Innovation and Continuous Improvement in Pharmaceutical Manufacturing

Pharmaceutical CGMPs for the 21st Century

The PAT Team and Manufacturing Science Working Group Report: A Summary of Learning, Contributions and Proposed Next Steps for Moving towards the "Desired State" of Pharmaceutical Manufacturing in the 21st Century

Executive Summary

The health of our citizens depends on the availability of safe, effective and affordable medicines. In the future, pharmaceutical manufacturing will need to employ innovation, cutting edge scientific and engineering knowledge, and the best principles of quality management to respond to the challenges of new discoveries (e.g., complex drug delivery systems and nanotechnology) and ways of doing business such as individualized therapies or genetically tailored treatments.

"Pharmaceutical cGMPs for the 21st Century" was intended to enhance and modernize the regulation of pharmaceutical manufacturing and product quality. This report provides an overview of the PAT Team's and Manufacturing Science Working Group's collaborative efforts, accomplishments, and points to consider as the initiative moves into its next phase (implementation and continuous improvement).

The FDA Science Board and the Advisory Committee for Pharmaceutical Science (ACPS) discussions provided information on the current state of pharmaceutical manufacturing, challenges faced, and opportunities for improvement. These discussions are the primary basis of this report.

Pharmaceutical manufacturing operations are inefficient and costly. The cost of low efficiency is generally not understood or appreciated (e.g., manufacturing costs far exceed those for research and development operations). Low efficiency is predominantly due to "self-imposed" constraints in the system (e.g., static manufacturing processes, focus on testing as opposed to quality by design, approach to specifications based on discrete or the so called "zero tolerance" criteria, a less than optimal understanding of variability, etc.). These constraints keep the system in a corrective action mode.

Continuous improvement is an essential element in a modern quality system and it aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. In the current system continuous improvement is difficult, if not impossible. Reducing variability provides a "win-win" opportunity from both public health and industry perspectives, therefore continuous improvement needs to be facilitated.

The PAT Team and the Manufacturing Science Group cooperated internationally to develop a framework to facilitate innovation, application of cutting edge scientific and engineering knowledge, and the principles of modern quality management systems in pharmaceutical manufacturing. A systems approach was adopted to support the

initiative's objectives and conform to its guiding principles. The "desired state" for pharmaceutical manufacturing in the 21st Century was articulated and international consensus established. A regulatory framework to support innovation was developed and described in the *PAT Guidance* document. The principles of this framework are being incorporated into the emerging ICH guidance on *Pharmaceutical Development* (ICH Q8).

Quality by design and process understanding principles were used to develop a flexible regulatory system to support innovation in the PAT Guidance. A team approach to CMC review and CGMP inspections, a recognized best practice (e.g., Team Bio), was used to create the PAT Team to provide appropriate risk coverage. Teambuilding and joint training processes were successful in reducing organizational and communication barriers that existed at the beginning of the initiative. Two assignments, a PAT inspection and pre-operational site visit, have been successfully completed by this team.

The pharmaceutical community was asked take on the responsibility for developing standards to support the introduction of innovative tools and technologies under the PAT framework. The ASTM International provided the process to develop these standards using technical expertise in all relevant disciplines from the pharmaceutical community and other industrial sectors. A significant support infrastructure for the desired state is emerging in several academic and scientific organizations and associations.

A second PAT team is planned and will include CDER's Office of Biotechnology, Office of Compliance and ORA Team-Bio representatives. Formation of the second PAT Team will provide an additional opportunity to develop close collaboration and cooperation between the PAT team and Team-Bio. Lessons learned from the PAT Team and Team-Bio should also be utilized to identify best practices and to develop recommendations for a broader team approach.

ICH Q8 will describe the suggested contents for the 3.2.P.2 Pharmaceutical Development section of a regulatory submission in the ICH M4 Common Technical Document (CTD) format. It is not intended to be a "how to" guidance. It will provide sponsors of drug applications an opportunity to present knowledge gained during development of a product and its manufacturing process and relevant prior knowledge. It will indicate areas where the provision of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches to support continuous improvement.

The PAT framework and ICH Q8 will provide a basis for risk mitigation. Risk management principles and tools being developed under ICH Q9 will be necessary to describe and communicate the level of risk-mitigation achieved through quality by design and process understanding.

Although to a large degree consensus has been established on the "desired state," it is recognized that there is often a tendency for a consensus on collective ends to attenuate when specifics are addressed. This is often due to divergent understanding of the problem being addressed and/or differences in interests and issues in representation of the problem being addressed.

Under the ACPS Manufacturing Subcommittee a working group will be formed to identify specific steps needed to move towards the desired state. The group will also develop illustrative case studies to support the ICH Q8 document and CPG 7132c.08. ICH Q8 and illustrative examples should then be a basis to develop the draft comparability guidance to facilitate continuous improvements.

The combined work products of the CGMP Initiative are positioned well to provide a comprehensive set of regulatory tools to facilitate a move towards the desired state. Only companies that achieve a high level of process understanding will have the opportunity to use their information to justify a more flexible regulatory path towards continuous improvement. The proposed ICH Q10 should utilize these regulatory polices to provide additional guidance on quality system for change control under CGMPs to facilitate continuous improvement.

Significant challenges lie ahead for the pharmaceutical community and for regulators to move to the "desired state" for pharmaceutical manufacturing in the 21st century. Nevertheless, critically important steps have already been taken.

Pharmaceuticals will have an increasingly prominent role in the health care of the future. The health of our citizens depends on the availability of safe, effective and affordable medicines. In the future, pharmaceutical manufacturing will need to employ innovation, cutting edge scientific and engineering knowledge, and the best principles of quality management to respond to the challenges of new discoveries (e.g., complex drug delivery systems and nanotechnology) and ways of doing business such as individualized therapies or genetically tailored treatments.

Regulation of the future will also need to meet these challenges, by incorporating new scientific information into regulatory standards and policies. Both industry and regulatory practices will need to be informed by the best techniques of risk assessment and management. "Pharmaceutical cGMPs for the 21st Century" is intended to enhance and modernize the regulation of pharmaceutical manufacturing and product quality.

Under the CGMP Initiative the PAT Team and the Manufacturing Science Group cooperated internationally to develop a framework to facilitate innovation, application of cutting edge scientific and engineering knowledge, and the principles of modern quality management systems in pharmaceutical manufacturing. This report provides an overview of these collaborative efforts, accomplishments, and points to consider as the initiative moves into its next phase (implementation and continuous improvement).

The FDA Science Board (1) and the Advisory Committee for Pharmaceutical Science (2) discussions on the current state of pharmaceutical manufacturing, challenges faced, and opportunities for improvement are the primary basis of this report. Information gathered at several national and international scientific workshops provided examples of scientific and technological opportunities and afforded the opportunity to debate and develop a shared vision for the future. This vision is articulated as the "desired state" for pharmaceutical manufacturing in the 21st Century.

The PAT Initiative and the PAT Team preceded the CGMP Initiative by about a year; subsequently, the PAT Initiative became a part of the broader CGMP Initiative. Their efforts were directed towards developing a regulatory framework to *encourage the early adoption of new technological advances by the pharmaceutical industry*. The Manufacturing Science Working Group's efforts were directed towards enhancing manufacturing science knowledge available to the agency to ensure that *regulatory review and inspection policies are based on state-of-the-art pharmaceutical science.*

A systems approach was adopted to ensure appropriate linkage and support for all objectives of the CGMP Initiative; i.e., *(1) encourage the early adoption of new technological advances by the pharmaceutical industry, (2) base regulatory review and inspection policies on state-of-the-art pharmaceutical science, (3) facilitate industry application of modern quality management systems, (4) use risk-based approaches that*

focus both industry and agency attention on critical areas; and *(5) incorporate enhanced quality system approaches into the agency's business processes.* Inspiration for a systems approach was derived from the body of work by leaders in modern quality management such as Shewhart, Deming, Juran, Box, Taguchi, and others (3-6). This is reflected in the "desired state" and the regulatory framework described in the *PAT Guidance* document. The principles of this framework were presented to the ICH and these are being considered in the emerging guidance on *Pharmaceutical Development* (ICH Q8).

Continuous improvement is an essential element in a modern quality system that aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. Improvement efforts are carried out in a structured manner with appropriate pre-defined protocol and oversight. These efforts are primarily directed towards reducing variability in process and product quality characteristics and are not for changing the fundamental design of a manufacturing process (5). For continuous improvement products should already be in compliance with their specifications and process improvement steps (e.g., adjustment of process parameters, introduction of new equipment of the same design,and operating principles with advanced control options) should be within the original "design space." That is, such improvement steps are not considered as "changes" because product quality and performance (e.g., bioavailability, shelf-life) are assured.

Generally the term *continuous improvement* is broadly used for all improvement efforts including *corrective actions* and the ensuing *preventive actions*. In the regulatory setting a distinction between corrective action and continuous improvement is essential. Need for corrective actions occur when product quality characteristics are in question (e.g., out of specification). Such a situation can require urgent risk assessment and sound quality decisions to prevent any adverse impact on patients.

Innovation is different from continuous improvement since it is not a part of routine production operations and requires significant investment of resources and may require changes in production design and operation. Therefore, three types of improvement approaches-- *innovation*, *continuous improvement*, and *corrective actions*-- are distinguished. These approaches and their roles in a quality system are shown in Figure 1. The simple phrases used in Figure 1 to describe a modern quality system were suggested by the FDA's Quality System Working Group. Some distinguishing characteristics of the three improvement approaches and the contributions of the two groups are summarized in Table 1. A need for similar distinction between improvement approaches was previously suggested in the automotive industry (7).

The report is organized into six sections. The following section (section 2) describes the "current state" and the "desired state." The primary contributions of the two groups are described in section 3, followed by "points to consider" (section 4) and recommendations for other groups of the initiative (section 5). The final section (section 6) proposes next steps and identifies broad areas for research and training under the Critical Path Initiative. Table 2 provides a summary of primary accomplishments of the two groups within the context of the Initiative's five guiding principles and objectives (dark shading). Contributions to, or impact on, other objectives are outlined as "points to consider."

Many of these "points to consider" are based on some of the 14 points for a quality management system articulated by Deming (3). In Table 2, current and/or planned collaborations with other groups are based on the lessons learned [ ]; recommendations for other groups in the initiative are identified { }.

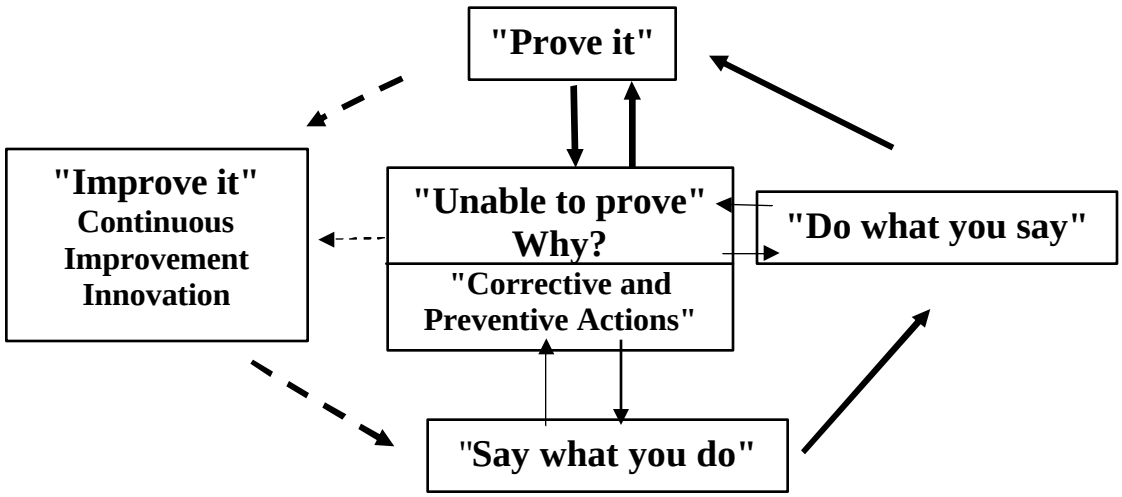

Figure 1: Types of "improvement"

Table 1: Types of improvement and their relation to the objectives of the FDA Initiatives

Improvement Approaches		Characteristics and Objectives
Innovation	Primary focus area of the PAT Team. Manufacturing Science WG is contributing to harmonization of the PAT framework in ICH	Revolutionary, to be a leader Focused applications - project based Significant capital expenditure, ROI, Top-down Strong research component Technical experts involved New findings and improved knowledge CGMP Initiative Objective #1
Continuous Improvement	PAT Framework provides many options and opportunities including research data collection in production. Manufacturing Science WG creating regulatory flexibility through ICH Q8.	Product is in specification Acceptance criteria - variable/continuous data Evolutionary, incremental process optimization, continuous, daily activity Carried out by plant and quality staff CGMP Initiative Objective #1-5
Corrective Actions	PAT opens the door for new tools for root cause investigations and data collection in production. Manufacturing Science provides the foundation for more effective approaches.	Product is out of specification (OOS) or Procedural deviations "Crisis" - immediate action needed Required by regulators CGMP Initiative Objectives: #1-5

Table 2. Report of the of the FDA's CGMP for the 21st Century Initiative's PAT Team and the Manufacturing Science Working Group

Current and/or planned collaborations with other groups, based on lessons learned are shown in [ ]; recommendations for other groups in the initiative are identified in{ }.

Guiding Principles	Objectives				
	Encourage new technological advances	*State-of-the-art pharmaceutical science*	*Risk-based approaches focus industry and agency attention on critical areas*	*Facilitate Industry application of modern quality management*	*Enhanced quality systems approaches into the agency's business processes*
Strong Public Health Protection	Improve focus on process understanding and control	Improve focus on "quality by design" and clinical relevance	Reduce uncertainty to enable risk-based decisions	"Out of the Corrective Action Crisis" to Continuous Improvement	Team approach to CMC Review and CGMP Inspections
Science-based policies and standards	PAT Guidance ASTM Standards	ICH Q8; [CPG 7132c.08] [ICH Q9] [{Comparability Protocol}] {Proposed ICH Q10}	Critical variables - clinical relevance	Science based regulatory flexibility for continuous improvement	Scientific foundation of the FDA's quality system
Risk-based orientation	Regulatory scrutiny based on the level of scientific understanding	Mechanistic basis for understanding failure modes and variability	Sources of variability and "risk to quality"	"Drive out fear"	Continuous Improvement - Change Control & Life Cycle Management
Integrated quality systems orientation	PAT Team: Training, certification, and continuous learning [Team Bio]	Strengthen our education and research infrastructure [{Product Specialist - Pharmaceutical Inspectorate}]	Risk Communication: Knowledge transfer [Risk based site selection for CGMP Inspections]	"Pride of workman-ship" and Continuous Learning	"Pride of workmanship" and Continuous Learning
International cooperation	Communication, workshop, plans for joint training	ICH process, shared vision and "desired state"	Emerging infrastructure for the "desired state"	"Breakdown organizational barriers"	Continuous Improvement - Change Control & Life Cycle Management

Pharmaceutical manufacturing operations are inefficient and costly. Compared to other industrial sectors, the rate of introduction of modern engineering process design principles, new measurement and control technologies, and knowledge management systems is low. Opportunities for improving efficiency and quality assurance through an improved focus on design and control, from an engineering perspective, are not generally well recognized. For example, when discussions at the FDA Science Board and Advisory Committee for Pharmaceutical Science shed light on the current low efficiency and its cost implications (e.g., costs associated with manufacturing can far exceed those for research and development operations in innovator pharmaceutical firms) many at FDA had difficulty understanding this and common reactions were "how could this be possible?" or "this can't be true."

Discussion of the current state by major publications such as The Economist (8), the Wall Street Journal (9) and the Business Week (10) add to a growing awareness of a need for improvement. An excellent analysis of the current state of manufacturing process innovation in pharmaceutical and biotechnology industry was described in 1996 by Pisano (11).

Over the last decade a mind-set has evolved among many pharmaceutical business leaders and others that manufacturing is no longer a necessary "strategic competency." This view probably contributes to the general lack of private and public support for fundamental science and process innovation and to the perception that manufacturing is a "step-child" in this industry. Efficient manufacturing process can reduce manufacturing costs, and this itself can be a significant competitive advantage. Effective and efficient process development contributes more towards a company's ability to accelerate time to market, ramp up production rapidly, enhance customer acceptance of new products, and develop a stronger proprietary position (11).

The public health objectives and the competitive power of new product development are well recognized. Development of new more efficient and effective manufacturing process technology often fails to generate any excitement among academics, practitioners and the public at large; since these groups often only come in contact with innovative products and not with the manufacturing process that delivers these products. A recent estimate of potential world-wide cost-savings from efficiency improvement is suggested to be as high as US $ 90 billon (12). This would be equivalent to the current cost of developing 80-90 new drugs every year. A rigorous economic analysis to obtain robust estimates of cost savings may help to put an end to the lingering question - "how could this be possible?" - and to fully engage the pharmaceutical community for developing approaches to realize the potential "win-win" opportunities.

Quality and productivity improvement share a common element - reduction in variability through process understanding. Reducing variability provides a "win-win" opportunity from both public health and industry perspectives. And, since pharmaceutical product manufacturing technologies and practices are generally similar between both innovator and generic companies, facilitating efficiency improvements provide opportunities for both sectors of the pharmaceutical industry. An efficient and secure US pharmaceutical manufacturing sector will be essential in the 21st Century.

Often it is suggested that regulatory policies and practices contribute to the current low efficiency. Regulators and many in manufacturing operations express their frustration by suggesting that manufacturing is a "step-child" in this industry, and that there is no economic motivation (e.g., cost and price difference) for improvement. Other suggestions include a general lack of systems perspective, organizational barriers that inhibit exchange of knowledge, and the attitude that much of pharmaceutical formulation and process development is an "art." Some in pharmaceutical development suggest that there are very limited opportunities ("development time crunch") to realize and/or demonstrate the level of science underlying current formulation and process development efforts (13). Clearly these are complex and interrelated issues. Only regulatory and scientific challenges are discussed in the following sections.

Discussions at FDA Science Board and Advisory Committee meetings, scientific workshops and conferences identified the following major contributing factors:

- Routine pharmaceutical production is conducted by running a plant at rigidly defined operating conditions described in Standard Operating Procedures (SOP's). A regulatory submission may contain limited information (e.g., manufacturing process and parameters used for *bio-batch* manufacturing and its *executed batch record*) and these conditions then become regulatory commitments. Plant operators are then expected to always reproduce exactly these same set of conditions. During routine production adherence to conditions in SOP's and laboratory evaluation of in-process and final product characteristics provide assurance that products produced will have the safety and efficacy profile outlined in the approved product label. This type of operation may be considered a "static manufacturing operation." Because it is based on limited data, any change generally requires regulatory notification and in many cases prior approval.
- Static manufacturing can create, or is a result of, a mind-set that “the product is approved and validated - do not change.”
- Process control is predominantly based on documented evidence of conformance to SOP's, which generally include a “fixed process time” and laboratory based testing of in-process materials.

    This approach requires a high level of control on incoming raw material characteristics.

Physical characteristics of pharmaceutical materials (e.g., excipients), as related to their functionality in *process*, are not well understood.

- Deviations from established standard operating procedures and out of specification (OOS) observations can occur frequently.

  OOS investigations that follow take significant (time) resources and have a low rate of success in finding permanent corrective and preventive solutions.

  Often batches have to be rejected (internal failure) due to an inability to document quality assurance.

- Variability and/or uncertainty in a measurement system for physical characteristics such as particle size and dissolution can pose significant challenges when OOS results are observed.

- Acceptable quality characteristics, or specifications, are generally described in terms of discrete or attribute data (e.g., pass/fail; or no unit outside 75-125%) and are inappropriately referred to as "zero defect or tolerance" (since these are for the sample tested).

  The OOS rate can increase with increasing test sample size; investigations to identify sources of variability (beyond available information in batch records) and robust estimates of variability are difficult and discouraged (since increasing sample size increases the risk of OOS).

  It is difficult to differentiate inherent or natural variability (or common cause variability) from variability due to special causes.

- Information needed for process improvement can be in a different organization and often not available at the right time.

When OOS results are observed there are few, if any, means to re-examine the fundamental design aspects of a product/process and/or to evaluate the (clinical) relevance of established specification (quality by design). In production, the focus is predominantly limited to "quality of conformance." In terms of risk to conformance; *quality is inversely proportional to variability and quality improvement efforts are directed towards reducing variability* (14*).* Determining corrective and preventive actions without a sound understanding of sources of variability, and robust estimates of variability, are difficult. And, in the absence of good information, attempts to adjust a process can potentially create new problems. Since continuous improvement can only occur when a product is already in compliance, considering the challenges identified above (e.g., "zero tolerance," variability and/or uncertainty in measurement systems, etc.), continuous improvement is difficult (if not impossible) in the current state.

- Lack of information and knowledge creates an uncertain environment that precludes risk-based decisions.

  Static manufacturing processes and reliance on laboratory testing as a means for control are, in part, a result of insufficient information available during the CMC review process. In the absence of an adequate level of process understanding, specifications have to be established without adequate knowledge of variability in the clinical trial products and its clinical relevance.

- Measurement system variability can be a significant part of total variability.

  Estimates of process variability are based on measurement of variability in quality characteristics of in-process materials and products. The measurement system (sampling, sample preparation, analytical method, operator training, etc.) then is the "*lens through which we observe a process"* and its variability can contribute to OOS observations and can be the limit to which we can observe and/or improve a manufacturing process. Over the last three decades tremendous progress has been made in analytical chemistry and variability in chemical methods has been reduced dramatically. The situation is quite different for methods used to measure physical characteristics.

  Currently, significant challenges exist for managing variability in sampling and sample preparation (e.g., for blend uniformity and particle size testing), and analytical instruments for physical characteristics such as dissolution and particle size.

  - Current tests are generally destructive (i.e., sample is altered or destroyed) and robust estimates of measurement system variability (all aspects of the procedure including the operators) are difficult to obtain without using methods such as Gauge R&R - reproducibility and repeatability (14). Suitability of current methods then is based on calibration using a calibrator system that has its own built-in variability and other assumptions (e.g., in physical testing such characteristics as size, shape, density can alter aerodynamic and/or hydrodynamic behaviour of materials in a test system and contribute to systems variability).

  In the absence of robust estimates of measurement system variability and with the inability to verify the inherent assumptions in a measurement system, attempts at improving a manufacturing process can be difficult and, if attempted, can potentially create new problems (e.g., in case of common cause variability, process adjustments can make a system unstable) (3).

- The term "in-process testing" is synonymous with "process control." From an engineering perspective tests at the end of a process do not provide any direct means to keep a process under "control." It is well recognized that such tests "*simply accept or reject lots"* and depending on the operating characteristic curve of a test "*accepted lots are no better than the rejected ones"* (14).

A multidisciplinary communication challenge and a general lack of awareness of scientific developments in different disciplines contribute to a suspicion about the level of control achieved through product and process design (the "art" argument). The pharmaceutical science and engineering knowledge developed over the last two decades is not optimally relied upon for decision making in regulatory and/or quality assurance settings.

The value and utility of new advances in process technologies such as on-line process analyzers and controls (e.g., feedforward and feedback controls) are not widely recognized. A common misperception is that testing is the only valid approach; when in fact, reliance on testing for quality assurance is a 19th Century concept and is a lesser form of quality assurance compared to what can be achieved through design and control. The CGMP regulations and practices have long recognized this principle. The following quote from an FDA Warning Letter illustrates this principle: *"The practice of partial releases, no matter how stringent the re-sampling, raises doubt as to the safety and efficacy of the product being released. It is not acceptable to substitute testing over adequate control of a process."*

- Similar and repeating OOS observations (e.g., dissolution failures) for different products across the industry and the inability to find "root causes" suggest that some of these observations may be due to variability from "common causes" (i.e., inherent variability in raw materials, equipment, measurement system etc.).

  Furthermore, variable and unstable external calibrators (e.g., USP Prednisone Tablets RS) raise questions with regard to the stability of a measurement system. Organizational and functional barriers (e.g., analytical and production) add to this challenge through an information/knowledge gap or disconnect between measurement and manufacturing process and questions on stability, reproducibility, and repeatability of the measurement system in the context of variability and OOS may not be addressed adequately.

- When the source of variability is from common cause(s) it is essentially a part of the clinical trial materials and, therefore, included in the clinical assessment of safety and efficacy and part of the FDA approval decision.

  Adequate characterization of clinical trial materials to describe variability in quality characteristics and the application of "robust design" principles (6) can provide opportunities for reducing (regulatory) uncertainties regarding product failure modes, reliability of controls to prevent failures and the level of quality assurance achieved by design.

  Reducing uncertainty is a prerequisite for sound risk-based decisions.

Improving the foundation of manufacturing science in our current manufacturing practices should be the primary basis for moving away from the corrective action "crisis" to continuous improvement. Knowledge of the "variation theory" is, therefore, an essential element of manufacturing science. It requires an in-depth understanding of a process or system (15):

> *"Cease dependence on inspection* [testing]. *Depending on inspection is like treating a symptom while the disease is killing you. The need for inspection results from excessive variability in the process. The disease is variability. Ceasing dependence on inspection means you must understand your processes so well that you can predict the quality of their outputs from upstream activities and measurements. To accomplish this you must have a thorough understanding of the sources of variation in your processes and then work towards reducing the variation. Ceasing dependence on inspection forces you to reduce variability.*"

The "desired state" for pharmaceutical manufacturing in the 21st Century therefore emphasizes and aims to improve knowledge on design and understanding of product and processes. When such information and knowledge is shared with FDA it can then be a basis to recognize different levels of understanding achieved by companies and to utilize this information in risk-based decision criteria. With this as the background, the "desired state" was articulated in the second progress report of the CGMP Initiative (February 20th 2003):

> *Pharmaceutical manufacturing is evolving from an art form to one that is now science and engineering based. Effectively using this knowledge in regulatory decisions in establishing specifications and evaluating manufacturing processes can substantially improve the efficiency of both manufacturing and regulatory processes. This initiative is designed to do just that through an integrated systems approach to product quality regulation founded on sound science and engineering principles for assessing and mitigating risks of poor product and process quality in the context of the intended use of pharmaceutical products. In this regard, the desired future state of pharmaceutical manufacturing may be characterized as:*
>
> > *Product quality and performance achieved and assured by design of effective and efficient manufacturing processes*
> >
> > *Product specifications based on mechanistic understanding of how formulation and process factors impact product performance*
> >
> > *Continuous "real time" assurance of quality*
> >
> > *Regulatory policies and procedures tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability*
> >
> > *Risk based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors*

affect product quality and performance and the capability of process control strategies to prevent or mitigate risk of producing a poor quality product

This description reflects a view from the manufacturing side - "beginning with the end in mind." Therefore, the goal "*Product quality and performance achieved and assured by design of effective and efficient manufacturing processes"* is placed before "*Product specifications based on mechanistic understanding of how formulation and process factors impact product performance*."

Mechanistic understanding, as opposed to data derived from one-factor-at-time type of experiment or simple correlative information, provides a higher level of knowledge and an ability to generalize within certain constraints. This provides an opportunity to develop a flexible regulatory system with appropriate risk coverage; for example a team approach to CMC reviews and CGMP inspections (e.g., need for prior approval of post approval changes vs. information to be held on site and available during inspections).

A manufacturing process is generally considered well understood when (a) all critical sources of variability are identified and explained, (b) variability is managed by the process, and (c) product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, environmental and other conditions. The ability to predict reflects a high degree of process understanding. Companies that achieve a high level of process understanding should have an opportunity to use their information to justify a more flexible regulatory path towards continuous improvement.

Risk-based decision criteria would then have to relate to clinical relevance; different levels of understanding (e.g., correlative, causal, mechanistic) will need to be recognized within this context. This general approach is utilized in some current regulatory policies; in the desired state the approach can be extended to other areas. For example in current regulatory policies;

- Establishing *in vitro in vivo* correlation (IVIVC) for modified release dosage form provides a justification for waiving *in vivo* bioequivalence evaluation only for certain specified post approval changes. Since a correlation is dependent on the mechanism of drug release, it is not used in situations that could potentially alter its mechanism (16)
- Waiver of *in vivo* bioequivalence studies for major post approval manufacturing changes for the BCS Class I (Biopharmaceutics Classification System; highly soluble, highly permeable and rapidly dissolving) solid oral products is NOT recommended for narrow therapeutic index drugs (17).

An objective metric is needed to gauge the level of manufacturing process understandings and control achieved - *process capability* can be this metric. During development studies, process capability analysis can be performed in terms of probability distribution (type of distribution, mean and variability) without regard to specifications (14); such analysis can provide useful supporting information on variability and may provide additional support

for proposed regulatory acceptance criteria. Inherent variability in clinical materials can then be a benchmark and a basis for continuous improvement.

The quality of design (product and its manufacturing process)-- the ability to reliably predict quality and performance, process monitoring and controls, process capability and appropriate risk-mitigation strategies-- provides an opportunity to achieve "real time" quality assurance (the ultimate level of efficiency). This also provides an excellent opportunity to develop efficient and effective quality assurance systems as an alternative to market or public standards (18).

Assessment of process capability and statistical process control brings the ability to distinguish between a stable and un-stable process and provides a means to distinguish between different causes of variability, e.g., common cause, special cause, structural (e.g., seasonal), and tampering (e.g., deliberate or unintentional). Process understanding, quality by design and capability analysis can facilitate risk-based regulatory decisions for continuous improvements:

> *Regulatory policies and procedures tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability.*
>
> *Risk based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance and the capability of process control strategies to prevent or mitigate risk of producing a poor quality product.*

It is expected that different companies will develop different levels of process understanding and the level of understanding for a particular product can increase over time (life cycle). These differences will need to be accommodated in regulatory policies through a clear articulation of what is a minimum regulatory expectation (e.g., current requirements of CMC review information and process validation) and what is an optional opportunity for companies to improve efficiency while reducing risk to quality and regulatory concerns.

3.1.

3.1.1 Strong public health protection

The basic tenant of a modern quality system is that quality *cannot be tested into products; it should be built in by design*. An emphasis on *building quality into products* allows an improved focus on relevant multi-factorial relationships among material factors, manufacturing process and environmental variables, and their collective impact on quality. These relationships provide a basis for identifying and understanding interactions among various critical formulation and process factors and for developing effective risk mitigation strategies (e.g.,

product specifications, process controls, SOP's, training). This can improve identification and evaluation of product and process variables that are critical to product quality and performance. A higher level of process understanding should reduce uncertainty and improve FDA's ability to make scientific risk- based decisions.

The PAT guidance facilitates introduction of new measurement and control tools in conjunction with well-established statistical methods such as design of experiments and statistical process control. It, therefore, can provide more effective means for product and process design and control, alternate efficient approaches for quality assurance, and a means for moving away from the corrective action to a continuous improvement paradigm.

3.1.2 Science-based policies and standards

This guidance describes a regulatory framework that will encourage the voluntary development and implementation of innovative approaches in pharmaceutical development, manufacturing, and quality assurance. Many new technologies are currently available that provide information on physical, chemical, (micro)biological characteristics of materials to improve process understanding and to measure, control, and/or predict quality and performance. The guidance facilitates introduction of such new technologies to improve efficiency and effectiveness of manufacturing process design and control (e.g., feedforward and feedback controls) and quality assurance. Gains in quality and efficiency will vary depending on a process and a product, and are likely to come from:

Reducing production cycle times by using on-, in-, and/or at-line measurements and controls

Preventing rejects, scrap, and re-processing

Real time release

Increasing automation to improve operator safety and reduce human error

Improving energy and material use and increasing capacity

Facilitating continuous processing to improve efficiency and manage variability

Innovation in manufacturing is the responsibility of private sector and non-regulatory public sector. The PAT Guidance provided the regulatory framework to facilitate innovation in the interest of the public health. FDA resources are

limited and have to be focused on core regulatory responsibilities. Therefore, the broader pharmaceutical community should take on the responsibility for developing standards to support the introduction of innovative tools and technologies. In this regard, ASTM International provides an excellent process to develop standards in a timely manner using technical expertise in all relevant disciplines from the pharmaceutical community and other industrial sectors. Therefore, the FDA's PAT team worked with ASTM to establish Technical Committee E55 on Pharmaceutical Application of Process Analytical Technology.

Focusing on process monitoring and control, instead of testing, requires process control standards consistent with guiding principles of the control theory. ASTM provides an opportunity to bring a strong engineering process control perspective and to learn from other industrial sectors that have utilized process analyzers and controls for many years. The E55 committee is tasked with developing standards related to process analytical technology with the primary focus on process understanding and control. The PAT Team is represented on E55 committees. Three subcommittees of E55 include: PAT System Management, PAT System Implementation and Practice, and PAT Terminology. The standard *E2363-04: Standard Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry* was recently published.

3.1.3 Risk-based orientation

The PAT Guidance recognizes that within an established quality system and for a particular manufacturing process, one would expect an inverse relationship between the level of process understanding and the risk of producing a poor quality product. For processes that are well understood, opportunities exist to develop less restrictive regulatory approaches to manage change.

Collaboration with the Risk-Based Site Selection Working Group of the initiative is on-going. Development of ICH Q9 guidance will provide additional risk tools and principles and facilitate international harmonization of these principles.

3.1.4 Integrated quality system orientation

By definition PAT brings a systems perspective on design and control of manufacturing processes. Therefore, a systems approach is needed for regulatory assessment of PAT applications. To achieve this objective, the PAT Team for CMC review and CGMP inspection was created. It includes reviewers, investigators and compliance officers. A comprehensive scientific training program was developed with guidance from the Advisory Committee for Pharmaceutical Science's PAT Subcommittee. The training (didactic and practicum) was provided by academic and industrial experts. Three scientific disciplines, process analytical chemistry (University of Washington, Seattle; National Science Foundation (NSF) Center for Process Analytical Chemistry); industrial & physical pharmacy (Purdue University; NSF Center for Pharmaceutical Process Research), and chemical engineering (University of Tennessee; NSF Measurement Control Engineering Center) were included in training for the PAT Team.

The team members trained together. As a part of their certification process they were asked to work as a team to address comments received on the draft guidance. Two assignments, a PAT inspection and pre-operational site visit, have been successfully completed by this team. Several team members have participated in a number of scientific conferences. The feedback received from their instructors, conference participants and companies has been very positive. The many organizational and communication barriers that existed at the beginning of the initiative are being removed and the team members are functioning as a team committed to a common purpose.

The integrated quality system orientation afforded a flexible regulatory approach for implementation of PAT. For example, regulatory implementation plans can include:

PAT can be implemented under the facility's own quality system. CGMP inspections by the PAT Team or PAT certified investigator can precede, or follow, PAT implementation.

A supplement (CBE, CBE-30 or PAS) can be submitted to the Agency prior to implementation, and, if necessary, an inspection can be performed by a PAT Team or PAT-Certified Investigator before implementation.

A *comparability protocol* can be submitted to the Agency outlining PAT research, validation and implementation strategies, and time lines. Following approval of this *comparability protocol* by the Agency, one or a combination of the above regulatory pathways can be adopted for implementation.

3.1.5 International cooperation

Extensive international scientific collaboration was sought from the very beginning. For example, before the July 2001 ACPS discussion on PAT, FDA staff participated in the Royal Pharmaceutical Society's New Technology Forum (a collaborative effort between the Medicines Control Agency, now referred to as the Medicines and Healthcare Products Regulatory Agency, and the British pharmaceutical industry). These discussions were very valuable and contributed in the development of the FDA's PAT Initiative (21). The list of international scientific conferences and workshops on PAT in the past three years is too long to list. Almost every pharmaceutical scientific association in the US, Europe, and Japan has organized PAT conferences, and some have made PAT conferences an annual event (for example, the International Society of Pharmaceutical Engineering (ISPE) and the International Forum of Process Analytical Chemistry (IFPAC)). The Pharmaceutical Technology section of the American Association of Pharmaceutical Sciences in collaboration with the Royal Pharmaceutical Society organized two consecutive Arden House Conferences in the US and UK on the FDA Initiatives in 2003 (PAT Initiative) and the proposed "desired state" of pharmaceutical manufacturing (2004). These and other scientific conferences afforded an opportunity to discuss the FDA initiative with industry, academia and regulatory colleagues from Canada, Europe and Japan.

The European Medicines Agency has established an EMEA PAT team and established contact with FDA's PAT team. In the near future FDA plans to share with the EMEA Team PAT training materials and lessons learned.

Following the issuance of the PAT Guidance workshops are planned in the three ICH regions. The European Workshop will provide an opportunity for the EMEA and FDA PAT teams to further collaborate on regulatory implementation of PAT. Similarly the planned workshop in Japan will afford an opportunity to further strengthen the collaboration between FDA and MHLW. Health Canada has been invited to participate with FDA in the second PAT training program planned for the 2004-2005 fiscal year.

The definition of PAT in the FDA guidance and ASTM E55 and other concepts are being incorporated into the ICH Q8 guidance. The ASTM International provides another venue for international cooperation and the current E55 membership reflects broad international interest in these standards.

Several academic institutions in the US, Europe, Switzerland, and Japan have incorporated PAT concepts in their curricula. Some of the FDA PAT Team members have been requested to serve as adjunct professors to teach and to participate on doctoral dissertation committees on PAT research projects.

3.2.1 Strong public health protection

Information on pharmaceutical development studies in new drug applications is generally limited and varies from application to application. This creates an uncertain environment and curtails FDA reviewers' ability to make risk-based decisions and inhibits their ability to recognize and assess how quality was built in. Risk communication between review and inspection staff is also inhibited. Appropriate pharmaceutical development information can improve public health by improving FDA's risk-based decisions and by facilitating continuous improvement.

3.2.2 Science-based policies and standards

During the July 2003 ICH meeting in Brussels, agreement was reached on a common vision and approach for developing an international plan for a harmonized pharmaceutical quality system that would be applicable across the life cycle of a product. This plan emphasizes an integrated approach to review (assessment) and inspection based on scientific risk assessment and risk management. Several actions were outlined to implement this vision. An expert-working group (ICH Q8 EWG) was established to develop guidance for pharmaceutical development.

The "desired state" description was adopted with slight modification:

Product quality and performance achieved and assured by design of effective and efficient manufacturing processes.

Product specifications based on mechanistic understanding of how formulation and process factors impact product performance.

An ability to affect continuous improvement and continuous "real time" assurance of quality.

The ICH Q8 guidance is currently being developed and is expected to reach the ICH Step 2 in November 2004. It is intended to provide guidance on the contents of Section 3.2.P.2 (Pharmaceutical Development) for drug products as defined in the scope of Module 3 of the Common Technical Document (ICH topic M4).

3.2.3 Risk-based orientation

Collaboration with the ICH Q9 is an important element. This collaboration will provide a means to connect the scientific framework in ICH Q8 to risk-management principles being developed by ICH Q9.

ICH Q8 creates an opportunity for an applicant to demonstrate an enhanced knowledge of product performance over a wider range of material attributes (e.g. particle size distribution, moisture content, and flow properties), processing options and process parameters. This knowledge can be gained in a structured manner by, for example, applications of formal experimental designs, PAT concepts, or risk management tools (e.g., failure mode effect analysis or FMEA). Such knowledge can allow regulatory agencies to develop more flexible regulatory approaches, for example, to:

facilitate risk based regulatory decisions (reviews and inspections);
implement manufacturing process improvements, within the boundaries of the knowledge described in the dossier, without the need for regulatory review;
implement "real time" quality control, leading to a reduction of end-product release testing

3.2.4 Integrated quality system orientation

The ICH Q8 guidance on Pharmaceutical Development section is intended for use both by CMC reviewers and CGMP investigators. Because the aim of pharmaceutical development is to design a quality product and a manufacturing process to deliver the product in a reproducible manner, the information and knowledge gained from pharmaceutical development studies should provide additional scientific understanding to support establishing more relevant specifications and manufacturing controls.

Information from pharmaceutical development studies can be the basis for risk management when these studies are designed with the aim of demonstrating that

quality was *built in by design*. This document and the manufacturing science framework provide an area of "common interest" and opportunity for collaboration between the CMC review and CGMP investigations staff.

3.2.5 International cooperation

The Manufacturing Science Working Group collaborated with the Product Quality Research Institute (PQRI) to organize the first workshop (April, 2003) of the CGMP Initiative. This was an international workshop and provided an opportunity to explain the goals and objectives of the initiative and to seek stakeholder input (http://www.pqri.org/gmpworkshop/).

A second workshop was organized in The Netherlands (November 19-21, 2003) by the International Pharmaceutical Federation (FIP). This was in collaboration with FDA, EMEA, and other European trade and professional associations (EFPIA, EUFEPS, APIC/CEFIC and IPEC) http://www.qualityworkshop.nl/html/welkom.html .

4.1.1. Reduce uncertainty to enable risk-based decisions; critical variables and link to clinical relevance; sources of variability and "risk to quality"

Currently a high degree of uncertainty with respect to critical variables, sources of variability and their clinical relevance delays approval of certain complex drug delivery systems (e.g., inhalation products). With increasing complexity in drugs and drug delivery systems this challenge is anticipated to increase and is likely to result in multiple review cycles for new drug applications and/or an inability to approve generic drug products in a timely manner.

Furthermore, significant industry and FDA resources are spent debating issues related to acceptable variability, need for additional in-process testing and how specification acceptance limits should be established. Often these debates are focused on acceptance limits or the statistical aspects. In these debates a proportionate focus on the underlying manufacturing science is often missing. For example;

The protracted (about 10 years) debate on the issue of blend sampling and the relevance of in-process blend uniformity testing focused mainly on testing and statistics and did not fully leverage the manufacturing science aspect of the challenge. The PQRI proposal took a few steps in this direction (2, ACPS November 2001); today the full potential of a manufacturing science framework remains to be realized.

For the last three years FDA and an industry group (IPAC-RS) have been debating a parametric tolerance interval test (PTIT) for delivered dose uniformity of inhalation products. The proposed PTIT approach has many desirable features including an approach to move away from the discrete/attribute criteria. However, uncertainties in what is "acceptable" variability have continued the debate for an extended period of time. Additionally, a focus on statistics alone has created a situation where the discussions have focused on "hypothesis testing" in routine production - i.e., testing to document quality instead of process control principles. The concept of "hypothesis testing" should essentially end at the process validation stage (2, ACPS October 2003).

4.1.2. Risk communication: Knowledge transfer and management

A major element in risk management is risk communication. The challenge of risk communication between industry and FDA and within FDA should not be underestimated. It would be erroneous to assume that manufacturing science can resolve all important risk to quality issues. Manufacturing science principles combined with effective risk management tools such as fault trees, failure mode effect analysis (FMEA) can provide a structure for risk-based decisions. Effective and efficient risk-decisions will require communication and collaboration between the CMC review and CGMP inspection functions, common data/knowledge bases, and a continuous learning and improvement approach.

4.1.3. Emerging support infrastructure for the "desired state"

Several academic institutions in the US, Europe, Switzerland, and Japan have incorporated PAT concepts in their curricula and several graduate students at these institutions are engaged in PAT research. Industry and academic collaborations (e.g., Consortium for Advanced Manufacturing of Pharmaceuticals or CAMP) are providing additional support.

In addition to numerous commercial vendors, several international scientific associations and societies have developed programs to support the "desired state." A few examples are provided below.

- The Royal Pharmaceutical Society's New Technology Forum (NTF) has continued its discussions on PAT with participation of FDA PAT Team members.

  Forum 5: Multivariate mathematical approaches
  Forum 6: Rapid methods in microbiology

- The Product Quality Research Institute

  Several ongoing and planned projects are focused on manufacturing science. The Manufacturing Technical Committee

has been established and projects such as “Process Robustness of Oral Solid Dosage” are being developed (http://www.pqri.org). Several other PQRI projects (e.g., on excipients and dissolution testing) are essentially attempting to address common cause variability challenges in the current system.

The ASTM E55 and other efforts such as NTF and PQRI are intended to be complementary in supporting PAT and the manufacturing science framework and to create a path to move efficiently towards the "desired state." The ASTM E55 focus on innovation should provide a "pull" on the "current state" to move it towards the "desired state" while the PQRI efforts provide the "push." The efforts of E55 on developing a standard for process understanding should provide a basis to ensure alignment of efforts and to create a synergistic "pull and push" vector in the direction of the "desired state."

- International Forum for Process Analytical Technology Manufacturer’s Association (IFPATMA)

  http://www.ifpacma.org/ifpacMA-Benefits.html

  IFPATMA is a not-for-profit consortium of manufacturers/suppliers dedicated to the advancement of quality systems for PAT in the pharmaceutical and related industries. The organization has a goal of standardization of practices for process analyzers and reducing the sensor qualification burden on pharmaceutical companies. Its efforts are aligned with ASTM E55 activities and with other organizations having similar goals.

- International Society of Pharmaceutical Engineering (ISPE) is developing a number of programs to support the "desired state" of pharmaceutical manufacturing. For example:

  Discussions have been initiated to define the role and training needs of pharmaceutical engineering professionals.

  A process equipment manufacturers’ forum is under consideration to (a) enable and foster a risk-based approach to manufacturing and compliance, (b) accommodate new PAT technologies and implementation requirements, (c) speed the delivery of manufacturing capacity, and (d) improve quality while reducing costs, through a restructuring of current equipment qualification practices.

  Creation of a peer-reviewed journal for science, engineering and Process Analytical Technology. The first issue is anticipated in January of 2006.

- American Association of Pharmaceutical Scientists (AAPS)

  AAPS conferences (e.g., the Arden House Conference) and workshops provided help in defining the "desired state." An AAPS PAT focus group has been established. http://www.aapspharmaceutica.com/inside/focus_groups/PAT/index.asp

4.2. Facilitate industry application of modern quality management

4.2.1. "Out of the Corrective Action Crisis": Continuous Improvements

It can be argued that current low efficiency in pharmaceutical manufacturing is partly due to "self-imposed" constraints (e.g., approach to specifications based on discrete or the so called "zero tolerance" criteria, a less than optimal understanding of variability, etc.). This contributes towards keeping the current system in a corrective action mode. This approach also curtails our ability to prepare for future challenges.

Some would argue that corrective actions provide the necessary "constancy of purpose for improvement" and are necessary since manufacturing is a "step-child" of the industry because the difference between "cost of manufacturing" and the "price of drugs" is large. Keeping the system in "corrective action mode" provides the leverage for ensuring improvements (i.e., to ensure the "current" in the CGMP's).

The argument has some validity, but it is based on an assumption that current practices (e.g., including measurement systems and product specifications) provide efficient means for identifying, understanding and then reducing variability (i.e., improvement). Quality assurance in the 21st Century will need a sound basis for verifying such assumptions in the current system. To emphasize this point further, the case of dissolution test is cited again - the manner in which the current dissolution test is used provides good estimates of the mean dissolution profiles. However, in terms of variability (the dominant cause of OOS) the current approach to calibration and additional challenges in verifying certain inherent assumptions (e.g., relevance of hydrodynamic variability) makes it difficult for a commercial manufacturer to verify inherent assumptions and to document lower variability than the USP calibrator tablets. Therefore, without the ability to understand and document variability reduction (improvement) the "corrective action mode" may not be able to facilitate improvement in many situations. There are other undesirable consequences, such as:

- A constant "corrective action mode" amounts to "crying wolf" on a very frequent basis thus making the system less responsive to situations when a "real wolf" appears.
- This mode produces anxiety, fear, and disincentives to improvement among the production staff. This can set up an environment of high risk to quality and safety. Some aspects of this are further illustrated in section 4.2.3.

4.2.2. Science based regulatory flexibility for continuous improvements

The concept of continuous improvement has a long history and a well founded structure and format as exemplified by the Evolutionary Operations or EVOP (5) and the "Kizen" principles. Kizen (*Ky' zen)* is a Japanese word introduced in the West (~late 70's) and translated as "Continuous Improvement"—slow, incremental, but constant.

The basic philosophy of EVOP is that "it is inefficient to run an industrial process in such a way that only a product is produced, and that a process should be operated so as to produce not only a product but also information on how to improve the product." Effective knowledge transfer and communication between organizations is essential for continuous improvement; equally important is a system to collect and analyze information throughout a product's life cycle. Such a system can assist in identifying and addressing sources of variability and sharing this information with all organizations (e.g., development, regulatory, etc.).

In the current system the "fear" of finding a ("new") source of variability inhibits information collection on commercial products beyond the batch records. Although the PAT Guidance provides a regulatory mechanism to address this issue by clarifying that additional information is research data, it is limited to PAT applications. The concept of continued learning in the production setting should be encouraged in the entire regulatory system.

4.2.3. "Drive out fear" that inhibits continuous learning and improvement, and that which can increase risk

It is important to appreciate that there are many dimensions to the challenge of "fear." For those who may engage in amoral or unethical behaviour, the regulatory "fear" is a desirable deterrent. Quality by design and process understanding aspects of manufacturing science provide the regulatory system with additional means to address many of the "undesirable" and "desirable" dimensions of "fear."

- Fear is contradictory to continuous improvement and a broad regulatory approach is needed to address this challenge. Timely risk assessment, communication, information, and collaboration between CMC review and CGMP inspection functions will be

essential components of such a regulatory approach. In addition, common data bases and information systems will be necessary.

- A combination of "fear" (of failure) and insufficient process understanding can create situations that can increase risk. The following example illustrates this point.

  The Warning Letter citation below may be an example of a poorly understood process since OOS investigations were unable to determine the root cause(s) of the problem. In order to conform to in-process blend uniformity test specifications, powder blends were either enriched with additional drug or diluted with other ingredients. In an essentially closed system (blender) this is an unacceptable practice (a violation of *"Do what you say"*) and can pose significant risk to patients.

  The example emphasizes that process understanding and quality by design principles offer a more attractive means to mitigate risks posed in the following example:

PRODUCTION SYSTEM

4. Deviations from approved drug formulations are performed when in-process specifications are not met. The deviations consist of adding varying quantities of active ingredient or diluting the batch. There are no validation studies to assure that there is no adverse product impact throughout shelf life. Investigations do not always determine the cause of the abnormal assay result or corrective/preventive action. For example:

a. In-process assay of [redacted] revealed low potency results ranging from [redacted] (specifications are [redacted]. An additional quantity of [redacted] of the active ingredient was added to the batch. There is no determination into the cause of the low assay or preventative actions from recurrence.

4.2.4. "Pride of workmanship" and Continuous Learning

Frequent corrective actions take away the "pride of workmanship" from production operators and other staff in industrial operations. In addition, FDA's penalty system (e.g., Warning Letters) is often construed to be directed at industrial operations. The ability to distinguish between common cause and special cause variability can be an important element in the FDA's penalty system and facilitate a move towards a continuous improvement approach and help build/improve the "pride of workmanship" dimension.

4.3.1. PAT Team Approach to CMC Review and CGMP Inspections

The value and advantages of a team approach to CMC review and CGMP inspections has been recognized and practiced for many years (e.g., Team Bio). This principle was utilized to develop the PAT Team. However, to accommodate specific objectives of the initiative and the need for a systems approach in the PAT Team, a joint training and certification process with team building was developed. The entire team of CMC reviewers, CGMP investigators, and compliance officers trained together on all aspects of PAT.

To ensure that this team concept is "institutionalized" and for its continuous improvement, the PAT Team process will be under the FDA's Quality Systems Framework. This should also help in ensuring quality and consistency of reviews, inspections, and other regulatory activities.

4.3.2. Manufacturing Science foundation of the FDA's Quality System

The number of "quality movement" or trends in the 20th Century (1950's - Sampling plans; 1960's Zero-Defect Movement; 1980's - ISO-9000 & Malcolm Baldrige Award; 1990's - QS-9000, Total Quality Management, Six Sigma, etc) can create a perception that these trends are "lurching from fad to fad" or suggest that these trends represent continuous improvement towards an ideal quality system (22). An element that is essential to recognize is that of process understanding; without process understanding, the effectiveness of any quality system will be limited and without a sound manufacturing science foundation, a pharmaceutical quality system will fail to realize its full potential. A quality system should provide a sound framework for the transfer of process knowledge from development to the commercial manufacturing processes and for post development changes and optimization (23).

4.3.3. Continuous Improvement - Change Control and Life Cycle Management

A flexible, science and risk-based approach to post approval changes will be essential to facilitate continuous improvement. Regulatory mechanisms for "life cycle management" are necessary. "Change Control" is a well-known CGMP regulatory concept that focuses on managing change to prevent unintended consequences and this can be a path towards continuous improvement. In this regard, *change* towards continuous improvement should be encouraged. This means a manufacturer is empowered to make changes based on the variability of

materials used in manufacturing and optimization of the process from learning over time (23); therefore, a company's quality system should consider this opportunity. Regulatory management of a flexible "change control" process will require a team approach to CMC review and CGMP inspections, in many ways similar to the PAT team process.

4.3.4. "Pride of Workmanship" and "Continuous Learning"

Pride of workmanship of FDA staff should be an essential element of the FDA's Quality System. Manufacturing science and PAT training and professional development opportunities should provide a means for FDA staff to be recognized as leaders in a number of scientific and technical areas. Continuing education and training programs should therefore be supported and be a part of the quality system. The concept of "peer review" should be considered and mechanisms developed to recognize scientific and regulatory contributions that help the pharmaceutical community move towards the "desired state."

4.3.5. Break down organizational barriers

Success of the CGMP Initiative depends on a team approach to pharmaceutical quality. Lessons learned from the PAT team building activities suggest that organizational barriers can be removed through open dialogue and opportunities to engage in activities that relate to areas of common interests. The manufacturing science vocabulary and systems thinking it induces can also facilitate international discussions (e.g., in ICH and PIC/S) and cooperation.

5.1. Team Bio and PAT Team

During the course of the CGMP Initiative the PAT team was developed and implemented through collaboration between ORA, CVM and CDER. The Office of Biotechnology moved into CDER towards the end of the PAT training process. The final guidance extends the PAT framework to CDER's Office of Biotechnology (OBP). PAT applications will be managed through collaborations with the PAT Team. A second PAT team is planned and will include CDER's Office of Biotechnology, Office of Compliance and ORA Team-Bio representatives. Formation of the second PAT Team will provide an additional opportunity to develop close collaboration and cooperation between the PAT team and Team-Bio. This opportunity should be utilized to identify best practices and to develop recommendations for a broader team approach.

5.2. ICH Q9 & Risk based site selection model for CGMP inspections

A structured regulatory format for risk assessment and management will be essential for moving towards the "desired state." The PAT framework and ICH Q8 will provide a basis for risk mitigation. Risk management principles and tools will be necessary to describe and communicate the level of risk-mitigation achieved through quality by design and process understanding. Therefore, the principles and tools for risk management and communication currently being developed in ICH Q9 and the emerging risk based site selection model for CGMP inspections should connect well with the manufacturing science and the PAT framework to ensure:

> *Regulatory policies and procedures tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability*.
>
> *Risk based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance and the capability of process control strategies to prevent or mitigate risk of producing a poor quality product.*

5.3. Changes without prior review: draft guidance, Comparability Protocol

A flexible, science and risk-based approach to *post approval changes* will be essential to facilitate continuous improvement. The new compliance policy guide CPG 7132c.08 recognizes the role of emerging advanced engineering principles and control technologies in ensuring batch quality (24). For drugs produced using these new principles and technologies, this CPG provides for possible exceptions to the need for manufacturing multiple conformance batches prior to initial marketing. This version also deletes the previous reference to "three" validation (or conformance) batches at commercial scale as adequate minimum proof of process validity — a number is no longer suggested. This is a major step forward in facilitating continuous improvement.

As discussed in section 4.3.3. *Change* towards continuous improvement should be encouraged. Quality by design and process understanding can provide a basis to allow those manufacturer that have demonstrated adequate level of process understanding to make *changes without prior review* within the "change control" provisions of their quality system under the CGMP inspectional oversight.

Although progress on ICH Q8 has been significant, additional work is necessary to articulate the relationship between *"adequate level of process understanding and regulatory flexibility to make changes without prior review.*" At the recommendations of the ACPS Manufacturing Subcommittee (July 2004) a working group will be assembled to develop illustrative case examples. ICH Q8 and illustrative examples should then be a basis to further improve the draft comparability guidance to facilitate continuous improvements.

5.4. Proposed ICH Q10

Life cycle management and change control provide a mechanism for continuous improvement. To support continuous improvement through change control a quality system would need to be based on principles of manufacturing science and risk-management. The proposed ICH Q10 guidance is an opportunity to accomplish this task.

5.5. Product Specialists on Inspections and Pharmaceutical Inspectorate

The PAT team building and training program identified several challenges, of these the most critical challenge was of that of organizational barrier (review - compliance-inspections). An independent contractor was asked to apply principles of organizational engineering to understand different perspectives and based on this information, team building programs and joint training programs were developed.

Team building exercises and joint training programs were critical for overcoming the organizational barriers and communication challenges. It is recommended that similar team building and training opportunities be created for CMC reviewers, compliance officers and the Pharmaceutical Inspectorate. Lessons learned from the PAT Team and Team-Bio should also be utilized to support the "Product Specialists on Inspection" program.

The PAT process has been successful in bringing a systems perspective and a team approach to facilitate innovation. The PAT team has approved one application that included a joint team inspection and has recently completed a pre-operational visit for a major PAT application. Several PAT proposals have been received and it is expected that many of these will be received as applications in the near future. The next steps in the PAT process include:

- International scientific workshop on the PAT Guidance in the US, Europe and Japan
- Incorporation of the PAT process under the FDA's Quality System
- Continued participation in ASTM E55 Committee to support development of standards consistent with the PAT framework
- CBER and Team-Bio representative to join PAT Steering Committee
- Selection of the second PAT Team (to include Office of Biotechnology, Compliance and ORA Team-Bio CGMP Inspection staff)
- Teambuilding, training and certification of the second team
- Extend invitations to Health Canada, MHLW, and EMEA to participate in the second training program

- Share lessons learned and training materials with Health Canada, MHLW, and EMEA
- Continuing education for the current PAT team
- PAT Team and Team-Bio collaboration to identify best practices and lessons learned; recommendations on how to develop a team approach between "Product Specialists" and Pharmaceutical Inspectorate
- Critical Path Research and research collaborations (academia and industry)
- Strengthen the emerging support structure in scientific societies and association (e.g., AAPS, ISPE, IFPATMA, PDA, and others)
- Following the second PAT team training, expand the PAT program to include all *Product Specialist* and *Pharmaceutical Inspectorate*

ICH Q8 will describe the suggested contents for the 3.2.P.2 Pharmaceutical Development section of a regulatory submission in the ICH M4 Common Technical Document (CTD) format. It is not intended to be a "how to" guidance. It will provide sponsors of drug applications an opportunity to present knowledge gained during development of a product and its manufacturing process and relevant prior knowledge. It will indicate areas where the provision of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches to support continuous improvement.

- The FDA's goal at the next ICH meeting (November 2004, Japan) is to articulate and build consensus on a description of how a greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches needed to support continuous improvement.

  If this is agreed upon in November 2004, ICH Q8 would reach Step 2 and be available for public comment.

  It should be recognized that each section within 3.2.P.2 Pharmaceutical Development section will impact the other P2 sections and similarly other sections of a submission and the CGMP's inspection process. By recognizing this as a complex design system that involves multiple attributes, goals, constraints, multidisciplinary design teams (subsystems), different degrees of uncertainty, risk tolerance, etc., we may find opportunities to develop robust designs and design space that provides a sound basis for risk assessment and mitigation.

- Although to a large degree consensus has been established on the "desired state" it should be noted that there is often a tendency for a consensus on collective ends to attenuate when specifics are addressed. This is often due to divergent understanding of the problem being addressed and/or differences in interests and/or issues in representation of the problem

being addressed. It is hoped that this report will help in further consolidating and strengthening the consensus for moving towards the "desired state"

- Under the ACPS Manufacturing Subcommittee a working group will be formed to identify specific steps needed to move towards the desired state. The group will also develop illustrative case studies to support the ICH Q8 document and CPG 7132c.08

- ACPS recommendations on regulatory flexibility for post approval changes (e.g., reduce the need for prior review) will be considered for improving the draft Comparability Protocol Guidance (for small molecules only).

- A combination of the PAT Guidance, CPG 7132c.08, modified draft Comparability Protocol Guidance (for small molecules only) along with other work products of the CGMP Initiative are expected to facilitate a move towards the desired state. The proposed ICH Q10 will need to consider these concepts and policies and provide additional guidance on quality systems for change control to facilitate continuous improvement.

The effectiveness of the regulatory framework for innovation (PAT Guidance) and manufacturing science (emerging ICH Q8) when implemented should be evaluated periodically to guide continuous improvement. Objective metrics will need to be developed to measure the level of systems thinking achieved in the application of manufacturing science principles and opportunities realized within the agency, by the industry, and the larger pharmaceutical community. It is expected that a continuous improvement plan will be developed for both PAT and ICH Q8 under the FDA's Quality System.

In the short duration of the CGMP Initiative significant progress was made articulating, building consensus on, the "desired state" for pharmaceutical manufacturing, and developing a regulatory framework for innovation and continuous improvement. Some have characterized this progress as "revolutionary" (10). From the PAT Team and Manufacturing Science Working Group perspective the progress made to date was because we worked as team to identify and realize opportunities to improve our ability to meet our public health objectives.

Significant challenges lie ahead for the pharmaceutical community and for regulators to move to the "desired state" for pharmaceutical manufacturing in the 21st century. Nevertheless, important steps have already been taken. In addition, some of these challenges can be addressed through the FDA's Critical Path Initiative.

- The Executive Order 13329 Encouraging Innovation in Manufacturing (February 2004) recognizes that *"Continued technological innovation is critical to a strong manufacturing sector in the United States economy. The Federal Government has an important role, through the Small Business Innovation Research (SBIR) and the Small Business Technology Transfer (STTR) programs, in helping to advance innovation, including innovation in manufacturing, through small businesses.*"
  http://www.sba.gov/SBIR/execorder.html

  This provides an opportunity for FDA to support innovation by collaborating with other federal agencies to identify priority for pharmaceutical manufacturing-related research and development.

- The team approach and systems perspective under the CGMP Initiative only addressed a part of the pharmaceutical system. Quality by design and process understanding to a large extent is achieved in a research and development organization; ICH Q8 is the bridge between the CGMP Initiative and the rest of the regulatory system.

  Pharmaceutical product development is a complex and creative design process that involves many factors, many unknowns, many disciplines, many decision-makers, and has multiple iterations and a long life-cycle. Significant uncertainty is created when a particular disciplinary design team must try to connect their subsystem to another disciplinary subsystem (e.g., Clinical-CMC-CGMP). Each subsystem can have its own goals and constraints that must be satisfied along with the system-level goals and constraints. It is possible that goals of one subsystem may not necessarily be satisfactory from the view of another subsystem and design variables in one subsystem may be controlled by other disciplinary subsystems.

  Development of systematic regulatory framework based on complexity and scientific uncertainty should facilitate all three dimensions of the critical path. Such a system will also need to consider the multidisciplinary communication challenges in product development.

The scientific and technical challenges on the critical path towards the "desired state" are significant. The traditional empirical approaches will need to be replaced with a much more fundamental scientific understanding (26-27). This will require the talent and know-how of many scientific and technical disciplines. Without sufficient and sustained support our Nation's pharmaceutical education and research system will be unable to meet the needs of the desired state. Significant collaboration and cooperation among industry, academia, and public agencies (e.g., National Science Foundation

and National Institutes of Health) including FDA will be necessary to find solutions to this challenge.

We wish to acknowledge the contributions of the FDA Science Board, Advisory Committee for Pharmaceutical Science and its PAT and Manufacturing Subcommittees members and participants, scientists who participated in numerous conferences and workshops, and fellow regulators at FDA and around the world, and the FDA's PAT Research Team. Without vigorous discussions and debate our progress would not have been possible.

Both pure and applied science have gradually pushed further and further the requirements for accuracy and precision. However, applied science, particularly in the mass production of interchangeable parts, is even more exacting than pure science in certain matters of accuracy and precision. Walter A. Shewhart

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1.

- November 16, 2001: Emerging Science Issues in Pharmaceutical Manufacturing
  http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3799t1.htm
  http://www.fda.gov/ohrms/dockets/ac/01/slides/3799s1.htm
  http://www.fda.gov/cder/OPS/PAT.htm
- April 9, 2002: Emerging Science Issues in Pharmaceutical Manufacturing
  http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3853t1.rtf
  http://www.fda.gov/cder/OPS/PAT.htm

- July 19, 2001 ACPS Meeting
  Optimal Applications of At-line Process Controls on Pharmaceutical Production
  Orally Inhaled and Nasal Drug Products
  Risk-Based Chemistry, Manufacturing, and Controls Review
  http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3804t2.htm
  http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3804t2.doc
- November 28 - 29, 2001: ACPS Meeting
  Process Analytical Technology Subcommittee
  Stability testing and shelf-life
  Blend uniformity testing
  http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3804t1.doc
  http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3804t2.doc
- October 23, 2002 Process Analytical Technology Subcommittee Meeting
  Computer systems validation - Part 11 issues pertinent to PAT
  Rapid Microbiology Testing
  http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3901T1.pdf
- June 12-13, 2002 Process Analytical Technologies Subcommittee Meeting
  PAT Training
  Regulatory "risk"
  Product and Process Development
  Process and Analytical Validation
  http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3869T1.htm
  http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3869T2.htm
- February 25-26, 2002 Process Analytical Technologies Subcommittee Meeting
  Process Analytical Technologies Applications and Benefits
  Product and Process Development
  Process and Analytical Validation
  Chemometrics
  http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3841t1.pdf
  http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3841t2.pdf

- October 21-22, 2003 ACPS Meeting
  Draft PAT Guidance – Update
  Parametric Tolerance Interval Test for Dose Content Uniformity
  Risk-based CMC Review Proposals

http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3996T1.pdf
http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3996T2.pdf

- September 17-18, 2003 Manufacturing Subcommittee Meeting

  Defining Quality
  Considerations for "Quality by Design"
  Proposals for Regulatory Assessment of "Quality by Design"
  Quality by Design and Risk Based Regulatory Scrutiny: CMC Specifications and Post-Approval Changes
  http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3980T1.pdf
  http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3996T2.pdf

- May 21-22, 2003 Manufacturing Subcommittee Meeting

  Transition from Process Analytical Technologies (PAT) Subcommittee to Manufacturing Subcommittee
  Role of PAT in GMP Initiative
  Perspective on risk analysis for the GMP Initiative
  http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3951T1.pdf
  http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3951T2.pdf

- July 20-21, 2004 Manufacturing Subcommittee Meeting

  Update on ICH Q8, Q9 and Proposed Q10
  Update on Draft Guidance on Comparability Protocol
  Moving Towards the "Desired State"
  Manufacturing Science and Quality by Design as a Basis for Risk-based CMC Review
  Risk-based CMC Review Paradigm Under Quality by Design and Manufacturing Science Framework -- Opportunities, Challenges, Current Activities, and Next Step
  Pilot Model for Prioritizing Selection of Manufacturing Sites for GMP Inspection
  Applying Manufacturing Science and Knowledge: Regulatory Horizons
  http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4052T1.PDF
  http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4052T2.PDF

- April 13-14, 2004 ACPS Meeting

  Parametric Tolerance Interval Test for Dose Content Uniformity
  Process Analytical Technologies (PAT) – Next Steps
  PAT Applications for products in Office of Biotechnology Products (OBP)
  http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4034T2.pdf

3. W. E. Deming. Out of the Crisis. MIT Press International; (February 2, 1982)
4. J. M. Juran. Juran on quality by design: the new steps for planning quality into goods and services. Free Press; Revised edition (May 4, 1992)
5. G. Box and N. R. Draper. Evolutionary Operation: A Statistical Method for Process Improvement. Wiley-Interscience; New Ed edition (February 20, 1998)
6. G. Taguchi, S. Chowdhury, Y. Wu. Taguchi's Quality Engineering Handbook. Wiley-Interscience; (2004)
7. A. J. Peterson and R. D. Reid. Continuous Improvement: Method and Madness. American Society for Quality, Proceedings of the 53rd (1999).

8. Staff Reporter. Pharmaceuticals Trouble in the Making: Sloppy manufacturing comes under fire, but inefficiency is the real problem. *The Economist*. August 29, 2002.
9. L. Abboud and S. Henslye. New Prescription for Drug Makers: Update the Plant. *The Wall Street Journal*, September 3, 2003.
10. J. Carey and M. Arndt. Making Pills The Smart Way: Drug makers are revamping factories to save money and avoid production mishaps. *Business Week Online*, May 3, 2004. http://www.businessweek.com:/print/magazine/content/04_18/b3881602.htm?mz
11. G. P. Pisano. The Development Factory: Unlocking the Potential of Process Innovation. Harvard Business School Press; (November 1, 1996)
12. R. S. Benson and D. J. MacCabe. From Good Manufacturing Practice to Good Manufacturing Performance. Pharmaceutical Engineering. July/August 2004.
13. A. S. Hussain. A collaborative search for efficient methods for ensuring unchanged product quality and performance during scale-up of immediate release solid oral dosage forms. In, Pharmaceutical Process Scale-Up. Michael Levin (Ed.), Marcel Dekker, Drugs and the Pharmaceutical Sciences, Volume 118, 2002.
14. D. C. Montgomery. Introduction to Statistical Quality Control. 4th Edition, John Wiley & Sons.
15. B. L. Joiner and M. A. Gaudrad. Variation, Management and W. Edward Deming. Quality Progress. December 1990, pp. 29-37. http://deming.eng.clemson.edu/pub/den/files/varman.txt
16. Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation and Application of In Vitro/In Vivo Correlations. CDER/FDA, September 1997.
17. Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. CDER/FDA, August 2000.
18. A. S. Hussain. The Process Analytical Technology Initiative: PAT and the Pharmacopeias. *EDQM Spring Conference, Cannes, 3-4 May 2004.* http://www.fda.gov/cder/OPS/EDQM.ppt
19. Draft Guidance fro Industry: PAT — A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance. September 2003. http://www.fda.gov/cder/guidance/index.htm
20. ASTM International. Committee E55 on Pharmaceutical Application of Process Analytical Technology. http://www.astm.org/cgi-bin/SoftCart.exe/COMMIT/COMMITTEE/E55.htm?E+mystore
21. R. Alexander, J. A. Clements, R. Guest, P Hailey, K. Leiper, A. C. Moffat and K. Pugh. New Technologies Forum 4: Process Measurement and Control (2001). http://www.rpsgb.org.uk/pdfs/ntf4.pdf ; http://www.rpsgb.org.uk/members/science/ntf.htm
22. K. R. Bhote and A. K. Bhote. World Class Quality: Using Design of Experiments to Make it Happen. 2nd Edition. American Management Association (AMACOM) 2000.
23. Draft Guidance for Industry: Quality System Approach to Pharmaceutical Current Good Manufacturing Practice Regulations. FDA, September 2004.
24. Compliance Policy Guide 7132c.08. Sec. 490.100 Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market

Approval. FDA. http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg490-100.html
25. The Critical Path to New Medical Products. FDA, March 2004. http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html
26. H. Leuenberger and M. Lanz. Pharmaceutical Powder Technology - from Art to Science: The Challenge of the FDA's PAT Initiative. Advanced Powder Technology. In Press (Volume 16, No. 1., February 2005) Pre-Print available at: http://www.pharma.unibas.ch/technology/index.html
27. G. K. Raju. Pharmaceutical Manufacturing in the 21st Century: A Science Perspective. Submitted for publication Sloan Management Review.