates and raw materials for the pharmaceutical fine chemical industry.

Bioprocesses are indeed a great opportunity for sustainable engineering. However, from the experiences of the authors, bioprocesses are not by definition 'greener' than the chemocatalytic alternative. For instance, a comparison of processes using metal catalysts and one using biocatalysts for the enantioselective reduction of ketoesters in pharmaceutical synthesis was performed using a streamlined LCA methodology. The analysis identified some processes and reaction conditions that had the largest significance to the impacts of the synthesis. It was also concluded that whether the metal catalysts were better than biocatalysts depended mainly on the workup from the use of organic solvents and energy-intensive steps.[25] This example clearly expresses a need to better integrate bioprocessing design with engineering and life cycle principles to be able to develop greener, more effective and sustainable processes, which can be both chemo- or biobased, or have a hybrid structure.

3.2.1. Biopharmaceuticals. A subset of bioprocesses of special interest within the pharmaceutical industry is the production of biopharmaceuticals. There are opportunities to reduce the environmental footprint and the economic cost of biopharmaceutical processing. There have been dramatic improvements demonstrated in the performance of cell cultures, with much higher product titers and reactor productivities.[26] This could pave the way to much smaller and more flexible facilities with large reductions in the use of buffers, clean-in-place (CIP) and sterilize-in-place (SIP) systems.[27] Economic bottlenecks have shifted to downstream processing. At the same time, there are demonstrated areas for implementation of simpler and less water- and energy-intensive technologies and operations, such as membrane separations, high throughput process design, high throughput experimentation, protein crystallization, aqueous two-phase extraction, mixed-mode (resin) matrices instead of protein-A affinity chromatography, etc. As a consequence, the building of new biopharmaceutical plants (or retrofitting of existing ones) will allow a strong reduction of investment cost from the 200−1000 million range to 50−200 million range. It is envisioned that redesign of the whole biopharmaceutical manufacturing process with much lower eco-footprint[28] will be feasible in the near future.

The area of biopharmaceuticals has so far stayed rather remote from the recent advances in industrial biotechnology field. The new integrated factories (biorefineries) that convert biomass into biofuels, biomaterials, and neutraceutical/food/feed products are designed and constructed, governed by minimizing flows of

raw materials, use of alternative feed-stocks based on renewable resources such as biomass, and application of clean processes with reduced solvent inventories, lower energy input, renewable catalysts, and mild conditions for reaction and separation.[29]

Most likely this parallel development is due to emphasis on implementing biopharmaceutical processes effectively to meet the exacting regulatory demands placed on such products.[30] Hence, implementation of supply chains, rather than integration and optimization, has been the necessary focus of biopharmaceutical process engineering.[31,32] However, adapting the tools of industrial biotech to biopharmaceutical processes may yield processes with lower production cost and lower environmental impact.

3.2.2. Research Challenges and Opportunities for Bioprocesses. The new 'biobased economy' will require the development of a suitable infrastructure and, like the oil-based counterpart, will demand very high efficiency, meaning that research in process engineering for the future implementation and establishment of bioprocesses is needed.

In addition, research is needed that supports the timely identification of environmental, health, and safety issues to be managed within bioprocesses. This research needs to ensure that any claims of 'greenness' (i.e., an emphasis on environmental benefits) are considered in the wider framework of sustainability. Attempting to assess and compare the sustainability of bioprocesses must have a holistic scope based on life cycle thinking, which is strongly based on the output of systems engineering modeling and simulation techniques. Societal issues (food vs fuel, "land use", GMOs) have become part of the discussion and need to be addressed in an open and constructive way. Process systems engineering (PSE) can be helpful here by providing systematic tools for quantification based on transparent assumptions and (mass/energy) balancing principles.

Bioprocesses exhibit a wide applicability in the bulk, fine chemical, and pharmaceutical industries. A further integration of various communities working for the biotechnology business, with sharing of best practices and joint efforts, will undoubtedly support further growth and "greening" of the area. Opportunities in future research include:

- Biocatalysis
  - as a replacement for inefficient or hazardous chemical reactions such as amidation and redox chemistries, which are intensively used in the pharmaceutical and fine chemical industries
  - the application of biocatalysis in the production of more complex pharmaceuticals
- Integration and optimization of bioprocessing design with engineering and systems thinking, especially in biopharmaceutical (biologics) processing, so the gains achieved by the biotransformation are not lost during the workup and purification.
- Integration of life cycle thinking in the design of biopharmaceutical (biologics) processes to evaluate the true (economic, environmental, and societal) sustainability and renewability of the process.
- Application (extended) of process systems engineering and modeling tools to develop more rational and integrated (bio)process design, control, and improvement.[33] At the same time, this supports the recent FDA requirements for knowledge-based improvements and quality by design (QbD).

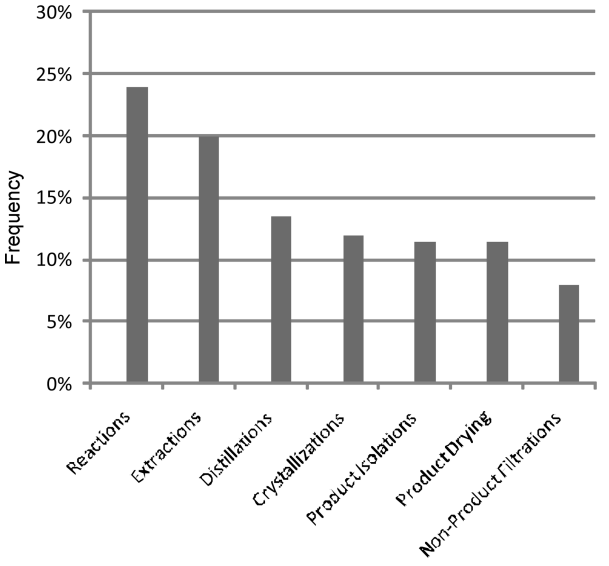

Figure 2. Frequency of unit operations used in pharmaceutical syntheses. Derived from GlaxoSmithKline's phase III and new product portfolio.

3.3. Reactions and Separations. The manufacture of API from starting materials typically involves a multistage sequence, with each stage utilizing a series of reaction and separation steps. While the reaction step often is the 'focal point' of the stage, it frequently requires only a fraction of the time, energy, and material mass relative to the subsequent isolation. Figure 2 shows the frequency of common unit operations in pharmaceutical syntheses. Separations consist of approximately three-fourths of the total number of unit operations used in a process. For every 2 reactions, approximately 2 extractions, 1 distillation, 1 crystallization, 1 product isolation, 1 product drying step, and 0.5 nonproduct filtrations (e.g., carbon or clarifying filtration) steps are performed. Separation steps are conducted primarily in a batch or semibatch mode, with continuous or intensified processing methods seldom employed in drug manufacture.

From a green engineering perspective, the separation steps across a pharmaceutical synthesis contribute a range of approximately 40−90% of the process mass intensity of a synthesis. In terms of energy utilization, distillation and drying steps alone often consume greater than 50% of the energy requirements of a process, while frequently bottlenecking throughput. As a result, the energy and time requirements for separation steps often dwarf those required for the reaction, lead to increased facility size and energy requirements, and are the predominant contributor to processing energy and costs.

Novel, intensified, integrated, and more energy efficient separation methods are required to drive a step change in the green and sustainable manufacture of pharmaceuticals. Instances of such technologies are often exemplified in the production of bulk chemicals. One such example is reactive distillation,[35] which has greatly intensified commercial processes for simple esters and ethers through integrating reaction and separation steps. However, analogous methods relevant to larger-molecular-weight materials are still largely in the developmental stage. Several authors have stressed the needs for the intensification of separation methods and their integration with reaction steps,[35,36] but few have concentrated on the specialized needs of fine chemicals and pharmaceuticals, where flexibility is critical, molecular

complexity is high, and a large batch processing infrastructure is currently in place.

In addition to the most typical unit operations as shown in Figure 2, there are ongoing trends taking place within the pharmaceutical industry. These trends are not by any means new in other chemical industries but have been traditionally less applied in pharmaceutical separation technologies. Some of these current trends are:

Process Analytical Technology (PAT). These have been extensively used in pharmaceutical R&D and sometimes in the manufacturing process. Examples include the applications of FBRM/PVM (Focused Beam Reflectance Measurement/Particle Vision Measurement) on crystallization monitoring and control, Raman in the determination of solute concentration, polymorph conversion and polymorph control, FTIR/NIR (Fourier Transform Infra-Red and Near Infra-Red) for solvent exchange and determination of solute concentration, mass spectroscopy to determine end-point of drying and conductivity to determine the end point of cake wash.[37−39] With the application of PAT tools, the data collection time is greatly shortened, and the understanding of the process is enhanced, improving the overall quality and minimizing failure. PAT can also enable the process monitoring and control for process intensification efforts.

Batch to Continuous Processing. The advantages of moving from batch to continuous processing have been discussed above. In terms of separation, filtration and distillation can be easily operated in a semicontinuous mode. There are also some examples of conducting crystallization in the (semi-)continuous mode that could provide the advantages of better control of quality or particle size distribution. Cases of producing small particle size via a semicontinuous impinging jet and continuous polymorph conversion under high shear techniques have been reported.[40,41]

Automation. Automation technologies have been extensively used in the development stages of separation processes as well as in manufacturing plants. Automation provides the opportunity for process scientists to develop and optimize with a small amount of material that generally results in a more efficient process. For instance, high throughput crystallization screening has been used in the early polymorph/salt screen to identify a suitable solid form for further development as well as to conduct polymorphism studies.[42] Automated solubility measurement is a common tool to screen for solvents for reaction and crystallization as well as for separation of impurities.

Process Modeling. Mathematical modeling is a key area that chemical engineers have skills that most chemists do not share. Ideally, modeling can contribute to the greenness of the process by generating predicted process information and outcomes without physically executing large numbers of experiments; thereby minimizing waste. On the other hand, modeling can also enable efficient overall process design and contribute to the process optimization through simulation of the entire process. Examples for this include modeling/prediction for solvent selection in reaction, extraction, crystallization, and cleaning.[43] Once a model is built, the effect of process operating conditions in scale-up could be predicted through simulation.

3.3.1. Research Challenges and Opportunities for Reactions and Separations. Two important (but not yet greatly studied and practiced) research areas in separation technologies that can facilitate green and sustainable manufacturing are intensified separations and hybrid systems combining reaction and separation. Intensified separations will enable the transition from batch to continuous processing, while hybrid systems will help improve on selectivity. The use of multiple separation steps in countercurrent operation will lead to a significant reduction of solvent use and product loss.

3.3.1.1. Development of Intensified Separations. The first research challenge is the development and implementation of intensified separation technologies with highly productive modular units performing conventional tasks such as: extraction, distillation, and filtration. This implies that a small module will be able to process a large continuous flow of material during its short residence time in that module. The modules should be small so that they fit within an existing multipurpose plant.

Although the aim is to have pharmaceutical production increasingly in continuous mode as discussed above, the pharmaceutical industry will probably continue to have campaign-based operations. Sharing the facility over several products is expected to remain beneficial, but adapting the plant to the next campaign should become much easier and faster. Mobile modules allow for offline cleaning, maintenance, reconfiguration, validation, etc. The plant will have some kind of 'backbone' interface allowing these modules to 'dock' to the appropriate position in the process. Final validation of the full process should take much less time with these preprepared modules.

One example of a separation used routinely in pharma that could benefit from intensification and enhancements is phase separation. Each separation step is based on the same principles:

- creating a second phase
- contacting both phases and allowing the component to reach a partition (thermodynamic equilibrium) over both phases
- separating the two phases

Developments on hydrophobic/hydrophilic membrane and centrifugal separators for phase separation have the potential to result in high efficiency liquid−liquid (L/L) and gas−liquid (G/L) separation systems. However, pharma production often has to deal with liquid−solid (L/S) systems. Hence, another opportunity lies in performing research that increases the availability of technologies that intensify L/S operations. For instance, the formation of suspension can be intensified and converted to continuous operation by the application of oscillating flow systems, but this excludes the batch operation of the S/L separation and drying (API milling, formulation).

3.3.1.2. Development of Hybrid Systems. Additional research and development on combining separation and reaction into one operation is needed. These hybrid systems should result in the in situ product removal reactor, which is a powerful tool capable of shifting chemical equilibrium or avoiding selectivity loss in case of follow-up chemistry degrading the desired product. Typical examples of such combinations are:

- reactive distillation
- reactive extraction
- reactive crystallization (production of optically pure substances)
- membrane reactor

Despite many ongoing research activities in the field, there still exist numerous technical and nontechnical barriers that hinder a wider introduction of reactive separations into industrial practice. Some research opportunities to overcome these challenges include:

- research to fill specific technical gaps, such as lack of simulation and scale-up capability, lack of validated

Table 3. Some solvent properties important for selected separation techniques[a]

	separation techniques requiring solvent design			
pure solvent properties	liquid−liquid extraction	extractive distillation	azeotropic distillation	gas absorption
viscosity	D			D
boiling point	E	E	E	E
vapor pressure		E	D	
heat of vaporization		D	D	
solubility	E	E	E	E
mixture properties	liquid−liquid extraction	extractive distillation	azeotropic distillation	gas absorption
phase split	E	E	E	
viscosity	E			
selectivity	D	D	D	E
azeotrope		D	E	

[a] E = essential, D = desirable.

thermodynamic and kinetic data, lack of materials (e.g., integrated catalysts/sorbents, membrane materials), and lack of high-level process synthesis methodology
- establishment of multidisciplinary team approaches to process integration, including demonstrations/prototypes on a reasonable scale (reactive separations are still regarded more as a science rather than a technology)
- fundamental research into new reactions that integrate separation technologies.

3.4. Solvent Selection and Optimization in API Synthesis. In 2007 and 2008, the Roundtable published an industry-wide mass efficiency benchmarking study to understand the typical composition of the materials used to manufacture an API, showing the large contribution of solvents to the process mass intensity (PMI).[44] Life Cycle Assessment of pharmaceuticals has also shown that solvents make a large contribution to the environmental impacts of manufacturing processes of APIs.[45,46] Constable et al.[47] reported on the state of solvent use in GlaxoSmithKline in 2005, showing how solvent use is evolving towards the use of greener solvents but also commented that there were still challenges ahead, in particular, a need to engage both the academic community and drug discovery scientists.

Solvent selection, optimization and minimization, and reuse/recycling are thus crucial in driving more sustainable pharmaceutical processes. Several pharmaceutical companies have already developed their own solvent selection guides based on physicochemical properties,[48−50] and the Roundtable has recently developed a consolidated guide; but more work is needed to develop solvent selection and optimization routes that account for the chemistry and engineering interactions. The decisive factors for solvent selection have been dealt with in detail in the literature.[51] Regarding process technology, it is mainly the effort to recycle a solvent that has an impact on the choice of a specific separation/recycling technology.

Gani and co-workers have worked on the combination of solvent parameters and separation techniques (Table 3).[52] Gani's model, linked to a solvent selection software, allows for the judicious choice of a solvent fitting the selected separation technique and equipment. This feature is especially useful in cases where a new synthesis has to fit existing multipurpose equipment.

3.4.1. Research Challenges and Opportunities for Solvent Selection and Optimization. There is often reluctance to make the best use of the predictive solvent selection tools already available; often they are complex and require an expert user, leading the typical development chemist to place less value on their use than the results of lab experimentation. Solvent selection can be one part of these considerations. Frequently, the chemistry does leave some freedom to choose a solvent meeting the requirements of effective recycling. This has to be done prior to the 'freezing of the process' to avoid reregistration. Given the fact that solvent handling is among the most energy intensive and wasteful parts in a typical pharma synthesis, any improvement in this field will directly translate into improved greenness metrics (such as the PMI) of a process.

It is encouraging to see that some academic groups have made concerted efforts in solvent selection and optimization, primarily in the fields of chemical engineering. However, these approaches are not yet completely developed, and there is need for further improvement:

- Inclusion of solvent selection as a design consideration in route selection. In addition, a great deal is to be gained by training people to have the manufacturing plant in mind while developing a synthetic route.
- Synthesis strategies to key intermediates or synthetically useful building blocks that optimize solvent use, reuse, and end-of-life considerations.
- Development of solvent options that provide the desired function (solubility and separability) without the undesirable chemical properties that cause environmental, health, and safety issues.
- Development of validated databases that rank solvents with respect to different chemistries, reactions, and effects of solvent variation on those chemistries.
- Inclusion of process parameters that are not typically incorporated in some solvent selection guides that cover safety, health, and environmental fate and effects. These parameters may include method and ease of recycling, factors in ease of separation, volatility, viscosity, azeotrope formation, stability/reactivity, and technology options that facilitate process intensification; e.g., new reactors, mixers, solvent-free reactions, etc.
- Identification of existing alternative solvents available at a meaningful scale to replace problematic solvents

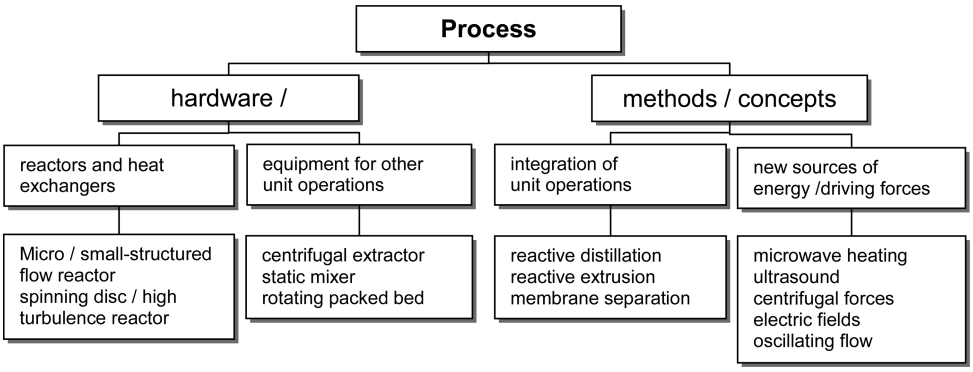

Figure 3. Process intensification methods and equipment, adapted from Stankiewicz and Moulijn, ref 53.

such as dichloromethane, dimethyl formamide, and other dipolar aprotic solvents with environment, health, and safety issues.

- Increased use of biotechnology to produce desired intermediates and APIs in media where the desired product is easily recoverable in the required form.
- A general methodology to verify the feasibility of eliminating solvents using options such as solid-phase reactions, aqueous media, or reactions in molten state, which are rarely applied in synthesis; usually the required equipment such as suitable mixers is not present in most laboratories.
- Development and enhancement of user-friendly guidance and tools that allow people to systematically explore options for solvent optimization. Frequently there is no systematic exploration of options such as:
  - Use of a reactant as solvent, if it is employed in excess over a second one to produce a desired selectivity.
  - Direct reuse of (some) solvent in the subsequent batch (e.g., wash solvents, distillates) where the required product/intermediate purity is lower than that achievable by the process.
  - Guidance and tools that suggest preferred methods of workup to ensure both product quality and high recycling rates at moderate effort.

3.5. Process Intensification. As seen above in the area of separations, Process Intensification denotes the effective use of a set of development and manufacturing tools aiming at:

- increasing space-time yields for reactions and separations
- improving the sustainability of manufacturing processes
- enlarging the practically applicable hazardous reaction space
- shortening the time to implement

Within Process Intensification two basic categories of technology can be distinguished: "hardware" technologies, i.e. novel equipment, and "software" technologies, i.e. new processing methods, as depicted in Figure 3.[53]

Process Intensification is driven by four generic principles:

1. Maximize the effectiveness of intra- and intermolecular events.
2. Give each molecule the same processing experience.
3. Optimize the driving forces at every scale and maximize the specific areas to which those driving forces apply.
4. Maximize the synergistic effects from events and partial processes.

For instance, instead of slowing down a reaction to fit into the limited capabilities of a batch-operated multipurpose plant, we analyze the requirements of the reaction and define the optimum reaction environment for the respective phase of the reaction. Thereby, costly and environmentally disadvantageous measures such as diluting or operating at very low temperatures become unnecessary. Equally the energy and environmental balances of an intensified process are better than those of a nonintensified process, so the goal of reducing the PMI will require intensifying selected process steps.

One can argue that continuous processing as described above may be one of the forms of process intensification. This was indeed one area of debate within the working group, but it was decided to maintain both areas separate as batch processes can also be intensified.

3.5.1. Research Challenges and Opportunities for Process Intensification. In general, the pharmaceutical industry needs procedures for in-depth analyses of existing processes and processes under development to identify opportunities to improve their greenness by intensifying steps or single-unit operations. These needs face the following hurdles to implementation in the pharmaceutical context:

- In pharma development, project delivery of API to time (dictated by clinical trials) and quality are paramount. New technologies are perceived as high risk, so there is often reluctance to take a chance and apply them; hence, getting new intensification technologies implemented, even at pilot level, can be very difficult.
- There are so many different options to intensify a process, that it is difficult for the typical project technical team (of nonprocess intensification experts) to easily identify what option might be best within the time constraints of a development project.
- Multipurpose batch plant is established, it is straightforward to find wherever production is planned and therefore an easy option. Developing specific technologies is difficult in earlier development if the long-term production site is not yet fixed.
- Attrition in development means people are less inclined to look really hard at novel solutions early for individual projects.

To overcome these hurdles, and to assist further implementation, our suggestions for research opportunities are the following:

- development of showcase examples of process intensification highlighting their benefits. This is intended to support the implementation of process intensification by increasing the visibility of the advantages of an intensified process in a development environment.

- development of guidance and tools to assist with the selection of the best intensification option
- development of methodologies and tools to integrate intensification considerations into a given process from early on
- establish procedures of analysis for production processes to define opportunities to intensify steps or unit operations to improve their PMI
- integrating process intensification into the curricula of new generations of chemists and engineers

3.6. Integration of Life Cycle Assessment Considerations. Life Cycle Inventory and Assessment (LCIA) is a methodology used to evaluate the environmental profile of an activity or process from the extraction of raw materials to its end-of-life. Resource consumption and emissions are inventoried and assessed from the extraction of raw materials, production, transportation, sales, distribution, use, and final fate. The results of these assessments can be reported as direct inventory data (for example life cycle energy, life cycle mass, life cycle emissions), measures of individual potential impacts (such as global warming or acidification), or as an aggregate score or index for high-level comparison (for example Eco-Indicator 99[54]). LCIA methodologies are described in detail in the literature.[55−60]

The application of LCIA is still not a widespread practice in pharmaceuticals. A few practitioners apply Life Cycle Assessment (LCA) metrics primarily using case studies to better understand the wider environmental implications of processes, to compare different chemical routes, or to compare the use of different unit operations. For instance, life cycle assessment has been applied as an additional metric in material selection as exemplified by both GSK and AstraZeneca who have incorporated life cycle considerations into their solvent assessment and selection guides.[61] At GSK, a cradle-to-gate life cycle inventory and assessment was performed to identify and analyze the environmental impacts in the synthesis of a typical API, amongst other applications that served to establish a well-documented approach and practical methodology to using LCA within GSK.[62] The assessment provided key insights, such as the large impact that solvent usage plays within a life cycle context. Another example is the LCA performed at Pfizer to evaluate several processes at different stages of development for the production of sertraline and its precursor.[63] This type of assessment has provided some key insights, such as the role of separations, a more systematic and holistic method to evaluating waste impacts, and the nuances of renewability.[64−69]

Given the labor-intensive nature of traditional LCIA methods, streamlined LCA has begun to be applied in pharma. For instance, a streamlined LCA methodology has been followed in assessing an API from Hoffmann La-Roche in comparison with the LCA of an API of GSK,[70] finding in general trade-offs on environmental impacts of the two APIs. Another example of these streamlined methodologies is GSK's Fast Life cycle Assessment of Synthetic Chemistry tool, or FLASC, which allows for screening synthetic routes rapidly in terms of the impacts associated with material manufacturing. In FLASC, processes are given a score between 1 (bad) and 5 (good) after consolidating the metrics for eight different environmental impacts and normalizing for the molecular weight of the API. Life Cycle Inventory data gaps are filled using principal component analysis. The FLASC tool allows scientists with no LCA expertise to perform fast comparisons of synthetic routes in different stages of development, from medicinal chemistry through manufacturing. The score is currently tracked for most of the GSK chemical routes under development.[71]

Developing life cycle inventories and assessing the LCIA impacts of pharmaceutical processes is not simple, given the large amount of data needed from different sources. The more materials that are involved in the process will require more life cycle inventory data to be collected, verified, and analyzed. One of the opportunities from the green engineering standpoint is the development of reliable, consistent, transparent, accurate, and easy-to-use modeling and streamlined techniques for LCIA of pharmaceutical processes. To routinely assess sustainability of pharmaceutical processes and to embed sustainability principles into the processes design and development, the following recommendations can be highlighted:

- generalized inclusion of life cycle thinking in product and process design and development
- better understanding of life cycle inventory and impacts of pharmaceutical processes, bioprocesses, complex starting materials, and bioderived materials
- continuous development of reliable, common, easy-to-use, streamlined LCA tools
- improved consistency and transparency of LCIA methodologies as applied to pharmaceutical processes
- improved streamlined LCIA methodologies that are easy to use by academia and industry alike
- enhanced understanding of the interactions of the environmental, social, and economic aspects of the LCIA of pharmaceutical processes for a holistic sustainability view
- integrating LCIA into the curricula of new generations of engineers

3.7. Scale-Up Aspects. Almost each process has to undergo major changes/adjustments in process technology or even recipe to deliver the desired product in the required quality/quantity on large scale. Frequently these process adaptations focus on quality and reliability, but not on leaving room for a continuous process improvement program. There are specific fields where scale-up features affect the environmental footprint of a process (e.g., PMI, energy) independently of production mode:

- Different macro and meso mixing behavior of large vs small reactors may decrease selectivity and thus increase waste cost and raw materials demand.
- Differences in dosing times, heating and cooling times may affect byproduct content, crystal size, and habit.
- Differences in filter cake height, cake washing and drying may affect isolation times, crystal shape, and size.

Avoiding such scale-up problems and the necessity to resort to less-than ideal solutions allows focusing on sustainability and learning curve aspects of a process. Research challenges and opportunities for scale-up include:

- enhancing tools and apparatus to mimic the behavior of large vessels (such as Continuous Flow Dynamics)
- development of models that would enhance understanding of filtration time and cake properties, which are frequently unpredictable
- development of models for crystallization operations
- increase understanding of mass and energy transfer in pharmaceutical and fine chemical operations
- integration of scale up considerations into the curricula of new chemists

- development of tools for scale up of unit operations such as reactors, filters, dryers, amongst others. Such tools can be:
  - mathematical models
  - model equipment (stirrers, vessels, filters)

3.8. Process Energy Intensity. Process energy measurement and optimization has been historically ignored as part of pharmaceutical process development, with very few examples found in the literature.[72] Although most of the energy requirements in pharmaceutical settings are related to the baseload energy of the facilities (i.e., the energy needed to run the plant independently of production), process energy requirements are in general in direct control of the chemists and engineers designing pharmaceutical routes. Some of the research challenges and opportunities in terms of process energy intensity are:

- Increase awareness of mass and energy balances in the chemistry curriculum.
- Develop easy-to-use estimation methods for chemists that relate process energy to reactions and routes that can be integrated into electronic notebooks.
- Integrate process energy calculations into pharmaceutical process design tools and methods.
- Develop a process energy intensity metric similar to the PMI.
- Benchmark process energy metrics for the pharmaceutical industry.

3.9. Mass and Energy Integration. Whereas the PMI focuses on the *output* of desired product vs waste of a chemical process, the internal mass and energy flows represent important parameters concerning the efficiency of a process. The following features strongly affect mass and energy balance:

- High dilution of reaction mixtures and reagents requires distillation and condensation of large amounts of solvents. The nature (boiling point, heat of evaporation, stability, and recycling rate) of the solvent in turn defines the related energy consumption.
- If a multistep process requires a large number of different solvents, the recycling of this large number of different solvents requires many vessels dealing with relatively small amounts of chemicals and leads to many different waste streams.
- Deep cooling of reagents or reaction mixtures to slow the reaction down to meet the capabilities of the reactor forces the removal of reaction heat at an inconvenient temperature level (−80 °C to −40 °C).

There is much literature on mass and energy integration in large-scale chemical manufacture (base chemicals production, refineries), but little on application of such concepts in pharmaceutical manufacturing. In general, the following are some of the key research challenges regarding mass and energy integration:

- developing and refining mass and energy integration techniques within the multioutput pharmaceutical plant
- training chemical engineering students on mass and energy integration with some pharmaceutical examples
- extending mass and energy integration beyond the boundaries of the single plant (i.e., industrial ecology approach)

3.10. Integration of Chemistry and Engineering. The umbrella framework that will enable the development and implementation of all the key research areas is precisely an integrated view of chemistry and engineering. It is very common that chemists working in large pharmaceutical companies discover a novel synthesis for a new pharmaceutical product and in many cases drive the development, transfer, and implementation of processes and designs. However, there are hundreds of engineering questions that need to be formulated and answered, such as the effect of kinetics, separation needs, process design, mass and energy integration, opportunities for process intensification, identification, and elimination and mitigation of inherent hazards in materials and processes amongst many others. If pharmaceutical processes are developed using chemistry in isolation, answering these questions retrospectively is not the most efficient way to design processes, and the processes will, in large part, be suboptimal at best.

On the other hand, a chemical engineer working on the scale-up of a laboratory synthesis to render an effective production process will need to closely understand how the chemical synthesis may be changed, since there are also many chemical questions that need to be answered to design sustainable processes, such as the function that the solvent is performing, potential alternative reaction pathways to avoid issues, reactivity issues, and alternative catalysts, amongst others.

Therefore it is necessary to achieve a cohesive application of chemistry and engineering. Chemical engineering has strived to do so since inception, but there is much work to do in terms of the truly effective application of both disciplines within the pharmaceutical industry. The decisions made during synthetic chemistries are either barriers to, or enablers of, engineering opportunities and vice versa. Chemistry and Chemical Engineering should operate seamlessly together if the desired outcome is an efficient, more sustainable process. For this, it is necessary to have academic curricula designed to promote awareness of and foster collaboration with the other discipline.

4. CONCLUSIONS

The Roundtable hopes that with the publication of these Key Research Areas there will be an increased emphasis of the green engineering aspects when designing pharmaceutical processes. We hope that as the Key Green Chemistry Research areas have motivated the academic community, the Top Key Green Engineering Research Areas will do the same to foster innovation to solve the pharmaceutical processes research challenges within chemical engineering circles. The first step has been to focus the 2010 Roundtable Grant call for proposals on one high impact area of green chemistry and green engineering: Solvents.

It is also the intention of the authors to highlight the need for the integration of chemistry and engineering in order to design truly green and sustainable pharmaceutical or chemical processes. Chemists and engineers need to also be aware of the impacts of their choices on materials, processes, and energy. There is the need to design by principle processes that minimize the short-, medium-, and long-term hazards and risks not only to humans but to other ecosystems as well. To achieve this, a true collaborative approach is needed. This type of systems thinking needs to be brought in from the moment we educate the next generation of professionals. In addition, there is the need to closely and effectively collaborate with other specialists such as toxicologists, environmental, health and safety professionals, economists, industrial engineers, and others to discuss and develop appropriate options for greener production. In short, there are a host of disciplines that are required to appropriately and successfully bring a product to market and ensure that this is done in a sustainable fashion. We also recognize that chemistry and engineering change and evolve, and these proposed areas will need to be refined and updated at some time in the future.

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ACKNOWLEDGMENT

We thank the many colleagues within our companies and from the wider academic community who provided input, comments, and feedback during the identification and prioritization of these key research areas. We especially thank Bob Peoples, Berkeley Cue, Gjalt Huisman, and John Grate from the Pharmaceutical Roundtable for their encouragement, input, and support, and John Hayler from GlaxoSmithKline for his useful comments.

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