National Institute for Pharmaceutical Technology and Education

Strategic Roadmap for Research and Education

NIPTE will be the pre-eminent interdisciplinary national resource for research and education on science and engineering based understanding of pharmaceutical development and manufacturing.

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NIPTE The National Institute for Pharmaceutical Technology and Education
Improving Quality and Lowering Cost of Pharmaceuticals
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Preface

Context

The pharmaceutical industry, a sector in which the U.S. remains a global leader, is at a critical juncture. On the positive side, prescription drugs are assuming an increasing role in healthcare by providing effective alternatives to expensive medical procedures and hospital stays. While in 1999 prescription drugs accounted for 8.2% of the total national healthcare spending, that share is expected to reach 14% by 2010. Innovative drug therapies are recognized as having significantly increased the quality of life and longevity of populations in the developed world. However, as overall costs of healthcare rapidly accelerate and the size of uninsured and underinsured populations continues to increase, the issue of drug prices is attaining high visibility. While the public has become more aware of the inefficiencies of the overall healthcare delivery system as a whole, nonetheless, drug pricing has moved to the center of the public agenda in America.

However, that public is unaware that the cost of bringing a new drug to the market place has been steadily increasing. 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. Indeed a more recent study projects a required investment of nearly $2 billion for a new therapy to progress from a laboratory idea to commercialization. The high level of investment and substantial risks associated with introducing an innovative new therapy are not appreciated by the public, who perceive prices offered by generic manufacturers and lower prices available in regulated markets as evidence that high US prices of patented drgus are unjustified. The critical questions are: how can cost reductions be achieved while also maintaining and indeed encouraging continued substantial investment in innovations? It is a key thesis of this report that an important component of the answer to these questions lies in selective investment in research that substantially improves the efficiency of the pharmaceutical product pipeline.

Current State

The pharmaceutical product pipeline consists of four major steps, as shown below:
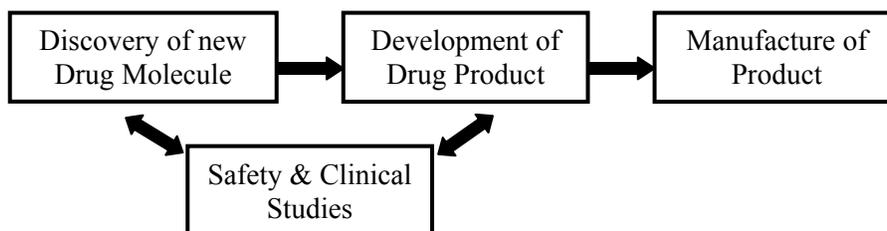
Considerable public excitement as well as industry and government funding are directed to the discovery and clinical trial steps of the pipeline. For instance, the NIH's annual

budget exceeds $28 billion and the pharmaceutical industry expends 20% of its $51 billion annual R&D budget on discovery. Discovery research is essential for the identification of new and improved therapies. But, given its sophistication and complexity these is little scope for substantial cost reduction and thus impact on the price of new pharmaceutical products. Industry-wide discovery research budgets have remained at about 15% of sales for a number of years. Clinical trials are a mandatory part of the product development pipeline and constitute up to 30% of the cost of developing a new product, but rising concerns with product safety, especially identification of side effects, suggest that significant reduction in cost in this area is likewise unlikely.

By contrast, although the cost of goods sold (COGS) for pharmaceutical products is estimated at upwards of 25% of sales, comparatively little funding is devoted by industry or government to new science and engineering technology for reducing the costs associated with the development and manufacturing steps of the pipeline. Indeed, the FDA has identified that new science and technology in product/process development and manufacturing are lagging substantially behind the tremendous advances in the basic sciences for discovery. A recent FDA-industry joint report suggests that world-wide cost savings from manufacturing improvements could be as high as $90 billion per year. Moreover, research conducted by NIPTE indicates that improvements in the science and engineering of product development alone could save an additional $5 to $7 billion in drug development cost in the US alone each year. Given these incentives, why is private and governmental attention not directed at improving development and manufacturing technology? The reasons to a considerable extent can be found in the interplay between regulatory and market factors as well as long standing gaps in federal research funding.

Once a new drug discovery is made, the key business driver is to bring the product to market as rapidly as possible so as to capture the new market and recover the huge investment before the expiration of the patent life of the product. As the result of a historical regulatory environment that effectively discouraged taking the risks inherent to technological change, product development and manufacturing have been left to traditional, tried and true practices, that, however imperfect, were familiar to industry and regulators alike. Furthermore, the interplay of tight FDA regulations to insure product safety and quality, the high cost of re-approval of process innovations and inadequate science-based understanding of pharmaceutical materials and manufacturing processes have tended to assure that, once a manufacturing process is approved, it is left substantively unchanged for the duration of the product life. Consequently, the beneficial learning curves and associated progressive reductions in costs typical of products sold in unregulated markets do not occur. Instead, product costs are only likely to increase as energy, input material, marketing and labor costs rise. As a result of these factors, industry has seen little incentive to invest in fundamental advances in product/process development and manufacturing technologies.

 While government has accepted the need for investment in discovery by steadily supporting the NIH, the FDA as a regulatory agency has not had the mandate to support research in pharmaceutical product development and manufacturing. Until very recently, the NSF has directed its attention to other areas of manufacturing research, motivated by

the desire and, perhaps political pressure, to retain industries important to national employment, if not technical supremacy. The other mission agencies have not seen the apparently very profitable pharmaceutical industry as in need of fundamental research support, by contrast to industries such as automotive, semiconductor, paper, steel and device manufacture. Finally, in the absence of significant research funding in pharmaceutical development and manufacturing available to universities, the number of faculty with expertise in these areas has steadily diminished (see for example the dramatic reduction in academic programs in industrial pharmacy). As a result, both the output of and the capabilities for academic research in these areas has been severely impacted. Most important, the educational programs that could prepare a new generation of scientists and engineers well versed in new manufacturing technologies are also very limited, adversely impacting the talent pipeline needed by the industry.

The Opportunity

In the last few years, the FDA has increasingly signaled a willingness to change regulatory practice to make regulations science driven and to encourage innovation in product development and manufacture. Concepts such as process analytical technology, quality by design, and design space have been widely discussed and initial attempts have been made to inject these concepts into practice. However, it is now generally recognized that the barriers to further progress 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, it is necessary to develop a coherent research plan, to identify the high priority areas of pre-competitive research and to identify the resources required to make substantive progress over a reasonable time period. With such a plan at hand, a concerted effort can be made to secure the necessary resources by engaging all stakeholders. This roadmap document represents a first step in defining the research agenda for pharmaceutical product development and manufacturing for the next decade. Recognizing the critical role of educational programs in preparing the new generation of scientists and engineers who will lead in the further development and implementation of this technology, a parallel effort has also been launched to develop a strategic plan for the development of innovative educational programs in this domain.

Organization of the Technology Roadmap

The Roadmap is divided into two closely linked parts: Part I focusing on research issues related to Pharmaceutical Materials and Products and Part II addressing research issues in Process Development, Design and Manufacturing. Each technical area is discussed using the established roadmapping framework which involves the following six components:

1. Preface: an explanatory statement or definition of the area
2. Current State: a brief synopsis of the current state of technology in this area

3. Future Desired State: the target state stated in terms of functionalities desired and attainable as a result of a ten year effort
4. Barriers: Limitations of current practice, technology or state of understanding that must be overcome
5. Research Needs: Lists of research activities to be undertaken to overcome the barriers and achieve the desired state. Activities should be prioritized, at least within a given area, and some time lines established.
6. Resources: Estimates of resources required to execute the proposed research activities

This Roadmap document is a draft and thus is incomplete in many respects. It will require further intensive input from technical experts in industry, government and academia to flesh out research needs, establish priorities, time lines and resource requirements. In its present state it only constitutes an initial framework for discussion by all stakeholders. The Roadmap will attain validity only upon convergence of the inputs from the stakeholders.

PART I: PHARMACEUTICAL MATERIALS & PRODUCTS

Introduction

The first part of the technology roadmap describes 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.

The section is organized into three subsections dealing with the measurement of pharmaceutical material properties, the prediction of properties, and product design based on material and performance properties.

In the subsection on the measurement of properties (Analytical Methods and Enabling Technologies) the research needs include specific measurement technologies aimed at supramolecular structure and dynamics, bulk and surface properties of solids, and biopolymer structure and dynamics. High priority research needs include access to a synchrotron beamline, development of relationships between mechanical and product quality attributes, imaging of composition and uniformity of mixtures and finished products, development of techniques for the characterization of biopolymer tertiary structure in amorphous solids, and mobility measurements which correlate to stability.

The subsection on prediction of properties describes the research needs associated with the prediction of solid form of API and excipients, bulk physical properties, biopolymer conformation, particle properties, hygroscopicity, stability, functional properties and bioavailability. High priority research needs include solubility prediction methods, glass transition temperature prediction based on molecular structure, development of a database for the effects of environmental stress on biopolymer conformation, systematic studies of physical instability mechanisms, development of rapid physical stability screening technologies, stability prediction based molecular mobility, functional properties prediction methods, and expanded database for excipient physical and functional properties.

The design subsection deals with strategies for the design of products based on achieving desired material and performance properties. The research needs for a variety of the specific desired properties have been addressed including the modification of solubility and release rate, physical and chemical stability, particle size and morphology and excipient functionality. An additional section on new product platforms acknowledges the ongoing need for translational research based on emerging product concepts. Research needs in this section have not yet been prioritized.

Analytical Methods and Enabling Technologies

Advanced Structural, Physical and Molecular Mobility (Dynamics) Characterization

Current State

Interdisciplinary approaches based on numerous methods (diffraction, spectroscopic, thermal, and others) have been developed to different levels of sophistication for characterization of crystal and amorphous forms. These approaches provide information about bulk and molecular characteristics of the components and to some extent the products. Crystal structure determinations from single crystals are fairly routine, while solutions from small quantity powder samples remain limited relative to need. Speed is important to keep pace with rapid polymorph screening techniques. Determination of amorphous structure in individual components and product is very limited. Methods for characterizing molecular mobility are emerging. In multi-component mixtures, the complexity of all of these measurements is significantly increased, and the ability to fully characterize such systems is decreased.

Future Desired State

- Ability to perform rapid supramolecular structural determination and dynamic characterization very early in the development cycle
- Determination of surface properties and particle domains
- Micro-scale and nano-scale dynamics characterization
- Ability to differentiate between crystalline and amorphous forms
- Measurements of short range dynamics and structure for amorphous materials
- Ability to measure structural, physical and dynamics properties in mixtures and products
- Use of all of the above techniques for reliable prediction and control of properties for the purpose of process chemistry feedback (in the case of API) and product performance (in the case of formulations)

Barriers

- Analytical techniques, in general need improved power, resolution, and specificity for pharmaceutically relevant materials
- Laboratory X-ray diffraction instruments have insufficient power to allow accurate structure solutions from powder samples for many small molecule organic solids. This inadequacy is significantly more pronounced as the numbers of atoms in the molecular structure is increased. Power limitations also restrict collection of small angle and wide angle data, which are essential for elucidating microstructure in disordered systems.
- The timeframe of structural determinations is limited by a bottleneck created by the time required to solve structures relative to the time required to isolate different solid forms using high throughput procedures. The time deficit for structure determinations is due in part to computational limitations and in part to the limited availability of high power instrumentation

- Even with higher quality diffraction data, extant computational techniques used for structural solution may be inappropriate for use with larger molecules, masking benefits of instrumental improvements
- Measurements of dynamics (molecular mobility) are hindered by the absence of routine techniques for evaluation, and limited understanding of how different types of mobility (local dynamics vs. global dynamics) contribute to product quality. Further problems arise from the inability to separate different types of mobility using currently available techniques and analyses. Measurements of dynamics are further complicated in multi-component and multi-phase systems, particularly for characterization of low weight fraction components.
- Solid state NMR is used for measurements of mobility, however, the technique at present is difficult to use and it is seldom available outside of Big Pharma companies and a few universities.
- The complexity of dosage forms makes the characterization of individual components very difficult

Research Needs

- Regular, reliable access to a synchrotron beamline; opportunities for automated, high-volume throughput and analysis would be required. Beamline power must be sufficient to satisfy demands imposed by structures containing large numbers of atoms *(SHORT-TERM; HIGH PRIORITY)*
- Improved computational techniques for continued advancement of structural analyses from diffraction data (pairwise distribution functions, small angle scattering, structure solution from powder data) *(MID-TERM; MEDIUM PRIORITY)*
- More powerful, more readily accessible, easier to use solid state NMR spectrometers. Although the improvement of general SSNMR instrumentation falls outside the purview of pharmaceutical technology, it is deemed an enabling technology for mobility measurements from which developing improved methodology and applications will be key to pharmaceutical research *(MID-TERM; HIGH PRIORITY)*

Resources

- Establish a NIPTE beamline at an accessible North American synchrotron (ALS, APS, Brookhaven, CLS, etc.) affording the opportunity to perform high quality structural characterizations of materials ranging from highly crystalline to amorphous (and all steps in between), having substantially enhanced sensitivity to detect and quantify processing and storage induced phase transformations in products
- Establish a "Mobility Centre" for the purposes of studying, characterizing and measuring types of mobility pertinent to pharmaceutical systems. The centre could be "virtual," splitting resources across several partner locations. Solid state NMR is anticipated to be a key technique, and the centre will serve as a focus for the development of new techniques and software. The Mobility Centre will also establish a means through which new technologies and types of mobility analysis can be discovered.

Direct Methods for Measurements of Bulk and Surface Properties of Materials and Products

Preamble

Properties considered in this section include: component distribution, compressibility, consolidation, electrostatic characteristics, wettability, adhesion, cohesion, rheological (single or multiphase flow), particle size and morphology distribution, surface roughness, coating thickness, permeation, etc.

Current State

- Some bulk properties are related to surrogate measurements (*i.e.*, wettability, compressibility, various measurements of excipient/dosage form functionality, etc.).
- Particle size and particle size distribution analysis methods are available; however, none are particularly well tuned for pharmaceutically relevant systems

Future Desired State

- Availability of reliable direct methods for measurement of material and product bulk and surface properties
- Properties measured should be both efficient and capable of being used to predict relevant behavior of the material

Barriers

- In general each of these properties is difficult to define and measure in terms of fundamental properties. Some analytical techniques are borrowed from parallel materials industries without the benefit of specific development for pharmaceutically relevant materials.
- Particle interactions and process history confound measurements in mixtures and products
- Inferences made from surrogate measurements are dependent upon the accuracy of the models used and not necessarily grounded in performance attribute. In many cases users are unaware of the limitations of the methods themselves…
- Measurements pertaining to excipient function within a drug product are limited by numerous, inter-related phenomena, none of which have direct methods for measurement
- Many analytical techniques work well in idealized cases, but fail to provide useful quantities in real systems (i.e. shear cells for flow, Faraday cages for electrostatic characteristics). The fundamental properties that affect product quality attributes are, in general, unknown
- The magnitudes of values measured by current techniques seldom reflect the differences manifest as material behavior, making batch-to-batch, lot-to-lot, and supplier-to-supplier variability difficult to evaluate
- Indicators of compressibility (elastic moduli, fracture toughness) are very difficult to predict from crystallographic structure owing to the anisotropy of pharmaceutically relevant solids, and made more difficult as the complexity of mixing and processing is increased

- Estimates of electrostatic character (triboelectrification potential) are often ill-defined owing to limited understanding about the origins and dissipation of electrostatic charge on organic solid particles. Techniques for measuring electrostatics are borrowed from other industries without any ability to modify for use with pharmaceutically relevant materials.
- Wettability, cohesion, and adhesion all rely on measurements of solid interfacial energies, which are difficult to obtain for real (non-ideal) samples. Measurements made on porous compacts, powders, polycrystals, etc. have limited meaning
- Disparate techniques for particle size analysis do not provide absolute/universal measurements. Morphological measurements are restricted to image analysis, which can be time consuming.
- Analytical methods for characterizing nano-particulate systems are limited. Distinguishing between amorphous systems and nano-crystals is difficult; rapid particle size analysis at the nano-scale is unavailable. Current methods may work, but only under idealized circumstances

Research Needs

- Develop alternatives to Faraday Cage/Pail instrumentation for measurements of triboelectric properties *(LONG-TERM/LOW PRIORITY)*
- Develop relationships between mechanical properties and desired product quality attributes to better establish "real systems" *(MID-TERM/HIGH PRIORITY)*
- Better methodology and instrumentation for measurements of compaction/tableting indices (i.e. Hiestand Indices), compressibility and modes of consolidation *(SHORT-TERM/LOW PRIORITY)*
- Replacements/advancements of existing particle sizing technologies that would span the enormous range of pharmaceutically relevant materials (nano through coarse particulate systems). Development of methodologies based on the needs of organic systems is needed *(VERY LONG-TERM/MED PRIORITY)*
- Advanced methodology for characterization of particle size, morphology and microstructure of dosage forms and process intermediates.*(LONG-TERM/MED PRIORITY)*
- Determining useful correlations between surface measurements and processability for porous and non-porous samples…some improvement of contact angle *(LONG-TERM/LOW PRIORITY)*
- Investigate measurements of surface roughness that have relevance, meaning and usefulness *(MID-TERM/LOW PRIORITY)*
- Adaptation of coating thickness and adhesion measurements to pharmaceutical applications from parallel industries *(SHORT-TERM/MED PRIORITY)*
- "Mapping" or imaging composition and uniformity of mixtures and finished products *(SHORT-TERM/HIGH PRIORITY)*

Resources

- A partnering strategy with equipment technology developers to facilitate development of instrumentation (enabling technologies) more appropriately designed for pharmaceutically relevant materials. For example the recent purchase of Fisher

Scientific by Thermo could provide the opportunity to develop such a partnering arrangement.

- A formal program to identify instrumentation needs should be established to facilitate NIPTE's lobby with instrument groups to produce appropriate instrumentation for measurements of mechanical properties.
- Allow NIPTE sponsored programs for instrument development (open grant process using NSF model); specifically adaptation of measurement techniques for pharmaceutically relevant materials. NIPTE could enable initial funding for instrumentation to be leveraged with other funding programs
- Partner with NIST to establish a useful, readily accessible database of critical mechanical properties and standard techniques for their measurement. Utilize data to become change agents for USP monographs and specifications (this last sentence may be more appropriate elsewhere – education?)
- Establish a NIPTE centre for instrumentation and expertise in sizing over the nano-through coarse ranges for use by NIPTE institutions. The centre would ultimately provide both measurement services while developing research methodologies

Advanced Structural and Dynamic Characterization: Proteins, Vaccines and other Biomolecules, Polysaccharides and Products Derived from These

Current State

- Reliable methods for characterization of tertiary structure in solid state do not exist. Reliable methods are only available for secondary structure
- No structural information is available for vaccines
- Various methods are available for characterizing biomolecule binding
- Characterization of internal mobility in solution and the solid state is generally limited to measures of relaxation times by various techniques; the impact on important properties is uncertain
- Crystal Structure determination from powder patterns has been "proposed" but not yet realized
- Assays for the characterization of vaccines are restricted to semi-quantitative measures of bioactivity
- No analytical techniques for determining the changes in vaccine protein structural changes that correlate with vaccine activity

Future Desired State

- Characterize changes in protein tertiary structure in the solid state as a result of processes such as lyophilization
- Improved characterization of protein dynamics that are relevant to pharmaceutical properties
- Protein structure determination resulting in useful detail from powder patterns
- Precise quantitative measures of vaccine activity (*i.e.*, ±5%)
- Analytical methodology to elucidate and quantify degradation pathways

- Techniques to characterize the dynamics of the protein and the knowledge to understand what types of dynamics are important for preservation of product quality, both in solution and solid state
- Knowledge of the relationships between various measurements of mobility and the extent to which these measures of mobility are relevant to stability

Barriers

- Methods for tertiary structure evaluation in solids are not reliable and/or are controversial
- Cannot routinely characterize protein tertiary structure in amorphous or poorly crystalline proteins, which represent the greatest practical source of samples
- Solving protein tertiary structure by NMR requires at least microcrystalline samples, which are isotopically labeled
- Fundamental understanding of what happens to protein tertiary structure during processing is lacking.
- With any analytical techniques available, physical characterization of proteins and or vaccines present in low concentrations is limited
- Quantification and characterization of proteins in vaccines is insufficiently precise to assess stability in a timeframe relevant to development. The characterization of the degradation pathway is virtually nonexistent
- Limited understanding of physical meanings of the various measures of mobility, and how these apply to dynamics of practical significance (i.e. instability)
- Lack of methods for studying weak interactions between biomolecules and other formulation components (or surfaces, co-solutes, solid mixtures)
- Properties of polyelectrolytes depend not only on the conformation of the protein, but on the small quantities of salt ions present in the local environment

Research Needs

- Techniques for characterization of protein tertiary structure in the amorphous solid state *(LONG-TERM/HIGH PRIORITY)*
- Identification of which other measurements of mobility best correlate with long-term and short-term stability. Multiple methods (i.e. spectroscopic, calorimetric, electrical, and scattering techniques) should be used to assess mobility for a core set of proteins *(MID-TERM/HIGH PRIORITY)*
- Development of analytical methodology for chemical and structural characterization of vaccines and proteins at very low concentrations, particularly for applications to stability *(LONG-TERM/MED PRIORITY*) *may require breakthrough enabling technology*
- Quantitative measurement techniques for determining aggregate structure, size and distribution *(MID-TERM/MED PRIORITY)*
- Establish techniques for measuring charge and charge distribution on the surface of polyelectrolyte molecules and in ambient media *(MID-TERM/MED PRIORITY)*
- Establish techniques for sensitive measurements of subpopulations of conformation and states of aggregation *(LONG-TERM/LOW PRIORITY)*

Resources

- Establish a "Mobility Centre" for the purposes of studying, characterizing and measuring types of mobility pertinent to pharmaceutical systems. The centre could be "virtual," splitting resources across several partner locations. Solid state NMR is anticipated to be a key technique, and the centre will serve as a focus for the development of new techniques and software. The Mobility Centre will also establish a means through which new technologies and types of mobility analysis can be discovered.
- Establish a center for the study of biomolecule aggregation and its consequences
- Partner with other programs (DARPA, DOD) to provide development and manufacturing services for vaccine and protein projects.

Prediction of Properties

Solid Form of API and Excipients

Preamble

Forms to be considered include: crystalline, solvate, salt form, disordered forms, and defect structure

Current State

At present the solid form/defect structure cannot be predicted with sufficient reliability to be useful. The relationship between defect structure and functional behavior is important but largely unknown. Alterations of excipient solid form during processing, handling and storage are rarely considered.

Future Desired State

- Existence of Form: reliable (>80% certanty) prediction of thermodynamically possible states and the kinetics of their phase transformations. Forms of interest include crystal form, amorphous form, polymorphs, hydrates, and solvates. Such structural information provides critical input for predicting material behavior.
- Predict form changes in API and excipients as a result of processing and handling
- Defect structure: predict reliably supra-molecular structure: qualitative nature of defect (*i.e.*, dislocations, substitutional defects, cracks, grain boundaries, etc.), concentration of defects and product performance consequence of the "supra-molecular structure."
- Given a molecule, can we predict which counterions would result in the formation of a desirable (hygroscopicity, mechanical, stability, etc.) crystalline salt?

Barriers

- Algorithms for polymorph predictions (*i.e.,* forcefields) used to predict intra and intermolecular interactions in pharmaceutically relevant systems are inadequate to

discriminate between different forms, particularly for more complex small molecules, salts, etc.
- As processing conditions are changed, there is an inability to predict or control the resulting solid forms, especially where multiple forms having similar energies occur
- Poor understanding of how and why defects and amorphous regions arise in crystals

Research Needs

- The ability to predict the thermodynamically and/or kinetically favored forms of key formulation components that occur as a result of different processing conditions *(LONG-TERM/MED PRIORITY)*
- The ability to predict defect structure and amorphous content given a crystal structure and processing conditions, in order to guide solid/salt-form selection *(LONG-TERM/MED PRIORITY)*
- Determine the conditions under which materials have the ability to eliminate defects and amorphous materials (self-healing) *(SHORT-TERM/MED PRIORITY)*

Resources

Forcefield and algorithm development is enabling technology, which can be applied to pharmaceutical problems. Interaction with computational chemists is required to elucidate the specialized problems associated with pharmaceutical materials, to guide useful software development

Bulk Physical Properties

Preamble

Examples of bulk physical properties include: solubility, melting point, glass transition temperature, etc.

Current State

Prediction of solubility is possible for some systems based on molecular structure, but only with very approximate accuracy. Semi-quantitative estimates based on molecular structure are feasible; quantitative predictions of variations in these properties due variation in physical form, salt form or co-crystals not possible. Huge gaps still exist with respect to *ab initio* predictions of solubility. Prediction of melting points and glass transition temperatures semi-quantitative, at best.

Future Desired State

- Solubility: Predict 90% of cases within 25% accuracy
- Transition Temperatures: Predict 90% of cases within 5 to 20 degrees depending upon how close transition is to room temperature (more accuracy needed when transition is close to ambient)

Barriers

- Current methods used for solubility predictions are based on combining measurements from a finite number of functional groups in existing databases, which does not take into account solid form
- Applications of thermodynamics to solubility prediction have proven difficult
- Theoretical basis for solubility, melting temperature and glass transition temperature predictions is insufficiently complete to meet the desired state
- Current methods demand that the solid of interest be available, and that measurements be made before accurate solubility, melting temperature and glass transition temperature predictions for that form can be made

Research Needs

- Accurate predictions of solubility given the free energy difference between the crystalline and the amorphous state *(SHORT-TERM/HIGH PRIORITY)*
- Accurate predictions of melting temperatures based on the molecular structure. *(MID-TERM/LOW PRIORITY)*
- Improved ability to predict changes in physical form (*i.e.*, amorphous to crystal and polymorphic changes in crystalline systems) and the resulting impact on solubility and rate of dissolution. *(LONG-TERM/MED PRIORITY)*
- Better understanding and prediction of glass transition temperatures based on the molecular structure. *(LONG-TERM/HIGH PRIORITY)*

Resources

Partner with appropriate communities to develop something useful

Biopolymer Conformation in Processing, Storage, and Use (Maintenance of Conformations)

Current State

- Qualitative empirical rules and correlations available but not reliable
- Some advanced computational studies of native state in static dilute aqueous solution available, but conditions relevant to processing not studied

Future Desired State

Prediction of conformational changes (and consequences) under stresses in manufacturing (*i.e.*, shear and drying)

Barriers

- Inadequate analytical technology to measure conformational changes
- The ability to predict protein conformation in dilute aqueous solution is not adequately developed
- Lack of understanding of the impact of stresses imposed by processing on protein conformation

Research Needs

- Development of database from which empirical or semi-empirical predictions of the effect of environmental and processing stresses (*i.e.,* mixing, freezing, drying, shear…) on protein conformation can be made. (***LONG-TERM/HIGH PRIORITY***)
- Application of enabling technology development for predictions of protein conformation in dilute aqueous solutions to pharmaceutical stability problems.

Resources

Communicate with appropriate communities that address dilute protein solutions

Particle Intrinsic Properties

Preamble

- Surface Properties: surface energy, surface charge, specific surface area, size, and morphology (aerodynamic radius)
- Bulk and Mechanical Properties: powder density, plastic and elastic deformation, and fracture tendency

Current State

Can not be predicted; determined empirically; one company provides instrument that is believed to measure surface energy

Future Desired State

Stage 1: qualitative prediction sufficient to reliably (i.e., 80% certainty) choose optimum solid form, given molecular structure and the prediction of possible solid forms, as described above.

Barriers

- Incomplete understanding (and ambiguous definition) of the above listed properties. Most of the properties listed are recognized as important to dosage form development, but direct correlations with manufacturability and product quality attributes are not yet understood
- The limitations of existing empirical relationships used to describe consolidation behavior are not fully appreciated by workers in the field
- The complexity of property predictions implied by distributions of particle size and morphology in pharmaceutical powder systems are neither fully understood nor appreciated

Research Needs

- Require an understanding of the circumstances under which the above listed properties are relevant to the manufacturability and performance attributes of pharmaceutical dosage forms
- Theoretical foundation of the relationship between solid structure and particle surface, bulk, and mechanical properties

- Theoretical foundation of the relationship between particle and ensemble (distributions of particles) surface, bulk, and mechanical properties
- Rigorous testing and development of pharmaceutically relevant consolidation relationships

Resources

Exploration of advances made in entirely different fields studying similar properties (i.e., soil mechanics)

Hygroscopicity

Preamble

Hygroscopicity is defined for our purposes as thermodynamic and kinetic behavior; rate and extent of water sorption and desorption.

Current State

Limited qualitative prediction possible from knowledge of molecular structure and solid form

Future Desired State

Predict 90% of cases with useful accuracy (required accuracy depends on application)

Barriers

- There are variable definitions pertaining to the meaning of hygroscopicity, owing to both thermodynamic and kinetic components
- A lack of understanding of the complex contributions of material, surface and structural properties (*e.g.*, amorphous content, defect structure, specific surface area, surface chemistry, polarity and morphology) to hygroscopicity

Research Needs

- Develop a database based on rigorous experimentation, from which we can develop a set of rules to predict the importance of the material, surface and structure properties on the rate and extent of water uptake, as a function of water vapor pressure, including mixture rules for multi-component, multiphase, and single phase component *(MID-TERM/MED PRIORITY)*

Resources

Not yet determined, but probably not a center

Physical and Chemical Stability

Preamble

Stability is defined as the absence of an unacceptable level of chemical or physical changes such that desired properties are maintained in the presence of environmental stress. For small molecule API, physical change normally means crystallization of the

amorphous state or transformations of the chosen crystalline phase. For proteins, physical stability normally means conformational stability and resistance to irreversibly formed aggregates. Loss of physical stability may involve changes in non-covalent, associative interactions between API, excipients, packaging components and environmental moieties. Lack of physical stability may also involve phase separations, coalescence and/or Ostwald ripening, redistribution by mass transfer of formulation components (API and/or excipients) within or from the drug product, adsorption to product component surfaces, and permeation of environmental components into the drug product. Consequences of physical instability are often manifesting as product attribute failures for example: dissolution failures; mechanical failures; rheological changes; sedimentation; partitioning/separation; permeation of air, water and oxygen; sorption of water; and the loss of potency, preservative effectiveness, or package integrity. Loss of chemical stability involves changes at the covalent level, often as the result of hydrolysis, oxidation, photolysis and API/excipient interactions. The consequences of chemical instability may include loss of purity, loss of potency, appearance of toxic degradants, and the instigation of catastrophic physical instability.

Current State

Some general predictions of physical stability (*e.g.*, temperature dependence, T_g rules, relationship between crystal structure and desolvation, role of water vapor pressure, degradation in crystalline systems is strongly dependent on defect structure) for small molecules do exist; proteins and biomolecule systems are more complex, and therefore, less well understood

Future Desired State

- Ability to predict physical and chemical degradation rates (and other changes in stability) at different temperatures with useful accuracy.
- Ability to quantitatively predict rank order stability of a series of potential formulations
- Ability to predict relative stability of a series of drug analogs to lead candidate selection (may require crystal structural information and/or other information on the nature of the solid)
- Ability to predict physical and chemical degradation rates (and other changes in stability) at different temperatures with useful accuracy
- Use a surrogate measure (*e.g.*, mobility, defect structure…) to predict stability
- Ability to understand the role or lack of impurities in degradation processes
- Application of the above predictions with very small amounts of material
- Ability to stabilize vaccines at room temperature
- Use a surrogate measure (*e.g.*, dissolution…) to predict *in vivo* performance
- Minimize rejection of candidate molecules due to physical and/or chemical instability problems

Barriers

- Limited understanding of the physics and chemistry underlying the instabilities that are dealt with in pharmaceutical systems.

- Inability to predict stability from mobility due to a lack of understanding of how time and length scales of mobility measurements determine relevance to stability issues.
- Small samples may not be representative of large samples, which potentially limits ability to understand the role or lack of impurities in degradation processes
- During the early stages of product development, there is insufficient attention to impurities
- Inability to quantitatively identify impurities, particularly in small samples; impurities at the ppm range may have very serious consequences on stability
- Many tests are destructive, restricting application to very small samples

Research Needs

- Systematic study of the instabilities of model solid compounds (API and various formulations) to investigate the impact of mechanical and thermal history, and the physical form of the solid so as to elucidate the dominant physical mechanisms of instability in the compounds of interest *(MID-TERM/HIGH PRIORITY)*
- Development of theoretical models that allow reliable prediction of the kinetics of physical and chemical stability phenomena for multi-component systems. *(LONG-TERM/MED PRIORITY)*
- Determine the specific effects of trace impurities (*i.e.*, metals) on mechanisms of instability – providing the ability make predictions across scale *(SHORT-TERM/LOW PRIORITY)*
- Ability to conduct a small number of experiments with a limited amount of material so as to choose the appropriate physical form of the API *(MID-TERM/HIGH PRIORITY)*
- Ability to conduct a small number of experiments with a limited amount of material so as to choose the appropriate formulation *(MID-TERM/MED PRIORITY)*
- Very short-term stability and limited characterization studies to minimize the time required for first-in-man dosing *(MID-TERM/HIGH PRIORITY)*
- Develop a good understanding of the role of dynamics in solids (molecular mobility) on instability *(LONG-TERM/HIGH PRIORITY)*
- Develop a knowledge base to predict stability based on instability mechanisms through product and formulation characterization
- Predicting real-time stability from accelerated stability data

Resources

- Develop and implement a survey of the most common degradation pathways in small molecules, proteins and vaccines
- Establish a Center for stability studies

Functional Properties

Preamble

Prediction in this respect involves the ability to combine API and excipients to function according to the properties for which they are designed and included in the formulation. Properties could include: filterability, drying, flow (intrinsic and relative density), compaction behavior, disintegration/dissolution behavior, adhesive property, segregation behavior, aggregation, wetting, lubrication, thermomechanical properties…

Current State

Cannot be predicted for components or composites; determined empirically; relationships between structure and function have not been established

Future Desired State

Stage 1 goal: to predict qualitatively with useful certainty (i.e., >80%) the functional property from knowledge (predicted or measured) of the particle intrinsic properties
Stage 2 goal: to predict qualitatively with useful certainty (i.e., >80%) the functional property from knowledge of physical and chemical structure and microstructure.

Barriers

- Lack of knowledge of the relationship between the property of interest and the measurement thereof
- Most properties of interest are convolved by numerous inter-related, mutually dependent factors
- Specifications that do not fully characterize the material relative to its intended function, exacerbates intra- and inter vendor variability
- Excipient performance in products is empirically determined, and few models exist (*i.e.* mixing rules) that allow predictable product performance and rational product design.
- Depending on industry demand, some primary excipient manufacturers may be unwilling to respond to more stringent specifications imposed by pharmaceutical industry. The expense of transferring analytical technologies from the pharmaceutical industry is cost prohibitive relative to the percent revenue offered from pharmaceutical sector.
- The industry standard for excipient quality is defined by USP standards. This presents an education barrier in that existing USP tests do not adequately emphasize excipient functionality/performance

Research Needs

- Theoretical and systematic experimental studies designed to elucidate relationships between properties of interest (as described in the preamble to this section) and their prediction.; and develop predictive models. (***LONG-TERM/HIGH PRIORITY***)

- Development of useful mixing rules for predicting functional properties of formulations.*(LONG-TERM/MED PRIORITY)*
- Develop a knowledge base to identify systems from which decisions need to be made empirically; this may be a consequence of the first objective *(MID-TERM/MED PRIORITY)*
- Development of an expanded and detailed database for excipient properties and their function; *(MID-TERM/HIGH PRIORITY)*

Resources

As an enabling technology, we need to make every effort to form a collaborative partnership with excipient manufacturers to improve the processes for them and properties for us…

Bioavailability (in vivo from in vitro)

Preamble

The inherent physicochemical properties of the API and those properties as modified by its formulation are key determinants in efficacy of the drug products. The relationship between the inherent and formulation-modified physicochemical properties and *in vivo* pharmacological/toxicological response is encompassed by the pharmaceutical science discipline called "Biopharmaceutics". Herein, the critical aspects of the biopharmaceutical performance of API and drug products are the rate and extent of drug input upon administration (*i.e.*, bioavailability). The predictions of biopharmaceutical performance based on the physicochemical properties of the API or based on measurements of drug release play essential roles in drug candidate selection, in formulation design and in defining regulatory requirements for the drug product development process. Although the study of drug absorption and disposition mechanisms may also serve to critically define biopharmaceutical performance, we have chosen to specially focus on the study of mechanisms which are physicochemical-based rather than those which are inherently biochemical or biophysical in nature such as *in vivo* drug transport and metabolism.

Current State

- Development work pertaining to formulations/excipient systems that improve the aqueous solubility or dissolution rate is done empirically on a case-by-case basis.
- Proprietary excipient platforms that enhance API solubility may exist; however, these are neither widely reported nor well understood.
- Inherent physical chemical properties (e.g. partitioning, solubility, artificial-membrane permeability) of potential API candidates are routinely measured (e.g. using high-throughput screening methods) to predict "developability".
- Biopharmaceutical Classification System (BCS), in its originally proposed and modified formats, is routinely used to as a regulatory tool to define biopharmaceutical development requirements for product registration.

- Various methods for establishing predictive correlations between *in vitro* drug release and *in vivo* biopharmaceutical performance have been evaluated. But predictive reliability of any particular approach is elusive.

Future Desired State

- Based on the predictive capabilities described under bulk physical properties, and combining with known excipient physical properties, enhanced solubility platforms that could be disseminated to the industry/public domain are available.
- For those drugs where formulation factors can affect bioavailability (*i.e.*, excluding those drugs for which limited permeation or excessive metabolism are the critical issues) a database is available that catalogs the effects of formulation design on bioavailability which can then be used for the design and development of formulations for specific biopharmaceutical drug classes.
- Wide availability of excipient systems that allow design of desired bioavailability (rate and extent of drug absorption) through mechanisms such as enhanced drug release (*i.e.*, solubility, dissolution/disintegration rates).
- Wide availability of evaluation methods to screen the bioavailability and *in vivo* drug release performance of formulation strategies early in development.
- Availability of refinements to the BCS to be able to use it or its successor to reliably and quantitatively predict the probability for successful developability to streamline the development process.

Barriers

- Inability to predict solubility of API alone let alone in combination with a number of excipients
- Physicochemical changes in API or drug/excipient interactions, which decreases bioavailability i.e., protein degradation affecting biopharmaceutical performance from various dosage forms or phase transformations that can affect disintegration or dissolution

Research Needs

- Extend knowledge of solubility prediction of API to predict drug solubility and rate of dissolution from dosage forms
- Refer back to needs from solubility prediction section that capture points above
- Prediction and control of dissolution and solubility properties during storage, processing, shipping, etc.

Resources

Enabling Technology: Research into the limitations imposed by biological constraints (*i.e.*, limited permeability and/or excessive metabolism) and methodology by which these constraints may be overcome.

Design to Achieve Desired Properties

Definition of Property Design

This concerns the strategy for identifying and obtaining desired materials properties, driven/aided by data obtained via experimentation, serving as the heart of quality by design initiatives. Early implementation is particularly important, *i.e.*, at the discovery-development interface, enabling whole-product development. Property design occurs at two levels: 1) specific physicochemical properties of API and excipients, 2) design of collective (with defined synergies where appropriate) properties when combined into a dosage form. There are a number of critical quality attributes that depend on the specific dosage forms, including: solubility, physical and chemical stability, particle size, particle morphology, excipient functionality, etc.

Modification of Solubility and Control of Release Rate

Current State

Many new drugs have low solubility and, therefore, the potential for problems associated with bioavailability. Solubility optimization is currently addressed through formulation (*i.e.*, addition of solubilizing components such as substituted β-cyclodextrins), salt formation, formation of pro-drugs, polymorph selection, including limited applications of the amorphous state. Implementation of specific strategies among the various options is often done according to past practices and empirical data. For other drugs, solubility modification may also include controlled or limited solubility to consider reductions for optimum performance.

Future Desired State

Choice among the options should be aided by successful prediction, where the optimal solutions would be quickly identified, the obtainable solubility enhancement could be estimated with useful accuracy, and the manufacturing process requirements would be relatively obvious. A greater reliance on the amorphous state, co-crystals, nanocrystals, and cyclodextrin-complexed crystals of well defined stoichiometry is sought after and expected. Liquid crystal technology also needs to be assessed for purposes of solubilization. Specific product platforms (formulation of a general type that has wide application to a number of low dose drugs), less useful for high dose.

Barriers

- Inability to predict solubility in formulations with sufficient accuracy and reliability to be useful in product design
- Alternation of solubility during storage and/or administration due to physical changes.

Research Needs

- Comparative critical assessment of the potential for improving solubility and dissolution properties by manipulation of crystal size (*i.e.*,"nanocrystals), solid form (*i.e.*, crystal vs. amorphous), and complexation (*i.e.*, cyclodextrin, …) for example by

manipulation of formulations through development of new solubilizers or stabilizers for high energy states. *(MID-TERM/HIGH PRIORITY)*

- Development of new technologies (platforms, formulations, etc.) for improving solubility and dissolution properties. *(LONG-TERM/HIGH PRIORITY)*

Physical and Chemical Stability

Preamble

Current State

- Except for proteins, chemical stability problems with API are less common, but do occasionally occur with serious consequences. This is largely because small molecule APIs are normally highly crystalline solids having good chemical stability. Physical instability of small molecules usually involves either crystallization of amorphous solids or transformations between different crystalline forms. Some general predictions of physical stability (*e.g.*, temperature dependence, T_g rules, relationship between crystal structure and desolvation, role of water vapor pressure, degradation in crystalline systems is strongly dependent on defect structure) for small molecules; proteins and biomolecule systems are more complex, and therefore, less well understood.
- At present our mechanistic understanding of chemical instability is better developed than those of physical instability.
- Compatibility testing for API-excipient interactions is based on empirical evaluation and historical precedence.
- Little mechanistic understanding that separates contributions from individual components that result in changes in physical stability
- Predicting whether or not amorphous solids are stable is done largely according to empirical rules ($T_{storage} = T_g - 50$ K). However, these heuristic rules lack accuracy and reliability because they fail to address mechanisms of instability at a molecular level.
- The way in which stability is predicted (40/75 method) is done according to convention; methods are driven by adherence to regulatory guidelines rather than driven by underlying instability mechanisms.
- Excipient selection and formulation design is done according to historical precedence.

Future Desired State

- In the future, a greater reliance on metastable, high energy systems for enhanced aqueous solubility will make chemical stability problems with API more common. This will require greater emphasis on both chemical stability of amorphous API and stability of other systems designed to maximize solubility. Stabilization strategies will be developed, which enable design of formulations that are sufficiently robust to withstand stresses from processing, storage, and handling, resulting in a more stable drug product.
- Establish real time and accelerated stability metrics and protocols (both physical and chemical), which are predictive and designed according to scientific rationale. These indicators and methods for stability should be based on the fundamental mechanisms

of instability rather than convention (*i.e.*, different metrics and protocols for different formulations is satisfactory, if based on known mechanisms)

- Generation of specifications is consistently based based on scientific principles and relevant product performance attributes
- Stability protocols should focus on all relevant product components including API, excipients, and packaging. Maintaining, understanding, and predicting dosage form functionality in terms of the entire product is necessary. Stability concerns should, therefore, also address the link between excipient function and physical and chemical changes.
- Analytical technologies are available for measuring pertinent attributes related to stability
- Quantitative prediction of product stability based upon the combined properties of the API and excipients, formulation composition, other product components (packaging and device), and processes

Barriers

- Incomplete understanding of the underlying mechanisms of instability
- Incomplete understanding of the linkage between the stability indicating methods for physical stability and product performance
- Questionable mathematical/statistical methodology by which stability criteria are defined
- The role of excipients and other product components (*i.e.* packaging) as critical formulation components is poorly understood (and emphasized) at a fundamental level
- Historical tests are employed (including ridiculous ones…) resulting in measurements that fail to provide specific links between critical attributes that define stability.
- Reliance on traditional kinetic models (under all circumstances) has avoided realistic understandings of stability (whatever kind)
- Standards for stability test methods are driven by considerations other than science; not universally applicable, but universally adopted.
- Stability (however defined) is only considered with respect to the API in dosage forms. No present data is used to link the functionality of dosage forms with the physical and chemical stability/integrity of the excipients. The USP is the only standards to which excipients are held, and they fail to focus on performance properties.
- Complications due to dosage form complexity

Research Needs

- Devise stability indicating methods for physical instability phenomena
- Quantify time dependence of product-component interactions
- Quantify time dependence of product-container interactions
- Designing new, more effective stabilizers based on an understanding of the instability mechanisms
- Overcoming cold-chain storage requirements for biopharmaceutical products to improve product viability in non-ideal climates

Resources

- Survey: how many potential APIs were rejected for unsatisfactory stability
- Establish a Center for stability studies

Particle Morphology and Size

Current State

Routine particle size "design" is crudely accomplished using secondary mechanical processing (milling). Morphology often presents the limitation for successful crude particle size design. Mean particle size is designed at the level of industrial crystallization, however particle size distribution is not well controlled. Overall, the industry does not implement current technologies from other bulk chemical processing industries very well.

Future Desired State

Particles with specified morphology, having a given size and size distribution made at the crystallization level, decreasing reliance on crude mechanical control. When not accomplished at the crystallization level, development of more controlled milling procedures to accomplish the same goals without significant conversion and degradation of the API.

Barriers

Research Needs

Resources

Excipient Functionality

Preamble

Excipient functionality is the ability of the excipient to perform its desired functions in terms of product manufacturability or quality. This section addresses both the incorporation of excipients into product design based on functionality and the need for the invention and qualification of new excipients.

Current State

- Depending on the dosage form (in particular parenterals) the choices of available excipients are very limited, largely due to perceived toxicity issues. However there are currently limited choices of excipients within most existing categories (disintegrants, boundary lubricants, stabilizers, buffers, bulking agents/diluents, glidants, CR polymers, solubility enhancers, preservatives, sweeteners, flavorants, colorants, coatings, opacifiers, plasticizers, targeting agents, osmotic agents, viscosifiers, surfactants, emollients, etc.)
- Lack of meaningful, functional testing and parameterization makes standardized optimization and design difficult. Excipient performance in products is empirically

determined, and few models exist (*i.e.* mixing rules) that allow predictable product performance and rational product design.
- Many excipients are naturally derived and provided by various suppliers with limited drug-product-designer control over critical properties

Future Desired State

- Thorough understanding of the linkage between specific excipient characteristics and functional properties leading to meaningful metrics and analytical techniques thereby enabling predictive formulation design
- Excipients specifically designed for pharmaceutical use which meet the required performance attributes with acceptable safety properties
- Availability of multi-functional excipient which enable formulation design simplification
- Complete understanding of the range and effect of excipient variability on product performance (reduction of source-to-source and lot-to-lot variability)

Barriers

- Dosage form complexity
- Intrinsic variability of excipients terms of functionality is not well described
- Available excipients do not completely meet the functional need
- Regulatory approval process limits introduction of new excipients to the existing pool
- Excipient suppliers consider the demands of the pharmaceutical niche market too small to tailor their excipients to strict needs
- Lack of consensus on desirable excipient attributes (needs change from dosage form to dosage form)
- Articulation of metrics is inconsistent from company to company, restricting the sophistication with which excipients can be supplied

Research Needs

- Novel formulation paradigms to suit development of simplified dosage forms
- Quantitative assessment of the current state of excipient variability based on current best methods
- Development of meaningful metrics for excipient function as they relate to dosage form performance
- Development of a relational model allowing us to predict dosage form function from composition and excipient characteristics
- Design and engineering of new excipients to address unmet needs
- Fundamental research in understanding product physicochemical properties caused by API-excipient interactions
- Materials properties research in mixtures (solids and disperse systems)
- Development of prototype formulations for drugs having specific physicochemical properties using a broad base of current and future excipients covering various indications and routes of administration

Resources

Compilation and publication of an extensive database of excipient properties

New Product Platforms

Preamble

The driving impetus for new product platform innovation can include a variety of factors including improved stability, enhanced patient utility, specific therapeutic needs (e.g. individualized dosing) and biopharmaceutical properties associated with specific routes of administration (inhalation, topical, nasal, rectal, otic, buccal, site-directed, etc). Whatever the sources of inspiration and innovation for the design of new product platforms, the success of the design/development/commericalization process requires the translation of desired product performance characteristics into achievable, reliable and measurable physical and chemical product and product component attributes. It is the research and technology development associated with this translational process that is the subject of this part of the roadmap.

In many cases, this translational research deals with the product design issues that have been elaborated above: e.g. solubility, stability, particle size control, and excipient functionality. However translational research in the design of new product platforms may also address other issues such as delivery device functionality, active packaging properties, drug carrier-API interactions, etc. Rather than attempt to anticipate the research needs for all future, commercially-viable, new product platforms, we have focused our road-mapping efforts on individualized-dosing drug product platforms for which the need is currently well-recognized by the regulatory and medical communities. We recognize the ongoing need for additional translational research based on emerging product concepts.

Current State

- Range of drug products able to respond to individual needs is unavailable

Future Desired State

- Dosing specifically designed for pediatrics, neonates, geriatrics, persons with specific disease states when such specific design adds high value to the health care
- Flexible manufacturing/formulation allowing for large range of dosage forms for a given molecule
- Economic, small-scale manufacturing to enable individualized dosing regimens

Barriers

- Invention

Research Needs

- A small assembly of "platform technologies" that allow significant variation in dosing with slight modification of the basic platform formulation and manufacturing technologies.

Resources

- Reliable information early in development that defines what type/frequency,… of dosing is optimal.

PART II: PROCESS DEVELOPMENT, DESIGN AND MANUFACTURING

Introduction

The ultimate goal of pharmaceutical product manufacturing is to consistently produce a high quality product that meets patient needs. The patients' needs can only be met when the final product meets certain performance criteria. To accomplish this, the manufacturing process must be designed so that the product meets specifications on critical quality attributes. Thus, during process development it is very important that the impact of starting raw materials and process parameters on product quality is understood, that critical sources of process variability are identified and controlled, that appropriate means for their control are designed into the process, and that ultimately the process is continually monitored and controlled to allow for consistent quality over time. This approach is being widely professed by the FDA and the pharmaceutical industry in their new initiative called Quality by Design (QbD). By definition, for QbD to be effective, it should start early in development, since the full benefits of QbD are most easily obtained by building quality into a new process.

The research programs outlined in Part I will provide the scientific basis for understanding of relevant pharmaceutical material properties and for predicting the impact of component material properties on product functional properties. This will result in the creation of a knowledge-based framework for the rational design of pharmaceutical products, which meet desired performance requirements and ultimately the patients' needs. Building on the foundation developed in Part I, this part of the roadmap addresses the research required to develop, design and scale-up efficient processes for the manufacture of these products. Predictive tools that require a minimum of experimentation and trail-and-error are a critical component of developing this capability. Predictive tools will allow the pharmaceutical scientists to focus on targeted experimentation, facilitating continuous learning, minimizing unanticipated failures, reducing surprises during scale-up and ultimately promoting the implementation of more robust manufacturing processes. Furthermore, high quality process development and product design are not enough. The underlying science of pharmaceutical manufacturing must also be advanced. Thus, we advocate comprehensive research programs in manufacturing science that will result in robust manufacturing operations founded on the principle of continuous improvement. Such manufacturing operations will consistently produce safe, high quality products, on time, with minimum waste and optimized inventories.

The discussion is organized into ten areas of emphasis:

1. <u>Process Understanding</u>: Fundamental understanding of critical operations and critical process parameters. Such understanding will translate into quantitative

models for predicting performance of these unit operations and an understanding the relationships between of these unit operations. Process understanding includes the ability to predict how variation of one or more critical process parameters may impact not only the processing operation but also the performance of the intermediate products in the subsequent manufacturing steps and ultimately the performance of the final dosage form.

2. Process component selection methodologies: Systematic methods for designing and optimizing process step sequences.
3. Reliable scale-up methodologies: Systematic and reliable methods for scale-up/scale-down based on predictive models of material properties and processing operations.
4. On-line sensing & unit-level control: Identification of viable sensors, their implementation and adaptation for pharmaceutical processes. Multivariable closed loop control systems for all critical operations, with on-line sensors selected and located to support control and monitoring of critical process variables.
5. Integrated production line management: Real time process optimization based on integrated process information and supervisory control systems.
6. Multi-product plant operation: Model-based methods for operating multipurpose manufacturing plants with minimal down-time and materials waste.
7. Novel processing technologies: Continuous processing, process intensification and microprocessing alternatives to current batch operations.
8. Small scale manufacturing: Innovative facilities for rapid clinical supply, production of small volume products, hazardous operations, and technical support of larger scale operations.
9. Supply chain management: Model based methods for supply chain coordination, capacity planning and risk management.
10. Enabling Technology - Informatics-based Model Development and Integration Environment: Real-time intelligent ontological informatics-based environment for managing data, information and models for optimal decision-making.

Process Understanding

Preamble

There are a wide range of unit operations employed in the manufacture of pharmaceutical products. Whether these products include small molecules or biologicals, solid dosage form or liquid products, topicals, inhalables, transdermals, implantables, injectables or sustained release forms (see appendix A), most of the unit operations employed in manufacturing pharmaceutical have been in use for decades if not centuries. However, at a fundamental level, most are poorly understood. Some processing operations have been studied for many years with limited progress while others have received very little attention in the recent pharmaceutical and engineering literature. In this section we focus on those operations which are in wide-spread use and often critical to a successful process and for which a modest level of investment in research can be expected to yield significant advances. There are a number of operations which have already been studied

extensively and for which very substantial investment would be required to achieve incremental advances, e.g., chromatographic separations. These are given low priority in our discussion.

Current State

Generally, first principles understanding of most of these operations is incomplete. In many cases, critical variables and critical process parameters may be unknown. The understanding of the relationship between input material properties, processing conditions, and properties of the output materials are only qualitatively characterized. The knowledge base for these operations is widely scattered over multiple sources and organizations.

Future Desired State

In developing a new process, there are systematic procedures and decision support systems available to determine the optimum combination of unit operations resulting in the desired product quality and product specification. All unit operations are described by predictive models – ideally based on first principles but at least formulated at a semi-empirical level. The range of validity of these models is well established. The critical input and operating variables are known, critical phenomenological parameters identified and the design of a minimum set of experiments required to determine/validate those parameters has been established. We have systematic procedures to identify critical process parameters that affect the Critical Quality Attributes and the design space for each unit operation. These can be well defined in terms of quantitative relations. Models, associated information items and guidelines are embedded in an integrated model management system.

Barriers

- Material properties relevant to processing are poorly understood and methods for measuring and predicting them often inadequate.
- Interaction between fundamental material properties and functional properties is poorly understood.
- Traditional scale-up methodologies which are essentially step-wise knowledge gathering endeavors with increasing scale of operation are firmly entrenched
- The integration of engineering science into current pharmaceutical technology research, practice and education is inadequate.
- Implementation of QbD is hampered by a lack of clarity regarding the concept of "Design Space" and how that concept is applied in the practice of process development.
- Models of unit operations are largely inadequate, lacking predictive power.
- Knowledge, correlations and models when they exist are scattered across multiple sources and media. Design guidelines are incomplete and largely qualitative.
- Unit operations are often employed inappropriately, based on tradition rather than on true technical suitability.

Research Needs

- Develop decision support systems for rational knowledge-based selection of unit operations, process modules, and critical process parameters. The selection of optimum processes will allow implementation of Quality by Design and lead to the development of robust processes.
- Develop a suite of predictive models of high priority unit operations, with well characterized and defined regions of validity and reliability.
- Develop systematic procedures for the application of these predictive models for establishing design spaces for processes under development or for improving processes used in the manufacturing of marketed products.
- Associated with each unit operation, develop well defined procedures for (i) estimating key phenomenological coefficients and (ii) experimental designs to validate or improve those estimates.
- Develop a unit operations model management system for maintaining model libraries, with linkage to materials properties and product development informatics system. The system will provide workflow guidelines, model assumptions, regions of validity, definitions of design space and model explanation for each category of unit operation.
- Identify high priority operations: those in which $1 M of research funding for model development and validation could yield major advances. The general families of high priority unit operations are listed in the table below, divided into five categories:

Small Molecule API	Solid Products	Liquid Form Products
Chemical reaction	Size reduction	In-process characterization:
Multiphase	Wet granulation	(put into product/sensors)
Size reduction	Roller compaction	Sterility
Crystallization/precipitation	Fluid bed processing	Pyrogenicity
Suspension mixing	Drying	Isotonicity
Biological API	Coating	Particulates
Solid liquid separation	Granulation	Mixing
Centrifugation	Lubrication	Terminal sterilization
Microfiltration	Powder flow & handling	**Semi-solid products**
Deep-bed filtration	Tumble coating	Homogenization
Lyophilization	Compaction	In-process quality control
Spray drying/coating	Granular systems modeling	

Process Component Selection Methodologies

Preamble

One of the key requirements to implementation of QbD is that product design should start early in the process development effort. The identification of critical quality attributes

and critical process parameters should be based on desired/targeted product performance requirements. A systematic methodology of product design will lead to the selection of the most effective process to meet the desired/targeted product performance requirements.

The systematic selection of process components, often called process synthesis methodology, offers considerable promise for developing cost effective and robust manufacturing processes. However, such methodology does require the availability of predictive models of unit operations, methods for predicting properties of intermediate process streams and access to all relevant experimental data. Progress in this area will depend on advances in the methods of process design and development that are defined in this roadmap.

Current State

Selection of the sequence of unit operations is usually based on broad guidelines and/or on following past practices within a specific organization. The expertise normally resides with a few people possessing many years of experience in the field and the decisions may not be based on proven scientific principles. Rather, those decisions are often based on the process developers experience with what has worked in the past. Multiple manufacturing routes are seldom fully explored, quantitatively compared or optimized. Innovation in the selection of step sequences and introduction of new operations requires time-consuming, trial-and-error approaches, significant expensive and as a result tends to be discouraged. Operating variables are chosen for expected feasibility with limited screening of alternatives. Expected feasibility is often not attained, requiring time-consuming and costly process retrofits. Time pressures allow little or no systematic optimization or cost vs. robustness trade-off studies. Due to unavailability of appropriate process assessment tools, experimentation and improvement projects are often chosen based only on experience and may not result in the desired improvements in the process or in product. This leads to wasted efforts and loss of time. Finally, industrial regulatory teams are slow to embrace new methods and technologies due to the perception that such new methods may not be readily accepted by the FDA and that old and proven methods are more likely to be accepted by the regulators.

Future Desired State

Process component candidate sequences are systematically developed based on input material properties, intermediate stream property predictions and product performance requirements using knowledge-based and structured methods. Unit operations models are used to predict output material characteristics and overall process performance. Unit design and operating variables are optimized using relevant optimization software tools. Cost estimates and prediction of robustness to input variability are used in quantitative trade-off studies to identify most promising process candidates.

Quantitative risk analysis and process assessments are performed early in process development, using the methodologies mentioned above to develop risk assessment

strategies. The proposed process development methodology and software tools simplify the efforts required to identify critical process parameters and acceptable operating ranges while facilitating the establishment of appropriate process control strategies to understand and minimize the effects of variability of critical process parameters on Critical to Quality Attributes.

Barriers

- Level of understanding and paucity of suitable models of unit operations.
- Systematic procedures for generating process alternatives are not available.
- A well defined framework for executing process design and optimization of pharmaceutical processes is currently unavailable.
- Model-based approaches for conducting process assessments, risk assessments and investigating process robustness to input and operating uncertainties have not been adapted to pharmaceutical applications.

Research Needs

- Develop structured process synthesis knowledge base for pharmaceutical products.
- Develop systematic methods for generating and evaluating candidate processes that are consistent with the proposed knowledge base.
- Develop model based approaches for multi-unit process optimization. These models shall be fully integrated within the unit operations model management system.
- Investigate computational strategies for developing trade-off surfaces of cost vs. robustness incorporating known and unanticipated process, model and input material uncertainties.

Reliable Scale-up and Scale-down Methodologies

Preamble

Processes that are synthesized and investigated at a developmental scale must ultimately be translated to a manufacturing scale. Translations in scale often introduce or reveal nonidealities in the underlying transport processes that were not seen at smaller scale or not captured in unit operations models used for process selection and development purposes. The data, information and knowledge from the prior developmental activities must be available and readily accessible to support this translation process. In pharmaceutical product development, it is customary to make the product, either API or finished dosage forms, multiple times in the pilot plant or in a manufacturing plant for preparation of clinical supplies. This provides a great opportunity to obtain the right data and information required to validate a new process if systematic process selection is conducted guided by unit operations models.

Current State

Scale-up of key operations is accomplished by reliance on extensive experimentation and pilot plant studies due to a lack of fundamental understanding, limited availability of reliable models and regulatory pressures. API process scale-up is performed with very limited use of available Computational Fluid Dynamics (CFD) tools (used to study fluid mixing, particulate flow patters and particle mixing). Frequent delays in scale-up occur because of differences in the equipment used in process development and manufacturing. Most failures in scale-up occur due to either lack of understanding of the impact of variability of material properties on the process or due to a lack of understanding of factors related to the equipment and its design on the process. There is typically little transfer of knowledge and information from development to manufacturing and no transfer of knowledge and experience back to development. Because of limited systematic institutional memory for knowledge generated over time, relearning occupies over 25% of developmental resources.

Future Desired State

We are able to scale up processes with predictable behavior directly from the laboratory or pilot plant to the desired scale of manufacturing. Scale-up/scale-down is carried out using systematic and reliable procedures, based on predictive models that incorporate effects of material properties and processing conditions on product structure and performance. This methodology minimizes or eliminates experiments on multiple scales and is capable of scale-up over three orders of magnitude with model parameters generated from a minimum of small scale experiments. All data, information, observations, knowledge and models are managed (stored, retrieved, manipulated, analyzed, maintained, validated and communicated) in an integrated fashion to assist in the translation to manufacturing.

Barriers

- While methodologies exist for building and managing data, constructing web-based interfaces, etc., there does not exist an informatics platform with all of the required functionalities.
- Complex flow behavior and the complexity of key product attributes (purity, homogeneity, and material properties) are often poorly understood. There is particularly limited fundamental knowledge of multiphase systems in which phase properties and characteristics are continuously changing.
- There is a gap in reduction of understanding of physical phenomena to rigorous models and simulations, especially representing systems dynamics.
- If unit operations models are available, they are usually not at a level of detail useful for understanding or predicting the effects of scale of operation.

Research Needs

- Identification of key material properties affecting scale up/down.
- Identification of relevant product properties that must be preserved through scale-up, and development of suitable methods for measuring them.
- Identification of key equipment attributes which should be the focus of scale up (e.g. mixing power vs. vessel geometry).
- Development of predictive models for all major unit operations suitable for capturing effects of scale.
- Systematic semi-empirical approaches to scale up/down for complex operations that are not amenable to *a priori* predictive modeling.
- New equipment designs that are amenable to fundamental modeling and provide simple scaling behaviors.
- Design, development and implementation of an ontology-based decision support framework for process development and scale-up.

On-Line Sensing and Unit-level Control

Preamble

The key requirements for automatic control of a dynamic process to achieve a desired end-point consist of the following:

- The existence of a sufficient number of variables with adequate influence on the process that can be manipulated to drive the process to the desired end-point.
- The ability to measure, track and predict the variables or properties defining the desired end point.
- The logic or control laws for adjusting the manipulated variables so as to drive the process to achieve the desired end-point.
- The desired performance criterion (e.g., minimum time, minimum control action, minimum deviation, etc).

Additionally, the ability to measure input disturbances to the process can often be exploited to take anticipatory (feed forward) control action to compensate for that disturbance, providing knowledge of the cause-effect relationship exists. On-line measurement and control logic constitute the two most important research issues.

On-Line Sensing

Current State

Typically only a limited number of on-line measurements are available which are focused on critical process parameters rather than on critical performance attributes. Input disturbances related to raw materials variability are not measured. The analysis frequency obtained via off-line laboratory analysis is rarely sufficient to develop an adequate understanding of the linkages between raw material and equipment variability to variability observed in the product. Many quality control measurements are indirect

measurements with some correlated or qualitative relation to actual product performance. Most product measurements are focused on bulk properties and rarely provide information on the microscopic level that can be critical to product performance. Current technology is well developed for measuring temperature, pressure, mass flow/weight, moisture content, pH and flow of evolved gasses. There exists sensor technology that is in use to at least some extent in other industries but has not been adequately exploited in the pharmaceutical processing. This includes: particle size measurement and use of NIR, Raman spectroscopy, NMR and mass-spectrometry for selected compositional information. Measurements that can not be performed at present on-line but are promising include: chemical imaging (commercial equipment with speed needed not yet available), light scattering to measure aggregation (esp. in bio materials) and use of NIR for content uniformity of blends with low composition, high potency components. Measurement of functional properties, such as product potency and content uniformity is at present largely obtained via off-line measurements.

Future Desired State

On-line sensors are routinely deployed to allow either direct tracking of key variables or properties or their inferential prediction via high reliability "soft-sensor" models, by means of which measurements of the physical and chemical properties of in-process materials or final products are translated to measures of product specifications or critical quality attributes. Inputs, outputs and the state of the operation are known continuously and with high reliability.

Barriers

- Limited availability of sensors suitable for on-line tracking of critical product performance attributes. There are no effective real time sensors for monitoring small amounts of impurities or degradation products. Some critical physical properties of granular systems can not be obtained in real time.
- Lack of fast, sensitive high resolution on-line analytical technologies for application to solids and liquids.
- In many cases sensor signals are complex and thus difficult to deconvolute and interpret in real time.
- Lack of standards for integrating data from various sensor sources. There exist a large variety of information systems provided by sensor vendors and a lack of appropriate IT systems for integrating diverse sensor data at the manufacturing stage.
- Lack of practical and cost effective approaches to computer validation.
- Residual fears of traditional regulatory barriers impede innovation.
- Transfer of appropriate knowledge in sensor innovations and supporting technologies is inadequate. Knowledge gaps are substantial in understanding of analytical technology, chemometrics, data reduction and statistical analysis, and risk assessment.
- For many on-line technologies, issues of sample handling present major challenges

- Cost of some analytical devices, e.g. terahertz range instruments, is too high for deployment in manufacturing.
- There is a general lack of reliable on-line technologies for monitoring sterile conditions.

Research Needs

- Development and deployment of sensors, direct or inferential, for on-line measurement of critical product performance attributes for each major unit operation.
- Development of new sensor techniques for online physical and chemical characterization of product state.
- Transfer of knowledge and understanding to development and manufacturing staff.
- Development of thorough understanding of advantages /disadvantages of the range of sensor technology, including reliability and accuracy issues.
- Development of reliable sampling techniques and good interfaces to process units.
- Methodology for monitoring of package integrity online, esp. sterile conditions, leakage of microbial agents.
- Rigorous studies and technology development are needed in spectroscopic particle characterization for online measurement.
- Integration of tunable lasers with existing sensors/cameras to achieve high speed process imaging. Integration with performance monitoring via multivariate data analysis.
- Development of robust sensing technologies capable of performing high resolution, high sensitivity analysis on-line (analyzer-on-a-chip).

Unit-level Control

Current State

Although in a few instances, sensors are utilized in feedback control of operating variables, the control of operations is largely based on operator personal experience and intuition, in-process product testing and end-product testing. Feed property variations are commonly encountered but no quantitative compensatory action is taken. In most cases, batch end points are determined by duration of the processing task rather than directly measuring or predicting the achievement of the critical product performance attribute that the unit operation was designed to achieve. Failure of a batch based on end-product testing provides little or no information about why the failure occurred and thus makes root cause failure analysis difficult.

Future Desired State

All critical unit operations are driven by automatic multivariable control relying on appropriate technologies such as model predictive control systems. Statistically-based trend monitoring methods provide early identification of abnormal process behavior, incipient fault diagnosis is made in real time and appropriate corrective action is taken automatically or proposed in sufficient time to prevent failure. Each batch operation performs within acceptable limits of process variability. Process controls are designed based on process knowledge gained during development and the experience gained in development is fully exploited in manufacturing.

Barriers

- Dynamic models are not available to identify critical variables and to determine appropriate sensor locations for measuring critical variables.
- Lack of robust, accurate and fast fault diagnosis methodology tailored to pharmaceutical operations, especially for complex process signal patterns.
- Limited availability of model-based trajectory control methodology relevant to pharmaceutical operations.

Research Needs

- Development of process monitoring and fault detection methods.
- Adaptation and refinement of machine learning-based classification algorithms for incipient fault diagnosis.
- Development of dynamic models suitable for control of all common unit operations. These models may initially be data driven but ultimately will be derived from first principles.
- Application, adaptation and experimental validation of trajectory control methods for all common unit operations.
- Develop model-based design space constructions for all standard unit operations used in the industry.

Integrated Production Line Management

Preamble

Integrated management of production lines requires appropriate real time knowledge of the state of the process, including real time access to all relevant process information, understanding of the design space within which the process must operate, plant-wide trend monitoring and fault diagnosis, supervisory control across multiple process units, and real time optimization of the line in response to disturbances, such as feed material and utility systems changes, deviations in the outputs of key unit operations as well as improvements in process knowledge.

Sensor Deployment

Current State

Very limited use of on-line sensors and sensor placement is dictated by convenience. Measurement redundancy is not exploited to obtain desired reliability in establishing the state of the process. Knowledge of the state of the process at any point in time is only at the macroscopic level and largely retrospective.

Future Desired State

Sensor networks provide reliable state of the manufacturing system at all times within acceptable and fully characterized uncertainty limits and with the highest reliability for monitoring of critical variables.

Barriers

- Dynamic models are not available to identify critical variables and to determine appropriate locations for measuring critical variables.
- Smart and/or pervasive sensors are not available.
- Lack of broad industry understanding of measurement uncertainty requirements to ensure proper deployment of sensing and/or modeling technologies for control applications.

Research Needs

- Adapt and apply methodology for determination of optimum sensor location relevant to pharmaceutical operations.
- Development of sensing technologies, incorporated within the machine used to perform a unit operation, capable of monitoring multiple unit doses without impacting the processing of the unit dose.
- Robust methods to monitor and determine when a sensor or "soft sensor" is no longer accurately predicting the parameter of interest. This should include predicting impending sensor failure as well as process changes that are no longer within the validated calibration range.
- Reduction in analyzer/sensor size to facilitate integration of sensing technologies within the processing machine; thus, ensuring sensors are installed in the most desirable location to meet their intended use.

Process Information Management

Current State

Isolated information systems, including batch and cleaning validation records, associated process and sensor information as well as operator logs are designed for specific functions and are separated from each other. No distinction is made between data, information and knowledge.

Future Desired State

All manufacturing information and knowledge components are fully integrated in electronic form to allow information sharing across all systems and enable process optimization to occur in real time. Functionalities provided include knowledge based tools for continuous process improvement.

Barriers

- Lack of standardized protocols for representing and integrating different types and sources of data to facilitate decision making.
- Lack of mechanistic models to translate data into understanding.

Research needs

- Development of standards and related ontologies for representing data and models.
- Intelligent real time model development environment.

Trend Monitoring and Fault Diagnosis

Current State

Trend monitoring based on operator expertise, automated systems relying on Shewhart charts or other single-variable based techniques that leave the burden of information integration to plant personnel are the norm. Fault detection and diagnosis are carried out offline, relying upon expertise of plant personnel, with recovery procedures dependent on the experience and knowledge of operators.

Future Desired State

Automated trend monitoring, fault detection, and abnormal events management systems based on *multivariate* statistical process control, systems science, and machine learning

techniques that interpret data collected from sensors, extract refined knowledge about process status, interpret knowledge, detect faults and diagnose their source causes, and recommend standardized recovery procedures.

Barriers

- Limited availability of physical and inferential sensors.
- Limited acceptance in the pharmaceutical industry of multivariate statistical process control and machine learning techniques that have yielded significant improvements in monitoring and diagnosis activities in other industries.
- Lack of techniques that can accommodate challenges offered by multistage multi-product pharmaceutical processes.

Research Needs

- Development of multivariate statistical process control and machine learning techniques for monitoring of multistage multi-product pharmaceutical processes and the detection, isolation and diagnosis of incipient faults in these processes.

Process-wide Automatic Control

Current State

Limited automated control of individual equipment makes process-wide automatic control very challenging. Integrated operation of plants caused by material and energy feedback spreads disturbances across many operations.

Future Desired State

Process-wide and supervisory automatic control that prevents the propagation of disturbances, assures safe and stable operation and provides the foundation for optimal operation.

Barriers

- Limited availability of sensors, models and automated control systems.
- Isolated information and control systems.
- Need to extend plant-wide control techniques developed for continuous processes to hybrid batch-continuous processes prevalent in pharmaceutical industries.

Research Needs

- Development of process-wide and supervisory control techniques for hybrid batch-continuous processes prevalent in pharmaceutical industries.

- Integration of information systems, trend monitoring and fault diagnosis systems, and automatic control systems of individual equipment to provide process-wide supervisory control.

Real-Time Process Optimization

Current State

Process operating conditions are fixed, providing no continuous improvement
Design space concept is encouraged by PAT guidance but is not implemented.

Future Desired State

Model based methods are used to define the design space for each unit and the entire process from feedstocks to product. Initial design space limits are automatically updated as process experience, understanding and refinements are realized. Process operating set-points and operating variables are optimized in real time within the current design space limits for the process.

Barriers

- Lack of models to define design spaces for a wide range of unit operations.
- Lack of methodology for the development of process design space.

Research Needs

- Develop a suite of models (first principles as well as semi-empirical) to define the design space for the suite of critical unit operations.
- Develop methods for formulating and updating the process design space.
- Adapt and refine relevant real time process optimization strategies.

Multiproduct Plant Operations

Preamble

As the industry moves from a focus on block-buster products to smaller volume products and increasingly to a wider range of "personalized" product formulations, the shared use of multi-purpose production facilities and thus flexible, multi-product operation will become essential for effective capital utilization. Management of change-overs between product campaigns and efficient scheduling and planning to insure balance between effective utilization of production facilities and control of inventory costs will become increasingly important.

Equipment Change-over

Current State

API and pharmaceutical manufacturing plants are increasingly multipurpose but changeovers are resource intensive and cleaning validations are very complicated. Much empirical R&D is conducted to improve cleaning procedures and validation but systems are very labor and resource intensive. Long equipment idle times while bringing units to operating state (typically 2-3 days) are common.

Future Desired State

Plants are multipurpose, operate with zero or minimal downtime and are efficiently utilized.

Barriers

- No fundamental work at science-based understanding of basic phenomena causing challenges in the removal of residues. Fundamental understanding is lacking of why compounds adhere to surfaces. (e.g., adsorption of proteins on surfaces is studied but desorption not considered).
- Lack of portable analytical instrumentation for fast detection of residues in equipment at low concentration.
- Lack of rapid and reliable methods for monitoring and detection of microbiological contaminants.

Research Needs

- Development and use of rigorous models to understand causes of heterogeneity on surfaces and to generate design and operational changes to reduce residues.
- Development of surface coatings designed to minimize residues and facilitate cleaning.
- Implement existing and novel detection methods in portable configurations.

Scheduling and planning technology

Current State

Wide variation in schedules because of delays in arrival of needed materials, demand fluctuations, rejection of lots of raw material due to poor quality and loss of product due to poor process control.
Evidence: Each month the FDA lists drug shortages that arise due to manufacturing problems.

Future Desired State

Operators are guided by predicted schedule targets and allowable time bands for execution of all recipe tasks. Plants are operated to deliver products just-in time, with

optimum work-in-process and final product inventory levels. Intermediate and final products are released in real time.

Barriers

- High computational complexity of scheduling and planning problems which involve steps with widely varying time scales and data uncertainty.
- Lack of methods to insure effective coordination between scheduling and planning decision levels.
- Inadequate understanding of process flow issues, and little use of available software and methods for managing process flow.

Research Needs

- Development and validation of efficient continuous time scheduling formulations and algorithm engineering to achieve solution times acceptable for routine use for scheduling decision support.
- Investigation and implementation of effective computational strategies for generating robust predictive schedules in presence of parametric and operational uncertainties.
- Development of hierarchical planning and scheduling strategies to effectively link medium term planning predictions and short term schedule readjustments.

Innovative Manufacturing Systems

Preamble

There have been quantitative gains in the efficiency of individual unit operations. However, the processing modalities (and technology platforms) used by the pharmaceutical industry have hardly evolved qualitatively in the last 50 years. To a large extent this reflects the fact that product forms have also remained largely unchanged. The conversion from batch to continuous mode achieved in other industries to capitalize on improvements in economy, controllability, and quality have not been pursued aggressively. Isolated instances of process intensification designed to achieve process simplification have been reported. Use of micro-scale equipment to screen reaction path alternatives is growing but no comprehensive programs to convert significant production step sequences to micro-scale continuous mode have been reported. The introduction of innovative methods of generating and using nano-particles and nano-materials processing methods is at the embryonic stage.

Current State

Batch manufacturing methods are pervasive, using traditional unit operations which are operated using recipe steps defined in terms of fixed processing time.

Future Desired State

Production lines consisting of traditional unit operations are replaced with a single innovative continuous operation or with multiunit but continuous operations. Advanced multivariable control systems are used to control operation to tight quality specifications. Real time monitoring, diagnosis and optimization are routinely employed. Selective application of micro-scale and nano-materials processing methods is widely practiced.

Barriers

- Understanding and rigorous modeling of phenomena which occur at wide range of time and length scales.
- Computational complexity and size of models resulting from need to represent multiple phases with continuous variation of phase properties.
- Fundamental understanding of nano-scale particle formation and processing steps.

Research Needs

- Investigate conversion of traditional batch operations to continuous operation, starting with less complex operations such as blending, dry granulations, size reduction, and drying, and progressing to more complex operations such as crystallization.
- Develop and validate combined operations such as reaction/separation processes, size reduction, mixing, granulation and drying.
- Develop entirely new unit operations aimed at the manufacture of novel product forms. Operations based on drop-on-demand technologies, micro/nano coating, film casting, and multi-layered deposition require investigation and development of fundamental understanding and model based design and operation.
- Investigate micro-scale reaction, separation and particle formation systems relevant to pharmaceutical operation.
- Develop understanding of fundamentals and investigate computational strategies for efficiently dealing with multi-scale phenomena arising in such novel operations.
- Investigate and develop new product forms employing nano-particle technologies capable of facilitating tight control of active material delivery properties.
- Develop lab-scale proof of concept systems, simulation tools to describe lab-scale process, and tools for scale-up and pilot demonstration. Partnering with equipment and process sensor vendors will speed development.

Small Scale Manufacturing

Preamble

Small scale manufacturing occurs to make clinical trial amounts of API, to manufacture small volume or unstable products, and to generate scale up information.

Current State

Clinical supply manufacturing is time driven and largely separated from product design and manufacturing goals, resulting in no knowledge gained /retained for process development and scale-up. Generally there is no difference in manufacturing equipment used to make small volume and large volume products. Small volume products are produced opportunistically during campaign breaks between larger volume products and stored for later use. Abnormal situations arising in normal manufacturing often can not be seen or encountered at the clinical manufacturing scale.

Future Desired State

Clinical supply runs are directly used to predict full scale process performance. Small volume products are produced just in time using specialized facilities and requiring minimum product inventory. The experienced gained in small scale operations is used to diagnose and resolve process abnormalities, while facilitating the validation of large scale processes but with zero disruption of normal manufacturing operations.

Barriers

There is a lack of understanding of the dominant mechanisms and comparable critical measurements and measurement locations at the small and large scales.

Research Needs

- Development of systematic guidelines and protocols to insure data necessary for scale up models are generated and validated.
- Innovative approaches to scale-down, including use of rigorous models to identify critical measurements and measurement locations.

Supply Chain Management

Preamble

Many current issues point to the need for decision support tools for managing large scale systems with numerous uncertainties. Important issues include 1) the shift to smaller

volume and personalized dosage forms 2) high potency but less stable products 3) globalization of the manufacturing, distribution and marketing of products, 4) risks underlying demand forecasting, capacity planning and investment, and 5) the increasing cost and risk of managing product development pipelines.

Current State

Limited use of multi-time period, linear models to plan production via rolling horizon strategies. Limited use of discrete event, Monte Carlo simulation tools to study effects of uncertainties and develop risk profiles in supply chain operation. Isolated efforts in employing quantitative models to guide project selection and resource allocation decisions in product development pipeline management and capacity planning.

Future Desired State

Supply chain and product pipeline management decision are supported by quantitative tools that allow evaluation of risk reward tradeoffs for all major strategic and tactical decisions in time scales commensurate with natural business decision cycles.

Barriers

- Absence of institutionalized practice for gathering and modeling technical, market and economic uncertainties. Except for marketing data, most relevant data is recorded in averaged form, if recorded at all.
- Computational challenges of solving large scale decision problems featuring intensive processing times and extensive data storage needs.
- Model formulations and solution algorithms that can accommodate non-Markovian stochastic elements and investigation of competitor actions.

Research Needs

- Supply chain modeling and solution tools integrating strategic and tactical decision levels and spanning production planning, logistics and inventory management functions. Incorporation of effects of uncertainties is critically important.
- Application of prototype pipeline management decision support tools to full scale problems capturing stochastic aspects of development and clinical failure, resource requirements and demands.
- Strategies, such as agent-based systems, for investigating capacity planning and other investment decisions in the presence of competitor and governmental actions.

Enabling Technology: Informatics-based Model Development and Integration Infrastructure

Preamble

From early process development through scale-up to process design and manufacturing, a staggering amount of information of different types, ranging from raw data to lab reports to sophisticated mathematical models, is shared and revised by tools in each stage. Subsequent to process development, technical specifications and reports must be developed to satisfy regulatory requirements. Informatics infrastructure plays a crucial role in supporting all these different activities by streamlining information gathering, data integration, model development, decision making and managing all these for easy and timely access and reuse. Such an infrastructure has a major impact on all nine areas highlighted in this roadmap. The foundation of such an infrastructure is the explicitly and formally modeled information. This foundation enables knowledge in different forms, including best manufacturing practices, to be modeled and captured for use in tools that support product life cycle management.

Current State

Despite progress in IT applications such as World Wide Web, informatics is a relatively new area in general, and particularly so for pharmaceutical development and manufacturing, with very little research to address the core issues in a comprehensive manner. Even with rapid progress on information integration and sharing in business functions (such as Enterprise Resource Planning (ERP) systems) and on plant floor (such as Manufacturing Execution Systems (MES)), this problem is yet to be addressed adequately. No distinction is made between data, information and knowledge. Many individual islands of automation exist but no comprehensive, integrated decision support environment is currently available to link these islands. Therefore, practitioners must make do with a limited computer-based assistance to acquire, manage, analyze and interpret complex product and processing information with enormous amounts of human intervention. This increases the inefficiencies, uncertainties, costs, delays, and product quality concerns all along the product life cycle.

Future Desired State

Use of knowledge-based software systems that effectively manage (i.e. store, retrieve, analyze, update, maintain, and communicate) information and models to support efficient decision making by the user. All product/process development and manufacturing information and knowledge components are fully integrated in electronic form, are available in real time and flexibly searchable, are fully validated and structured to meet regulatory requirements. Knowledge based tools with capabilities to support activities such as quality by design, tracking of deviations to support quality control, continuous process improvements, etc., are available and in use.

Barriers

- Lack of formal standards and protocols for representing, sharing and integrating different types and sources of data and models to facilitate automated decision making.
- Lack of mechanistic models to translate data into understanding.

Research Needs

- Development of standards and related formal structures such as ontologies for representing and sharing data and models.
- Creation of a software infrastructure that supports real-time model development
- Automated methodologies for the testing, verification, validation and maintenance of models.

Appendix A: Assessment of Unit Operations common in the Pharmaceutical Industry

The operations were grouped into three priority classes: H high, M medium and L low, based on an assessment of their importance, prevalence and the potential of the impact of an investment of $1 million in research towards improved understanding and rigorous model development in that category of unit operations. Some operations, such as chromatography, have already attracted research investment several orders of magnitude larger than $1 million and, given the state of understanding of that operation, major breakthroughs are unlikely as a result of an incremental research investment of that magnitude. Others, such as chemical reactors have likewise seen extensive research but are poised for significant progress given developments in high throughput screening, reaction calorimetry, real time instrumentation, CFD capabilities and wide availability of computing power.

API Processing: Small Molecules
- Chemical reactor: H
- Liquid-liquid extraction L
- Solid-liquid separation M
- Drying M
- Solubilization L
- Mixer
  - Liquid-liquid L
  - Suspension mixing H
- Size Reduction: H
  - Nanomilling
- Membrane separation M
- Chromatographic separation L
- Batch distillation/evaporation L
- Crystallizer/precipitator H
- Supercritical processing M

API Processing: Biologicals
- Biological Synthesis   L
  - Fermentation
  - Cell culture
- Absorption   L
- Cell disruption L
- Flocculation M
- Foam fractionation M
- Solid-liquid separation H
  - Centrifugation H

- Deep bed filtration H
- Microfiltration H
- Lyophilization H
- Spray drying/coating H
- Ultrafiltration L
- Chromatographic separation M
- Precipitation M
- Extraction L
- Sterilization/Depyrogenization M

Solid Products

- Size reduction   H
- Size enlargement
  - Wet granulation   H
  - Dry granulations
    - Roller compaction H
    - Pelletizing & slugging L
- Extrusion   M
- Fluid bed processing
  - Coating   H
  - Granulation H
  - Drying H
- Drying
  - Tray L
  - Tumble L
  - Spray drying M
- Blending M
- Flow & handling H
- Compaction H
- Capsule filling L
- Tumbling Coating
  - Tablet/capsule H
- Packaging L
- Labeling & Branding L
- Drilling L
- Capsule forming L

Sterile Liquid and Solid Products

- **Comment:** In-Process Characterization is a need that significant issue for most of the unit operations listed below. Particulates, sterility, pyrogen content and degradation (for biologics) are quality attributes of particular importance.

- Sterile filtration   M
- Terminal sterilization H

- Preparation of container closure systems L
- Filling M
- Stoppering & Capping L
- Mixing M
- Materials handling via Isolators & Barrier Technology H
- Lyophilization H
- Spray Drying M
- Alternate Drying Processes (i.e., foam drying, super-critical fluid, …) M
- Fill Blow Sealing L
- Packaging & Labeling L

Topical/Semi-solid Products

- Mixing/homogenizing   H
- Filling tubes   M
- Heating M
- Sterilization M
- Bioburden control   L
- In-Process Product quality control   H
- Extrusion   M

Other Product Forms with specialized unit operations

- Inhalables
- Natural products
- Cell culture
- Film casting
- Drug release in stents
- Transdermal patches
- Osmotic pump
- Micro-needles
- Implantables & sustained release injectables

Appendix - B

Acknowledgement of Contribution to The Pharmaceutical Technology Roadmap

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Pharmaceutical Technology & Education Roadmap
Revision 0

<u>A Preliminary Proposal for Enhancing Pharmaceutical Technology Education</u>

<u>National Institute for Pharmaceutical Technology and Education</u>

<u>Executive Summary</u>

This document provides a draft proposal for enhancing Pharmaceutical Technology Education developed by the education subcommittee of NIIPTE. Main elements can be summarized as follows:

(1) The committee's assessment of the state of pharmaceutical technology education concluded that the traditional activities broadly described as "industrial pharmacy" have experienced a rapid decline in number, size, and quality, and are currently insufficient to meet society's needs. Emerging activities, broadly defined as "pharmaceutical engineering" have experienced rapid growth, but display a wide scatter of foci and would benefit from standardization. Post-graduate training activities are plentiful, but are largely remedial rather than developmental and lack a uniform quality standard.

(2) The proposed "desired state" of education in the field of pharmaceutical technology is presented. For Formal Education programs, the desired state would be best captured by the creation of a standard curriculum that synergistically integrate and intimately combine core concepts and methods from Pharmaceutics and Engineering, to train professionals capable of facilitating systematic product and process design, optimization, and control. Elements of the standard curriculum would generate curricular content suitable to enrich undergraduate and graduate programs, and also to facilitate high quality, systematic, post-graduate programs capable of updating and upgrading the skills of large populations of pharmaceutical scientists in industry and government. Professional Education could be conducted at a wide range of settings (universities, companies, public venues), provided that they share a high standard of quality, established based on an objective evaluation of effectiveness.

(3) Main barriers for achieving this desired state include (i) a lack of a shared vision by the relevant stakeholder community, (ii) an acute shortage of active faculty in the area (caused by a shortage of funding in the area and a lack of post-doctoral training programs that can help train the next generation of faculty), (iii) a lack of resources needed to launch the new graduate programs, and (iv) a lack of shareable instructional materials, such as textbooks and laboratory experiments, that would facilitate course development by other institutions

(4) The action plan for overcoming these barriers calls for a workshop carried out by a working group of academics, industrialists, and government officials, who would develop recommended curricular guidelines and an implementation plan, and would identify activities suitable for future funding by NIPTE.

Table of Contents:

Background

The development and deployment of educational resources are essential to create the human resource component needed to transform pharmaceutical product and process design, development, optimization and continuous improvement. The purpose of this document is to motivate discussion and create consensus by the stake holder community (academia, industry, government, professional organizations, and the target student population) in order to identify and attract the resources needed for meting society's needs.

Scope and Mission

Knowledge	Education	Practice

Figure 1: Role of Education: the vehicle for translating research into practice

NIPTE defines itself as the National Organization engaged in the development **and implementation** of a scientific foundation for Pharmaceutical Development and Manufacturing. This mission statement implies two interconnected components: articulation of a vigorous research agenda leading to the development of necessary knowledge, and the development of a strong human resource needed both to generate and to implement new knowledge and concepts into the field. These components are inter-dependent: education is the vehicle for translating research into widespread practice (Fig. 1).

Rejuvenation of pharmaceutical technology education is a major opportunity for impact by NIPTE. In multiple discussions with the FDA, educational programs that would enable upgrading the skills of examiners and inspectors were identified as perhaps the most important short-term FDA need that NIPTE could help meet. In further discussions with industrial colleagues, lack of properly trained human resource has been repeatedly identified as the major roadblock for implementation of the quality by design, the PAT initiative, and the skill set underlining application of the GMP for the 21st century.

The main mission of the educational component of NIPTE is to create a "pipeline" (Fig. 2) of diverse talent that commences at the undergraduate level and continues throughout both formal graduate and postgraduate programs, and through an effective professional education resource, augmenting the available workforce in academia, industry, and government. Integral to the creation and maintenance of this stream of talent is an integrated education and training plan which incorporates NIPTE research findings into the skill set of the work force available to Industry, Government, Academia, and society.

Figure 2: The Pharmaceutical Technology Educational Pipeline, training the best minds at all levels

Current State of the Field

The committee performed an initial survey of the state of pharmaceutical technology education, which can be summarized as follows:

(1)   The need for coherent, comprehensive training in pharmaceutical manufacturing methods has grown rapidly in recent years. Both industry and government have a growing need of pharmaceutical scientists and engineers highly skilled in product and process design and optimization in order to meet the technical challenges posed by the PAT and QbD initiatives and the GMPs for the 21st century, all of which emphasize the integrative application of materials science, pharmaceutics, and engineering methods in order to achieve increased process understanding.

(2)   The set of traditional educational activities broadly described as "industrial pharmacy" have experienced a rapid decline in number, size, and quality in recent years, and are currently insufficient to meet society's needs. Currently, only a small number of graduate pharmaceutics programs survive where enough critical mass is present to sustain credible training activities in pharmaceutical technology. A substantial shortage of faculty active in either research or teaching is clearly evident. Many senior faculty members are approaching retirement, and if recent trends continue, they would not be replaced by colleagues working in pharmaceutical technology areas. This situation will inevitably lead to a loss of capacity and an irreplaceable loss of an opportunity to train a younger generation of faculty. The decline in pharmaceutical technology focus has been pronounced at the graduate education level, and even more extensive at the undergraduate level, where the adoption of PharmD programs has led many schools to develop a stronger clinical emphasis, coinciding with the elimination or watering down of many technology-oriented courses.

(3)   An emerging host of activities, broadly defined as "pharmaceutical engineering" have experienced rapid growth. The last decade has witnessed the emergence of seven training programs at the graduate or undergraduate level (Rutgers, Michigan, NJIT, UPR, Purdue, IIT, Stevens Institute of Technology). Several additional institutions have expressed interest in developing programs in the field (University of Maryland at College Park, University of Iowa, University of Connecticut). However, these activities display a wide scatter of foci and content, reflecting the expertise of the small number of faculty present at each of them, and would benefit from standardization of curriculum requirements and from the availability of shareable textbooks and other instructional resources. Moreover, most of these activities have focused on activities offered at the graduate level, even though much of the teaching material is clearly suitable for undergraduates.

(4)   Of particular notice is the shortage of organized academic training opportunities at the post-doctoral level either in industrial pharmacy or in pharmaceutical engineering, which the committee considered to be a substantial factor limiting the availability of young faculty candidates.

(5)   Many professional education activities is available, conducted by professional associations, for-profit entities, consultants, etc. However, these activities are largely piece-meal, and often lack the structural framework that could lead to effective development and long-term professional growth. Moreover, due to a lack of a uniform quality standard, they are offered (and taken) on a buyer-beware basis, leading to further loss of effectiveness.

Desired State of the Field

As shown in Figure 2, a comprehensive educational program requires two main modalities of implementation: Formal Education, and Professional Education.

Regarding Formal Education, we propose to create an educational model that synergistically integrate and intimately combine core concepts and methods from Pharmaceutics and Engineering, to train professionals capable of facilitating systematic product and process design, optimization, and control. The name of "Pharmaceutical Engineering and Science" (PES) describes the essence of this emerging paradigm of multidisciplinary education. The integration of disciplines should be used throughout higher educational systems including undergraduate, graduate and post-graduate programs.

Drug product design, development, and manufacturing are manifestly multi-disciplinary tasks: Drug product development requires both knowledge of materials science as well as understanding of the unit operations used to turn ingredients into structured products with desired properties. Design and formulation of the drug product requires understanding the evolution of therapeutic entities in the enormously complex environment of the human body. Drug manufacturing relies on pharmaceutics *and* engineering. In order to develop systematic methods for optimizing performance of complex products and the processes required to manufacture them, cross-disciplinary training is a must. A list on desirable educational components would include:

- *Background: physics, calculus, English, computer literacy.*

- *Applied mathematics: Statistics, ODE's and PDE's, Numerical analysis, Linear algebra, optimization methods.*

- *Chemical principles: Organic chemistry, Analytical chemistry.*

- *Biotechnology principles, biochemistry, biophysical chemistry, biopolymers and applied microbiology.*

- *Physicochemical principles: chemical kinetics, thermodynamics, complex equilibria, solubility and ionic equilibria for organic systems, transport phenomena, interfacial phenomena.*

- *Materials science: fundamental material properties, polymers, composites, mechanics, rheology, continuum mechanics, granular systems.*

- *Product design and optimization: pharmaceutical materials, dosage forms, biopharmaceutics/pharmacokinetics, materials interaction pharmacology, product characterization/quality/performance, basic anatomy/physiology.*

- *Process design, optimization and control. Process components: design/interactions/integration, process modeling, sensing and monitoring, control methodologies.*

- *Manufacturing science: Regulatory issues, quality systems, real time optimization, risk analysis, process economics, change management.*

- *Professional Development: Project management, communication skills, team building, organization dynamics, professional ethics.*

Out of these building blocks, institutions will develop locally optimized versions of the proposed model, reflecting their resident expertise, the student population that they most effectively attract, and the professional communities they intend to serve. The diversity of implementation should be built atop a bedrock foundation of minimum required contents and

shared academic standards that would provide identity, prestige, and quality to the field, attracting the best minds and promoting transformative change in the target professional and industrial communities.

Depth and sequencing will vary for UG, MS, D, PD, levels. Initial degree programs may focus on MS or certificate programs, where impact of new programs is most immediate. Graduate programs organized according to this model would rapidly generate curricular content suitable to enrich undergraduate activities, and also to facilitate high quality, systematic, post doctoral training programs that would serve as greenhouses for the next generation of faculty, and post-graduate programs capable of updating and upgrading the skills of large populations of pharmaceutical scientists in industry and government.

New curricular content developed by the aforementioned Formal Education programs will facilitate also the strengthening of Professional Education activities, creating vehicles for the improvement of skills of a large number of professionals currently employed in industry, government, and professional organizations. While such activities could be conducted at a wide range of settings (universities, companies, public venues), they should share a high standard of quality, established based on an objective evaluation of effectiveness.

Moreover, we propose that such activities should be structured as longitudinal professional education programs leading to long-lasting professional growth. In the desired state, such programs can be accessed by the intended audience through effective channels that can reach large populations without loss of quality. While NIPTE does not intend to become involved in accreditation processes, the subcommittee agreed that NIPTE should facilitate the development of shareable instructional resources that should be subjected to rigorous peer review prior to their incorporation into curricula.

Barriers to Achieve the Desired State

Main barriers for achieving the desired state described in the previous section include the following:

(1) Current lack of a consensual vision for the new paradigm shared by the relevant stakeholder communities: Academia, Industry, Government, Professional Organizations, and Students.

(2) Lack of a strategic implementation action plan that would make it possible to identify and marshal necessary intellectual and human resources.

(3) An acute shortage of active faculty in both Physical Pharmacy and Pharmaceutical Engineering. This shortage obeys to a historic lack of federal funding for research activities in this area, which have motivated young faculty pursuing tenure to focus in other areas of scientific inquiry. Corrective action is hindered by a complete lack of even a single post-doctoral training program that can help train the next generation of faculty.

(4) Diversity of student educational background entering the field, which poses a substantial difficulty in bringing them to a common knowledge base.

(5) A lack of resources needed to launch the new graduate programs. Even though emerging Pharmaceutical Engineering programs have quickly became self-sustaining, there is still a considerable cost involved in launching them, including the need to hire faculty and staff, development of courses, educational laboratories and teleconferencing facilities, etc. Given the budgeting process in most universities, internal resources can be extremely difficult to generate. While industry has occasionally supported such efforts, the

existence of an organized stream of financial resources devoted to the development of new educational capacity would serve to catalyze and accelerate the process.

(6) Even for institutions that have shown a substantial interest in developing the type of program proposed here, a lack of shareable educational materials, such as textbooks and portable laboratory experiments, has posed a formidable obstacle to the (typically small) faculty resources that can be devoted to new activities that would facilitate course development by other institutions

(7) Possibility that the proposed programs might be perceived as a competitor to continuing education efforts currently offered by professional organizations such as ISPE, CHPA, PDA, and also by for-profit organizations whose business model is based on providing professional education services.

Draft Action Plan

The previous section makes it possible to articulate what current needs must be met to bring about the proposed new educational paradigm:

- a shared vision by the stakeholder community,

- more faculty (and mechanisms for training them),

- mechanisms for funding research and educational activities, and

- a vigorous pipeline of students encompassing the field from the undergraduate level to the post-doctoral training level.

To this end, in order to address the aforementioned barriers, NIPTE seeks to facilitate the development of a shared vision with the stakeholder community, by means of a series of workshops conducted by a working group that would invite, in an inclusive manner, the essential input from all relevant stakeholders. A proposed set of actions is described next

1. Proposal: The "Plan to the Plan"

In order to develop a strategic implementation plan, three primary ingredients are needed: consensus on desired outcomes; a complete assessment of current state, need, barriers, and resources; and an engaged community of stake holders willing to develop and pursue a realistic implementation plan. In order to meet these needs, a three-stage planning program is proposed:

Stage 1 will consist of a first workshop, to be held in September 06, which will focus on three goals:

Goal I: Present and discuss the vision for the new educational discipline

Goal II: Develop preliminary answers to questions such as:

1. Given the proposed PES field, what are the required knowledge contents for
    a. Entry level scientist vs. Entry level senior scientist?
    b. FDA inspector vs. FDA reviewer?
    c. Regulatory affairs specialist?
    d. University young faculty member?
2. What are your most immediate needs in PES professional education?

3. Are structured longitudinal educational programs valuable? (compared to experiential discrete training)
4. What are effective mechanisms of delivering these materials to part-time students?
   a. University setting
   b. Summer institute
   c. On-site education
   d. Real-time distance education
   e. On-demand distance education
5. How can NIPTE support FDA educational needs?

Goal III: Create a working group, composed of academics, industrial representatives, government officials, and members of professional organizations, and define its charter

Stage 2 (anticipated duration: September 06 to August 07) will consist of a series of meetings and workshops conducted by the working group, which will involve all necessary partners in order to deliver on its charter, which might include some of the following elements:

i. Assess societal need
    a. How many programs do we need to have?
    b. How many BS/MS/PhD do we need to educate?
    c. How many current employees do we need to educate?
ii. Survey all existing educational resources
iii. Identify gaps, barriers, and needs in developing the infrastructure that meets societal needs
iv. Refine the model curricula
    a. Undergraduate
    b. MS
    c. PhD
    d. Postdoc
    e. Longitudinal Professional Education
v.   Develop implementation plan

Stage 3 will consist of a second workshop where findings, proposed curricula, and proposed implementation plans will be presented to all the interested parties, followed by discussion and collection of feedback regarding the implementation of the planned curriculum changes. Participants will include representatives from all contributed schools, pharmaceutical companies, FDA, professional organizations (AIChE, ISPE, AAPS, PDA, USP). The essential goal of this workshop will be to lead to the adoption of a shared vision for the desired state of education in Pharmaceutical Engineering Science, and to marshal all necessary resources and approvals for its implementation. At this point, it is anticipated that findings from the workshop will need to be incorporated into major proposals for funding directed at government granting agencies, industry, relevant agencies, professional organizations, and foundations. Several appropriate government grant programs have been identified, and it is clear from the standard procedures used by these programs that the findings of the working group will provide a highly necessary foundation for securing such funds.

Appendices: Available Educational Programs In Pharmaceutical Engineering and Science

As mentioned in the body of this document, several programs already exist attempting to combine Engineering and Pharmaceutics. Here we present a summary of the following programs

- NJIT M.S. program in Pharmaceutical Engineering
- Rutgers M.S. Program in Pharmaceutical Engineering and Science (proposed)
- Rutgers/NJIT/UPR Doctoral training program in Nanopharmaceutical Engineering
- Proposed Purdue M.S. Program in Pharmaceutical Engineering

Proposed Master in Pharmaceutical Engineering and Science – Rutgers University

Program Objectives and Scope:

The Master in Pharmaceutical Engineering and Science degree program will be administered by the School of Engineering at Rutgers University as a joint professional degree involving Engineering, Pharmacy, and Chemistry. The objective of this academic program is to educate students in the engineering and science needed to design and optimize pharmaceutical products, and to design, optimize, and control the associated manufacturing processes.

The curriculum reflects the emphasis on "Process Understanding" and "Risk Based Regulation" that has been identified by the US FDA as the guiding principles for awarding licenses to manufacture and commercialize drug products in the 21st century.

Core courses (five required courses):
1. Pharmaceutical Process Design I (Synthesis, separations & sterile processing)
2. Pharmaceutical Process Design II (Pharmaceutical unit operations)
3. 155:xxx Statistical Analysis and Design of Pharmaceutical Operations
4. 155:xxx Advanced Engineering Pharmacokinetics
5. 720:511 Pharmaceutical Formulations I

Electives (at least four courses):
1. Advanced Transport Phenomena I: Momentum Transfer
2. Advanced Transport Phenomena II : Heat and Mass Transfer
3. Advanced Chemical Engineering Thermodynamics
4. Kinetics, Catalysis, and Reactor Design
5. Analytical Methods in Chem. & Biochem. Engineering
6. Nanotechnology-based Drug Delivery
7. Industrial Chemistry of Drugs and Fine Chemicals
8. Fluid Particle Granular Flow
9. Advanced Pharmaceutics II
10. Pharmaceutical Formulations II
11. Advanced Pharmaceutics
12. Pharmaceutical Organic Nanotechnology
13. Regulatory affairs, process scale up and validation
14. Design and Operation of Pharmaceutical Facilities
15. Nanomaterials Processing
16. Pharmaceutical Materials
17. Instrumental Chemistry Methods for Pharmaceutical Applications
18. Intro to Packaging Engineering

Course Descriptions:

Core courses (five required courses):

Pharmaceutical Process Design I (Synthesis, separations & sterile processing)
The course focuses primarily on processes and operations required to synthesize and purify active pharmaceutical ingredients, including both organic and biological synthesis and reviewing both the primary synthesis routes and the design of the synthesis equipment. Extraction from natural sources is also briefly discussed. The course continues with

purification processes, including extraction, adsorption, and crystallization, often followed by milling. Sterile processing is also discussed.

Pharmaceutical Process Design II (Pharmaceutical unit operations)
The course provides an introduction to the essential operations used in the manufacture of solid-dose pharmaceutical products. The course discusses the pharmaceutical product life-cycle, variability, testing, and specifications of pharmaceutical ingredients. Unit operations including blending, granulation, fluidized bed operations, milling, capsule filling, compaction, tablet coating and other processes will be addressed. Students learn to recognize how the output of one process is the input to the next process, and how deviations can cascade along the production sequence until they cause process failures. The course emphasizes design, scale-up, trouble-shooting, and optimization.

Statistical Analysis and Design of Pharmaceutical Operations
The course provides an introduction to statistical analysis and experimental design methods and their applications to designing and optimizing pharmaceutical processes. Classic statistical concepts and methods will be discussed using pharmaceutical examples including product/process development scenarios, routine in-process and finished product testing, and failure investigations. Regulatory requirements for test of samples, sampling plans, tablet and capsule assay, content uniformity, hardness, friability, dissolution and bioavailability tests will be discussed in detail.

Advanced Engineering Pharmacokinetics
The course reviews concepts from transport phenomena, thermodynamics, and reaction engineering, as well as basic physiology, to provide students with an understanding of the fundamentals of drug delivery: kinetics of drug absorption, distribution, and elimination; clearance concepts; compartmental, noncompartmental, and physiological models. Fundamental issues relevant to the design of drug products having immediate release, delayed release, sustained release, and extended release profiles are reviewed. Generation and fate of metabolites is discussed.

Electives (at least four courses):

Advanced Transport Phenomena I (3)
Momentum transport processes in laminar- and turbulent-flow systems. Development and application of steady and unsteady boundary-layer processes, including growth, similitude principles, and separation. Potential flow theory coupled with viscous dissipation at boundaries. Momentum transport in fixed- and fluid-bed exchangers and reactors. Prerequisite: Undergraduate transport phenomena.

Advanced Transport Phenomena II:
Heat and Mass Transfer (3) Energy balances derived from first and second law approaches to open systems, with reaction. Conduction in fluids and solids, both steady and unsteady examples. Convection in laminar- and turbulent-flow systems. Diffusion and its treatment in stagnant and flowing media. Two-phase systems, coupled reaction, and mass transfer. Interphase transport. Prerequisite: Permission of instructor.

Advanced Chemical Engineering Thermodynamics (3)
Basic principles of classical chemical thermodynamics. Chemical and physical equilibria and their relationships in simple and reactive systems. Estimation and correlation of thermodynamic functions, applications of thermodynamic principles to transport and rate

processes. Irreversible and statistical thermodynamic topics also introduced. Prerequisite: Undergraduate or graduate degree in engineering or chemistry.

Kinetics, Catalysis, and Reactor Design (3)
Principles of applied chemical kinetics, reaction mechanisms and rate laws, and engineering design of reactor vessels. Applications to homogeneous and heterogeneous process reaction systems with internal, transphase, and external mass transfer. Noncatalytic gas-solid reaction and gas-liquid absorption with reaction. Micromixing and macromixing in reactor systems. Prerequisites: 16:155:501 and 507, or equivalent.

Analytical Methods in Chemical and Biochemical Engineering (3)
Analytical solutions to deterministic mathematical models encountered in chemical and biochemical engineering, including environmental and safety systems. Emphasis is on purpose, philosophy, classification, development, and analytical solutions of models occurring in transport phenomena, thermochemical, and reactor systems. Prerequisites: Undergraduate differential and integral calculus and differential equations or permission of the graduate director.

Industrial Chemistry of Drugs and Fine Chemicals (3)
Chemical process development, scale-up, and regulatory environment of drugs and fine chemicals; strategies and technologies for the synthesis and semisynthesis of drugs. Transition from the bench to the FDA-approved plant.

Fluid Particle Granular Flow (3)
Flow of granular materials and fluid-particle suspensions. Continuum and discrete modeling, process equipment. Applications in the chemical and pharmaceutical industries addressing hydrodynamics, mixing, segregation, granulation, and reactive multiphase flows.

Advanced Pharmaceutics II (3)
Kinetics aspects of the pharmaceutical sciences. Quantitative and mechanistic approaches to pharmacokinetics, dissolution rate, and chemical kinetics. Kong. Prerequisites: Ordinary differential equations (or equivalent) and pharmacokinetics.

Advanced Pharmaceutics I (3)
Application of physical-chemical principles to the study and evaluation of pharmaceutical systems: solubility phenomena, equilibria, complexation, phase transitions, and pharmaceutical stability, and the fundamentals of pharmacokinetics. Sinko. Prerequisites: Physical chemistry and associated math requirements.

Pharmaceutical Organic Nanotechnology.
The course provides an introduction to Organic Nanotechnology and experimental design methods and their applications to designing and manufacturing drug products. The uniqueness of this course lies in the fact that it focuses on applications in the pharmaceutical industry. Examples examine Nanoparticle Synthesis Methods such as precipitation, nanomilling, and polymer encapsulation. Processing methods are discussed in the context of crystallization, coating, granulation, and compaction. In this course, numerous examples, homework, and projects taken from the pharmaceutical industry will be introduced. This course does not have a significant relationship to courses offered by other graduate programs or undergraduate programs.

 Proposed Master of Science Program in Pharmaceutical Engineering at Purdue University

Program Summary

The mission of the Pharmaceutical Engineering Master of Science program at Purdue University is to graduate students who can effectively apply quantitative engineering principles to manufacturing processes in the pharmaceutical industry**.** The program integrates engineering and pharmaceutical science principles to prepare graduates for making significant contributions in the field of pharmaceutical manufacturing. Graduates from the program will not only be prepared to contribute in the present-day pharmaceutical manufacturing environment, but will also have the skills to design and implement new innovative and efficient manufacturing processes using analytical tools that are based on fundamental engineering principles.

M.S. in Pharmaceutical Engineering Curriculum (29 hrs total)

Fall (14 hrs)
Introduction to Pharmaceutical Engineering
Introduction to Pharmaceutical Manufacturing Processes (2hrs)[1]
Statistical Modeling and Analysis (3 hrs)
Transport Phenomena (3 hrs)
Elective (3 hrs)

Spring (12 hrs)
Process Development and Design of Active Pharmaceutical Ingredients (3 hrs)
Pharmaceutical Materials Science (3 hrs)
Advanced Bio-pharmaceutics (3 hrs)[1]
Elective (3 hrs)

Summer (3 hrs)
Internship or Research Project (*e.g.* ME 597, 3 hrs)

[1] BSPS students may have had equivalent courses before entering in the program. In such cases, these students, at the discretion of the Pharmaceutical Engineering Graduate Committee, would take either missing pre-requisites and/or additional electives.

A Sampling of Approved Elective Courses
Discrete Element Modeling
Engineering Optics
Instrumentation for Engineering Measurements
Intermediate Fluid Mechanics
Intermediate Heat Transfer
Mechanical Behavior of Materials
Pharmaceutical Solids
Powder Processing
Spray Applications and Theory
Sterile Product Systems

CORE COURSES

Principles of Pharmaceutical Engineering (ChE 597E)

Pre/Co-requisites: Consent of the instructor
Description: This course is designed to provide engineering and pharmacy students with an understanding of the structure, economic and regulatory context, product discovery and development pipeline dynamics and the manufacturing technology of the global pharmaceutical industry as it is today.

Introduction to Pharmaceutical Manufacturing Processes (IPPH 562)

Pre/Co-requisites: CHM 372 (Physical Chemistry), the equivalent or the permission of the instructor is required.
Description: A course intended to provide the student with basic understanding of both the theoretical and practical aspects of pharmaceutical manufacturing by combining a thorough classroom treatment of the underlying principles of each pharmaceutical unit operation with hands-on execution of these activities in the laboratory.
Notes: The course currently consists of a combined lecture and laboratory. The plan is to split the course into two separate components: a lecture (2 credits) and laboratory (1 credit) in order to allow distance education students to enroll in the lecture component without requiring the laboratory. The course will also be re-designed to include more engineering content so that the course can be co-listed for engineering credit.

Statistical Modeling and Analysis (CHE 697G)

Pre/Co-requisites: Consent of the instructor.
Description: Mathematical modeling is becoming increasing recognized as an invaluable aid to understanding and forecasting the behavior of a variety of biological and engineering systems. These models based on physical and scientific principals are inherently mathematically complex and require computational skills to solve the resultant equations. This course will develop the skills necessary to build such mathematical models. Statistical methods will be introduced for designing and analyzing experimental data which
will identify, validate and provide meaningful parameter estimates. Examples to demonstrate the utility of the methodology will be drawn from various application areas in the engineering sciences. The capstone project for the class will require the student to select a kinetic model from a family of models by designing, conducting and analyzing simulated experimental data.

Transport Phenomena (CHE 540)

Pre/Co-requisites: CHE 378 (Heat and Mass Transfer). Authorized equivalent courses or consent of instructor may be used in satisfying course pre- and co-requisites.
Description: Continuation of CHE 377 (Momentum Transfer) and 378 (Heat and Mass Transfer). Topics in fluid mechanics, heat transfer and mass transfer

including unsteady state transport problems, stream functions, potential flow, hydrodynamic and thermal layers, turbulence, and multicomponent diffusion.

Pharmaceutical Process Development and Design (CHE 597D)

Pre/Co-requisites: Consent of the instructor

Description: The development and design of processes for the production of pharmaceutical products involves three important tasks: translation of the recipe for the drug substance (or active pharmaceutical ingredient (API)) that was developed at the laboratory stage to a recipe usable in production, selection, preliminary design, and scale-up of the equipment used to carry out the steps of the recipe, and selection, preliminary design, and scale-up of the equipment used to make the formulation (e.g., tablet or capsule) that is the vehicle for delivery of the API to the patient. In this course the engineering methodology which underlies the first two tasks will be covered using references from the process systems engineering and pharmaceutical manufacturing literature. The features of the key unit operations used, such as batch reaction, solid-liquid separation, crystallization, drying, batch distillation and other separation systems will be reviewed. Both dedicated and multi-product production system design and batch and semi-continuous operating modes will be covered. Software for physical property estimation, simulation and optimization will be introduced and used to solve industrially relevant applications. The cGMP requirements will also be reviewed. Case studies will be used to demonstrate the overall design strategy and its operational implementation and to integrate the course material.

Pharmaceutical Materials Science (MSE 582)

Pre/Co-requisites:

Description: This course encompasses deformation-based microscopic mechanisms, including dislocation motion, diffusion, and viscoplasticity. Macroscopic mechanical response of metals, ceramics, polymers, and composites will be related to elasticity and plasticity concepts for single crystal, polycrystalline, and amorphous materials. Practical design considerations for deformation will be included as well as an introduction to fracture mechanisms.

Notes: This course currently exists as MSE 382. The plan is to add additional content concerning pharmaceutical materials and co-list the course as MSE 582.

Advanced Biopharmaceutics (IPPH 583)

Pre/Co-requisites: IPPH 475 (Biopharmaceutics and Pharmacokinetics I). Authorized equivalent courses or consent of instructor may be used in satisfying course pre- and co-requisites.

Description: A comprehensive course dealing with the interaction of biological and physico-chemical considerations relating to drug effectiveness and dosage form design.

Advanced Mechanical Engineering Projects I (ME 597)

Pre/Co-requisites: Masters Student Standing. Authorized equivalent courses or consent of instructor may be used in satisfying course pre- and co-requisites.

Description: Projects or special topics of contemporary importance or of special interest that are outside the scope of the standard graduate curriculum can be studied under the Mechanical Engineering Projects course. Interested students should seek a faculty advisor by meeting with individual faculty members who work in their area of special interest and prepare a brief description of the work to be undertaken in cooperation with their advisor.

Note: Other schools and departments offer similar project courses (*e.g.* CHE 597 – Special Topics in Chemical Engineering).

A SAMPLING OF ELECTIVE COURSES

Additional elective course may be approved at the discretion of the Pharmaceutical Engineering Graduate Committee.

Discrete Element Modeling (ME 595D)

Pre/Co-requisites: a first course in dynamics, calculus, and ordinary differential equations

Description: The goal of ME 595D is to introduce the fundamentals of discrete element modeling including cellular automata, Monte Carlo, hard particle, and soft particle methods. Students who complete the course successfully are prepared to read the current literature.

Engineering Optics (ME 587)

Pre/Co-requisites: First Semester Senior Standing or higher. Authorized equivalent courses or consent of instructor may be used in satisfying course pre- and co-requisites.

Description: Fundamentals of geometrical and physical optics as related to problems in engineering design and research. Characteristics of imaging systems; properties of light sources; optical properties of materials. Diffraction, interference, polarization, and scattering phenomena as related to optical measurement techniques. Introduction to lasers and holography. (Laboratory work can be undertaken for additional credit by special arrangement.)

Instrumentation for Engineering Measurements (ME 585)

Pre/Co-requisites: Instructor approval is required.

Description: Fundamental concepts of static and dynamic measurements are reviewed. Transducers, signal conditioning, data transmission, and digital data acquisition systems are discussed. Emphasis is on applications and dynamic measurements.

Mechanical Behavior of Materials (ME 569)

Pre/Co-requisites: Prerequisite: MSE 230 (Structure and Properties of Materials). Authorized equivalent courses or consent of instructor may be used in satisfying course pre- and co-requisites.

Description: A study of load and environmental conditions that influence the behavior of materials in service. Elastic and plastic behavior, fracture, fatigue,

low and high temperature behavior. Fracture mechanics. Failure analysis case studies emphasis on design.

Pharmaceutical Solids (IPPH 587)
Pre/Co-requisites: Prerequisite: CHM 372 (Physical Chemistry), IPPH 362 (Basic Pharmaceutics I), IPPH 363 (Basic Pharmaceutics II); one year of calculus. Authorized equivalent courses or consent of instructor may be used in satisfying course pre- and co-requisites.
Description: Provides students with the ability to identify and characterize polymorphs and hydrates and to understand their behavior in the presence of water. Both classical methods and new techniques for the study of pharmaceutical solids and their interaction with water are included. Scientific principles are blended with practical examples to provide a conceptual basis for understanding particular problems.

Powder Processing (MSE 512)
Pre/Co-requisites: First Semester Senior Standing or higher or Masters Student Standing or higher; in engineering or science. Authorized equivalent courses or consent of instructor may be used in satisfying course pre- and co-requisites.
Description: Processing of engineering materials from powders. Synthesis of metals, ceramics, and polymers in powder form. Characteristics of particulates. Behavior of collections of particles; surface forces, particle agglomeration and dispersion, gelation, particle packing. Consolidation of powders; mechanics of dry flow and compaction, slurry rheology, shaping processes. Densification and microstructural development; geometry, thermodynamics, and kinetics of sintering, liquid-phase sintering, reaction densification, infiltration. Powder processing of composites.

Spray Applications and Theory (ME 526)
Pre/Co-requisites: Prerequisite: M E 315 (Heat and Mass Transfer). Authorized equivalent courses or consent of instructor may be used in satisfying course pre- and co-requisites.
Description: Theory of spray formation and evolution as well as treating a host of spray applications. Topics include drop size distributions, breakup of liquid sheets and ligaments, drop formation and breakup, drop motion and the interaction between a spray and its surroundings, drop evaporation, nozzle internal fluid mechanics, external spray characteristics, nozzle performance, and experimental techniques relevant to these subjects. Applications include: (1) agricultural sprays, (2) consumer products, (3) gas turbine combustion, (4) heat transfer, (5) internal combustion engines, (6) paints and coatings, (7) pharmaceutical and medicinal sprays, and (8) spray drying.

Sterile Product Systems (IPPH 577)
Pre/Co-requisites: Consent of the instructor.
Description: A study of the design and manufacture of safe, effective, and reliable sterile pharmaceutical products with emphasis given to parenteral products.