Pharmaceutical Product Development and Manufacturing Science Research Strategic Plan

NIPTE Faculty Committee

Context

The global pharmaceutical industry is a major sector of the world economy with expected sales of over $700 billion in 2008 and expected growth rates of 4-5 percent – still solid growth despite the slowdown. The industry has added more than $177 billion of absolute growth since 2003[1]. However, despite the healthy growth outlook, the pharmaceutical industry is at a critical juncture. Patients are seeking safe and effective medicines for a widening range of medical conditions at a low price. The healthcare system recognizes drugs as effective and desirable alternatives to expensive medical procedures and hospital stays but seeks to obtain those benefits at low cost. Shareholders are seeking sustained growth through deep product pipelines, high success rates of products from discovery, and strong returns on investment. Yet, the complexity of modern drugs, the high risk of failure of a candidate drug during the development process and the decreasing tolerance of the public for the risk of side effects have caused significant increases in the cost of bringing a new drug to the market. The FDA White Paper, published in March 2004 estimates that the cost of bringing a new drug to market can be as high as $1.7 billion, a 50% increase in just five years[2]. The critical question is: how can we increase efficiency in the pharmaceutical product pipeline while also maintaining and indeed encouraging continued substantial investment in innovation? At least part of the answer lies in expanded research in pharmaceutical product development and manufacturing science and technology.

Current State

Of the four major steps of the pipeline--Discovery, Safety and Clinical Studies, Drug Product and Process Development, and Manufacture--the first two are well-funded by industry and the federal government. These two steps will continue to require high levels of investment and are not likely to be amenable to major cost reductions through significant new technical developments in the near to medium term. By contrast, although the cost of goods sold (COGS) for pharmaceutical products is estimated at upwards of 25% of sales [3,4] , comparatively little funding is devoted by industry or government to new science and engineering technology for reducing the costs associated with development and manufacturing. Indeed, according to the FDA, new science and technology in product/process development and manufacturing are lagging substantially behind the tremendous advances in the basic sciences for discovery. The reasons for this lag can be found in the interplay between regulatory and market factors as well as long standing gaps in federal research funding. The business need is to bring the product to market as rapidly as possible so as to capture market and recover the huge investment before expiration of product patent protection. FDA concerns with product safety have *de facto* resulted in a regulatory environment that has effectively discouraged taking the risks inherent to technological change. Industry thus has little incentive to invest in fundamental advances in product/process development and manufacturing technologies. In addition, federal NIH funding has focused on discovery research, while, until recently, NSF and the mission agencies have targeted research to support threatened manufacturing industry sectors or those sectors critically dependent on maintenance of technical supremacy. The absence of significant research funding in pharmaceutical development and manufacturing available to universities has had a compounding effect that the number of faculty experts in these areas has steadily diminished. As a result, not only has the output of, and the capabilities for, academic research in these areas been severely impacted, but the flow of trained scientists and engineers well versed in new manufacturing technologies has also diminished[1].

NIPTE Research Strategic Plan

One important impetus for increased focus on pharmaceutical development and manufacturing research has been provided by the US FDA which has recently signaled an increased willingness to change regulatory practice to make regulations science driven and to encourage innovation in product development and manufacture [5, 6]. Concepts such as process analytical technology [5], quality by design, and design space have been widely discussed and initial attempts have been made to inject these concepts into practice. However, the barriers to progress in development and manufacture methodology lie in the limited fundamental understanding of the complex materials and processes with which the industry must work. To build that understanding and to develop the basic tools needed to substantially advance these domains, the need for a systematic program of research has to be established. A strategic plan or Technology Roadmap has been developed by the National Institute for Pharmaceutical Technology and Education [7], a multi-university consortium, working in cooperation with industry and the FDA. That Roadmap is designed to reflect the understanding and technology needs of the stakeholders of the pharmaceutical industry.

The Pharmaceutical Technology Roadmap consists of two closely linked parts. The first part presents the key pharmaceutical research needs associated with the evaluation and incorporation of pharmaceutical materials and components into drug products that are capable of reliable performance based on desired product attributes. It deals with the measurement of pharmaceutical material properties, the prediction of properties, and systematic product design based on input material and desired product performance properties. Properties prediction needs include algorithms for predicting the thermodynamically and/or kinetically favored forms (crystalline, amorphous, polymorphism hydrates and solvates) of key drug product components that occur as a result of different processing conditions. Key physical property prediction needs include prediction of solubility, melting temperatures, changes in physical form and resulting impact on solubility and rate of dissolution, and glass transition temperature. To facilitate product formulation, rule-based systems are needed to predict the importance of the material, surface and structure properties on the rate and extent of water uptake, including mixture rules for multi-component and multi-phase systems.

Drug product performance is dependent on key quality attributes such as solubility, physical and chemical stability, particle size and size distribution, particle morphology, excipient properties and functionality, surface properties of the component materials as well as the impact of packaging components. At present there exists no systematic methodology for identifying and optimizing formulation design that can select from existing components to develop formulations meeting a suite of desired product attributes. Likewise there is a need to develop systematic methodology for selecting the most appropriate drug product form given the characteristics of the active ingredient and the desired administration profile. Such decisions are currently made based on heuristics, past experience and company historical practices [8]. Additionally, to address the potential for individualized dosing the challenge is to design innovative platform technologies that allow for significant variation in dosing with slight modification of the basic platform formulation and its associated manufacturing technologies.

The second part of the Roadmap describes the key research needs associated with the development, design, scale-up and operation of pharmaceutical processes. Specific process design issues include the development of predictive models and design spaces for a suite of high priority unit operations used in active pharmaceutical ingredient and key dosage form production. These include multiphase batch reactors, anti-solvent based crystallization, solid-liquid separation, size reduction, granulation, lyophilization and a variety of separation types, such as simulated moving beds. Systematic methods for the synthesis, design and optimization of integrated process step sequences for a range of dosage types, including not only solid oral but also aerosols, parenterals, and vaccines are necessary. Beyond classical process synthesis methods, there also exists the need for systematic and reliable methods for scale-up/scale-down based on rigorous CFD, DEM and FEM simulation models. There is considerable research required to adaptation of multivariable control systems design approaches as well as optimal control methods for these complex process operations. Operational issues include sensor network deployment, trend monitoring, incipient fault detection and fault diagnosis and corrective measures. With the growing interest in converting to a continuous processing mode, at least for portions of the processing train, applications of process-wide automatic control and real time process optimization methods need to be developed. With the anticipated departure from plants dedicated to a specific block buster drug, the multiproduct production mode is becoming important. This requires exploitation of optimization approaches for efficient equipment change-overs to minimize down time as well as adaptation of various planning and scheduling formulations and solution methodologies. Innovations in manufacturing beyond the conversion to continuous processing include process intensification and microprocessing alternatives to current batch operations as well as innovative facilities for rapid clinical supply, production of small volume products, and containment for hazardous operations. The research needs of the pharmaceutical product pipeline also include model-based support systems for enterprise level decisions [9]. Of particular importance are supply chain modeling and solution approaches which integrate strategic and tactical decision levels and support production planning, logistics and inventory management functions. The particular features of pharmaceutical supply chains which must be addressed are the accommodation of product shelf-life limitations, the potential separation of manufacturing of product components, secondary manufacturing as well as packaging functions, and the various governmental regulatory and financial incentives/constraints. Capacity expansion decision in the presence of uncertainties in market demands, pricing, competitor actions and regulatory outcomes present challenging stochastic multistage decision problems. Management of the product development pipeline involving the selection of products for development, the assignment of resources and resource levels, and the timing of development task likewise constitutes a stochastic multistage decision problem of considerable research challenge. While initial efforts to attack such enterprise-level problems have already been reported in the literature, the scope of practical applications still present major continuing challenges.

Finally, a key cross-cutting technology consists of development of informatics support systems real-time intelligent informatics-based environments for managing data, information and models for optimal process and product decision-making. Information and model management spanning the life cycle of a pharmaceutical product is of critical importance given the requirements of regulatory bodies, the need to support process improvements and the requirements to support post-market product innovations. The Technology Roadmap provides a comprehensive framework for identifying and discussing specific research challenges and opportunities for process systems engineering and assessing the contributions that our community has made to date and could make in the future in addressing these challenges.

Bibliography

1. IMS Health 2007 Annual Report
2. Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products, http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html
3. Reinhardt, U. E., Perspectives On the Pharmaceutical Industry, Health Affairs, 20(5), September/October 2001
4. Raymond H. Scherzer, Quality by Design: A Challenge to the Pharma Industry, http://www.fda.gov/cder/OPS/Scherzer-Camp/index.htm
5. FDA, PAT-A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance. Guidance for Industry (2004), http://www.fda.gov/cder/guidance/6419fnl.pdf
6. FDA, Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach Final Report - Fall 2004, www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.html
7. National Institute for Pharmaceutical Technology and Education, www.nipte.org
8. Zhao, C.-H , A. Jain, L. Hailemariam, P.Suresh, P.Akkisetti, G. Joglekar, V.Venkatasubramanian, G.V.Reklaitis, K. Morris, P. Basu, *Journal of Pharm.Innovation*, Vol 1, No. 1, pp.23-36 (2006)
9. Varma, V.A., G.E. Blau, J.F. Pekny and G.V. Reklaitis, *Computers & Chem Engr*, 31 (2007) (in press).