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# Perspectives on Process Systems Engineering R&D in Support of Pharmaceutical Product/Process Development and Manufacturing

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## Extended Abstract

The global pharmaceutical industry is major sector of the world economy with sales of $600 billion and growth rates of 10% and higher in the last decade. With an aging population in the developed countries and a burgeoning medical need in the developing countries, that growth rate is likely to continue. 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 market. The FDA White Paper, published in March 2004 (1) 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. The critical question is: how can increased efficiency be achieved in the pharmaceutical product pipeline while also maintaining and, indeed, encouraging continued substantial investment in innovations? At least part of the answer to this question lies in expanded research in pharmaceutical product development and manufacturing science and technology. It the thesis of this paper that process systems engineering methodology has an important role to play in this effort.

One important impetus for increased focus on pharmaceutical development and manufacturing research has been provided by the US FDA which has recently signalled an increased willingness to change regulatory practice to make regulations science driven and to encourage innovation in product development and manufacture(2,3). Concepts such as process analytical technology (2), 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 been established. In the past year, a strategic plan or Technology Roadmap has been under development by the National Institute for Pharmaceutical Technology and Education (4), a multi-university consortium in which PTEC is a lead member, 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 (crystaline, amorphous, polymorphsm 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. Process systems engineering methodology certainly has much to contribute to addressing these needs.

PSE methodology likewise is important in addressing the product design problem, which at root is a formulation type design problem. 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. This is a challenging problem requiring

computational approaches spanning multiple length scales from the molecular to particulate or granular levels. 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 (5). Additionally, to address the potential for individualized dosing there exists the challenge of designing 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. This technology component is unequivocally of relevance to the process systems engineering community. 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, antisolvent based crystallization, solid-liquid separation , size reduction, granulation, lyophilisation 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. 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 (6). Of particular importance are supply chain modelling 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 PSE 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.

**Keywords:** Process and product design, process operations and management, enterprise-wide decision making and information/model management

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