Message From Janet Woodcock, M.D., Deputy Commissioner For Operations and Chair, Council on Pharmaceutical Quality, FDA

Working on the Pharmaceutical Quality for the 21st Century has been a rewarding experience for all of us at the Food and Drug Administration (FDA). Not only have we made a great deal of progress in modernizing our regulatory processes, we have learned much about improving pharmaceutical product quality that has helped us to develop flexible regulatory approaches to support continuous improvement in those processes. I am extremely proud of the progress we have made since we began this Initiative in 2002. Although we reported out much of that progress in 2004, I did not want anyone to lose sight of the need to continue to improve in the area of product quality and of FDA’s continued efforts. The intent of this report is to bring everyone up-to-date on our activities and to ensure that the momentum of this extremely important Initiative is maintained.

Many improvements were made in the CGMP process at the beginning of the Initiative. Companies will agree that the focus of inspections has improved and that questions and concerns are addressed earlier in the process. We continue to improve the inspectional process as well as enhance consistency across programs both in the field and in the affected Centers. Although we continue to focus on various aspects of the CGMP program for improvement, the last two years, our efforts have been directed to building and maintaining a strong science based review process, which can provide more synergism across all programs. As you know, FDA cannot meet the goals of the Initiative alone. The success of the Initiative has been predicated on active participation and input from experts in industry, academia, government, and consumer groups. I want to thank everyone who has worked closely with us over the last few years by participating in workshops and conferences, by helping to better define our direction for the Initiative, and by educating us at FDA on manufacturing science and the other important aspects of improving the regulatory programs.

The journey has just begun. There is still much to learn and innovations to incorporate into all our processes. We, in the agency, will continue to emphasize the importance of the Initiative and look forward to many more improvements in our regulatory processes for ensuring product quality.

Council Mission Statement

To facilitate FDA’s modernization of the regulation of pharmaceutical manufacturing and product quality, the FDA Management Council establishes a Council on Pharmaceutical Quality (herein referred to as Council). The Council serves as the guiding body on activities and policy development related to the modernization of the regulation of cross-center and Office of Regulatory Affairs (ORA) pharmaceutical manufacturing and product quality. The Council also serves as a resource to the FDA Management Council and to the agency in general on matters relevant to this subject.

Organization

Introduction

FDA continues to make progress under the Pharmaceutical Quality for the 21st Century – A Risk Based Approach formally known as Pharmaceutical CGMP Initiative for the 21st Century – a Risk Based Approach. This Initiative, introduced by FDA in 2002, was intended to modernize FDA’s regulation of pharmaceutical quality for veterinary and human drugs and select human biological products such as vaccines. The name has been changed to capture the larger issue of product quality, with CGMPs being an important tool towards improving overall product quality. The following organizational components of FDA have been actively involved in working toward this modernization over the last four years: ORA, Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation (CDER) and the Center for Veterinary Medicine (CVM), along with various offices within the Office of the Commissioner. All of these organizations continue to promote the goals and objectives of the Initiative and are dedicated to continuing to improve the regulation of pharmaceuticals in the 21st Century.

This report is intended to provide an update on the Agency’s progress since the last report issued in September 2004 and to impress upon the pharmaceutical industry and our stakeholders the continued importance of this Initiative to the Agency.
The Initiative was originally issued with the following goals:

- Encourage the early adoption of new technological advances by the pharmaceutical industry
- Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance
- Encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas
- Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science
- Enhance the consistency and coordination of FDA's drug quality regulatory programs, in part, by further integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies concerning review and inspection activities

This report and the report issued in September 2004 specify the accomplishments that were made in achieving the goals of the Initiative. This report will set forth the current activities of the Agency as well as inform the public of the future direction of the Agency in implementing the goals of the Initiative.

This report highlights those general activities and projects of the Initiative that have been worked on under the auspices of the Council in the last two years. Over the last two years, the Council has identified additional objectives for continuing to improve drug quality regulation based on new challenges and the need for continuous improvement of the regulatory programs. A number of additional multidiscipline work groups have been established under the Council to focus on these activities. The current work groups are listed in the Organization Section of this report. Individual reports from all of the work groups are also attached which provide specific information on accomplishments and future goals of the each work group.

Key Accomplishments

Communication

Communication is an important aspect of implementing the Initiative and falls under the responsibilities of the Council. Besides organizing and/or participating in workshops both internally and externally to communicate changes in regulatory programs and to solicit information from industry and other stakeholders, several new guidelines or draft guidelines have been issued in the last two years to support the goals of the Initiative.

The Agency held the following workshops to discuss the modernization of regulatory programs since the last report on the Initiative:

- Workshop in March 2005 on setting specifications for biological products
- Workshop in April 2005 on setting specifications for small molecule products
- Pharmaceutical Quality Assessment Workshop in fall of 2005
- URI Workshop on CMC (21st Century Chemical, Manufacturing and Control Strategies – A New Paradigm) in fall 2006
- AAPS/ISPE/FDA Pharmaceutical Quality Initiatives Workshop in winter 2007

See Appendix 17 for more information on several of the workshops.

The following final and draft guidances issued since the last report:

- Draft Guidance – "INDs – Approaches to Complying with CGMPs for Phase 1 Drugs" – issued January 2006

International Collaboration

Collaboration with international health and regulatory organizations has been a vital part of the modernization efforts. The focus has been towards promoting international cooperation directed at assuring drug product quality and consistency of CGMPs. Ongoing activities include:

- Participation in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals of Human Use (ICH) Quality (Q) topics. FDA has participated in ICH to develop a pharmaceutical quality system based on an integrated approach to risk management and pharmaceutical science. FDA is participating in various expert working groups within ICH to develop guidelines for ensuring that drug regulatory processes are more efficient and uniform in the three regulatory regions.
  - ICH Q8R (Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria) seeks to establish consistent standards for selected pharmaceutical test methods in the three regional pharmacopoeias.
  - ICH Q8 (Pharmaceutical Development) incorporates elements of risk and quality by design throughout the life cycle of the product – final
  - ICH Q9 (Quality Risk Management) is focused on defining the principles by which risk management will be integrated into decisions by regulators and industry regarding quality – final
  - ICH Q10 (Pharmaceutical Quality Systems) is developing a framework for an integrated quality management system which will promote continual improvement in quality across the life cycle of the product – Step 1
- Development of appropriate documentation, etc., for membership in the Pharmaceutical Inspection Cooperation Scheme (PIC/S). Membership in the PIC/S provides networking opportunities among participating authorities, the development of mutual confidence among authorities, and mutual training of inspectors, as well as the exchange of information and experience in the field of CGMP and related areas.

Implementation of Quality by Design

Significant progress has been made in the implementation of the concepts of "Quality by Design" (QbD) into Agency processes. The focus of this concept is that quality should be built into a product with a thorough understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks. The chart in Appendix 19 demonstrates the essential aspects of QbD.

- In CDER's Office of New Drug Quality Assessment (ONDQA), a new risk-based pharmaceutical quality assessment system (PQAS) was established based on the application of product and process understanding. This includes not only implementing new review processes but also restructuring the office to accommodate new processes.
- Implementation of a CMC Pilot Program in ONDQA has allowed firms to submit CMC information demonstrating application of QbD principles, product knowledge, and understanding. Through the information reviewed under the Pilot, ONDQA will be able to evaluate the application of principles of QbC by companies and to ascertain the appropriate information to be included in future NDAs. Eleven applications have been accepted into the Pilot. As of January 1, 2007, the Agency had received seven applications, two of which have been approved.
- Implementation of a Question-Based Review (QBR) Process has occurred in CDER's Office of Generic Drugs. QBR serves a dual purpose of providing guidance to reviewers in preparing consistent and comprehensive evaluations of ANDAs while assessing critical formulation and manufacturing process variables and providing industry with guidance on which issues need to be addressed in applications where QbD is being implemented.
- CDER's Office of Compliance has played an active role in working with the field to develop appropriate inspectional processes for QbD.
- Implementation of QbD for Biologic License Applications (BLAs) is progressing.
Implementation of Process Analytical Technologies (PAT) as a tool for designing and analyzing pharmaceutical development and manufacturing is an important concept for meeting the goal of the Initiative of encouraging new manufacturing technologies. The Agency has been engaged in review of a number of applications for both new drugs and generic drug products in which companies are applying technologies, which are currently available to provide information on physical, chemical, (micro) biological characteristics of materials to improve process understanding and to measure, control, and/or predict quality and performance of products. There have also been a number of training programs, both internally and externally, to highlight the applicability of PAT and the regulatory pathways. In addition, an executive committee was established in ASTM (E55) to develop standards for implementation of PAT in pharmaceutical manufacturing.

**Pharmaceutical Inspectorate (PI)**

The PI was established in the ORA to enhance the Agency's overall inspection program. The following progress has been made in ensuring PI success:

- As of November 2006, 30 field inspectors have been credentialed as members of the PI cadre. These individuals are responsible mainly for drug quality inspections of prescription drug manufacturers and other complex or high-risk pharmaceutical operations.
- The members of the PI have received extensive training in pharmaceutical manufacturing practices as well as the concepts of modern pharmaceutical principles and practices in new technologies. Each has also performed a two-week rotation through review offices to improve their understanding of the programs and the application of assessment practices as they relate to inspectional activities.
- A special committee was formed to develop an internal quality management system for the PI.
- A work group was also formed to determine how best to enhance interaction between the review staff and inspectors. This work group will direct their recommendations to both the field staff in general and the PI in particular.

See Appendix 18 for additional information on the PI Training Program

**Scientific Collaboration Activities**

Scientific collaboration continues to be an important part of accomplishing the goals of the objectives. The Agency continues to be very active in collaborating with external constituents from both academia and industry. The collaborative efforts are also essential in meeting the critical path needs. There are a great many challenges, which exist in drug development and manufacturing that are being tackled while accomplishing the goals of the 21st Century Initiative. Many of the work groups under the Council are actively involved in developing or maintaining collaborations. The Council has also met with a number of outside organizations to understand what is happening in various areas that coincide with the efforts of the Council. Examples of some of these collaborative efforts are:

- Cooperative Research and Development Agreements (CRADAs) have been established with several outside groups to enhance understanding of concepts of manufacturing science and how these concepts are practically applied. (A CRADA is an agreement between one or more FDA laboratories and one or more non-Federal parties under which the FDA laboratory provides personnel, services, facilities, equipment, or other resources toward the conduct of specified research or development efforts.) (Examples of current CRADAs partners are Light Pharma, Inc. and Conforma Software, Inc.) There are other collaborations with outside groups to better define manufacturing performance factors.
- There are also several research CRADAs with industry to look at specific aspects of process analytical technologies and how they can best be applied.
- There are a number of research projects being conducted by collaborations outside the FDA (e.g., Product Quality Research Institute, National Institute for Pharmaceutical Technology and Education, etc.) to better understand specific issues under the changing regulations and to more clearly define manufacturing science and the regulatory gaps.
- The collaboration with the McDonough School of Business (Professor Jeffrey T. Macher, Ph.D.) at Georgetown University, Washington, DC, and the Olin School of Business (Professor Jackson A. Nickerson, Ph.D.) at Washington University, St. Louis has continued. This has helped the Agency identify the factors that predict manufacturing performance to refine our pharmaceutical manufacturing risk-based assessment. (See Appendix 16.)

Many of these collaborations also are significant elements of the Critical Path initiative that was established to focus on the modernization of techniques and methods used to evaluate safety, efficacy and quality of medical products. In enhancing the regulatory processes for ensuring quality pharmaceutical products, a number of research projects are being done in collaboration with industry and academia to improve manufacturing science.

**Use of Standards**

The Council supports Office of Management and Budget (OMB) Circular A-119, which establishes policy on use and development of voluntary consensus standards. The tenets of the 21st Century Initiative also emphasize the need to use consensus standards to support the regulation of pharmaceuticals. The Initiative promotes using standards for (1) understanding new technologies, (2) ensuring consistency across industry and Agency, (3) optimizing efficiency in regulating, and (4) promoting international harmonization. The Council has established a work group to determine how best to support and utilize standards across the pharmaceutical quality programs.

As FDA is a strong proponent of the use of standards, it encourages the pharmaceutical industry and other stakeholders to participate in standards-setting organizations where development of standards will be beneficial to the manufacture of high quality pharmaceuticals. FDA's primary role is to determine which standards, if accepted during application review, would support a more efficient review process and enhanced product quality assurance. Through guidelines and other external communications, FDA will acknowledge the applicability of specific standards. Industry is encouraged to use and cite appropriate standards in their submissions. FDA will access the suitability of cited standards within the context of the manufacturer's application.

FDA has also participated with ASTM in developing standards for implementing PAT. These standards will help the Agency have a better understanding of the technology and provide the industry with guidance on implementing PAT into their manufacturing processes.

**Conclusion**

FDA continues to facilitate the modernization of regulatory processes related to pharmaceutical products in the 21st Century. This report is being issued to emphasize the Agency's commitment to the goals and objectives in pursuit of more consistent and effective regulatory processes. The attached reports provide the public with a general idea of many of the Agency's activities in pursuing these goals and objectives.

**Where to Find More Information**

Separate guidance page:

**Questions**

Direct any questions on this report to Ted Sherwood who serves as the Project Manager for the Council of Pharmaceutical Quality.

Attention: Ted Sherwood
FDA, CDER, OPS, IO
10903 New Hampshire Ave.
Bldg 21, Room 528
Silver Spring MD 20903-0002
Tel: 301-796-1605
Fax: 301-796-9733
email: edward.sherwood@fda.hhs.gov

**APPENDIX 1**

**GMP REGULATIONS WORK GROUP**

Chairs: Fred Blumenschein and Mary Malarkey
Project Manager: Vikki Kinsey

Members: Pat Alcock, ORA, Diane Alexander, CBER, Neal Rataller, CVM, Fred Blumenschein, CDER, Walt Brown, ORA, James Cohen, OCP, Mary Davis-Lopez, CBER, Kevin Fair, OCC, Jo Galley, CVM, Brian Hasselbach, CDER, Vikki Kinsey, CBER, Joan Loreng, ORA, Mary Malarkey, CBER, Sharon May, OPPL, Grace McNally, CDER, James Nikao, CVM, Charles O'Brien, CVM, LuAnn Pallas, ORA, Michael Rogers, ORA, Jessica Tave, OCBQ

The CGMP Regulations Work Group was formed to implement modifications to 21 CFR Part 210/211. As described in the September 2004 Final Report "FDA will take an incremental approach to modifying parts 210/211, while pursuing international harmonization through ICH and PIC/S."
Goal(s) and Tasks

- Determine modifications; the ultimate goals of the modifications will be to encourage timely detection and response to emerging defects or indications that product quality has been compromised; to provide further clarity and modernize the regulations; and to harmonize various aspects of parts 210/211 with other Agency regulations and regulations of our international counterparts.
- Withdraw the 1996 proposed amendments to parts 210/211
- Implement incremental changes to parts 210/211 through rulemaking

APPENDIX 2
INTEGRATED SYSTEMS APPROACH TO CMC REVIEW AND CGMP INSPECTION (INTERACTION) WORK GROUP

Chair: Chris Watts
Facilitator: Sarah Mullikin (SVM Consulting)

Members: Julie Conwell, CVM, Gwyn Dickinson, ORA, Susan Pittinger, CDER, Sarah Pope, CDER, Edwin Rivera-Martinez, CDER, Nancy Rolli, ORA/NJ-DO, Robin Stone, CVM, Chris Watts, CDER

Background
A primary objective of the quality initiative is to “enhance the consistency and predictability of FDA’s approach to assuring product quality and safety among the FDA’s centers and field components.” In order to realize this objective, among other activities, the Council established this work group with the charge to improve the interaction between CMC review and CGMP inspection, thereby facilitating a consistent regulatory approach to product and process quality across various Agency components.

Goal(s) and Tasks
- Improve interaction between CMC Reviewers and CGMP Investigators
- Develop integrated training, in cooperation with ORA/Division of Human Resource Development (DHRD), for Pre-Approval Managers from the Field and Pharmaceutical Assessment Leads and Team Leaders from the Review Divisions, upon completion of the pre-approval program
- Develop MAPP for reviewers on the use of the Establishment Evaluation System
- Develop and implement training, in cooperation with ORA/DHRD, for CMC reviewers who participate on inspections
- Obtain Division File System (DFS) access for Pre-Approval Managers (and their back-ups) and develop training appropriate for use
- Obtain Establishment Inspection Reports (TurboEIR) Website access for Pharmaceutical Assessment Leads and Team Leaders and develop training appropriate for use
- Develop and distribute, in cooperation with Quality Systems project, reviewer contact list for investigators

APPENDIX 3
INTERNATIONAL ACTIVITIES WORK GROUP

Chair: Lois Ann Beaver
Project Manager: Tammie Bell

Members: Lois Beaver, OC, Dennis Bensley, CVM, Joan Blair, CBER, Monica Caphart, CDER, Katherine Cooper, OC, Doug Ellsworth, ORA, Joe Famulare, CDER, Sema Hashemi, OC, Brian Hasselbalch, CDER, Diana Kalolitis, ORA, Michelle Limoli, OC, Scott MacIntire, ORA, Justina Molzon, CDER, Anita Richardson, CBER, Michael Rogers, ORA, Merton Smith, CVM, Steve Solomon, ORA

Background
Developing harmonized international scientific standards is a continuing activity, with the FDA actively collaborating with other regulatory authorities, in multilateral, international forums, such as the International Conference on Harmonization of the Technical Requirements for Registration of Pharmaceuticals (ICH) and the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH). This Work Group leads efforts to promote international regulatory cooperation directed towards assuring drug product quality and GMPs

Goal(s) and Tasks
- Harmonize international scientific standards by establishing standards on drug product quality and GMPs that promote technological innovation for enhancing public health protection
- Promote and develop mechanisms that result in regulatory cooperation directed toward assuring drug product quality and CGMP compliance such as developing bilateral and multilateral confidentiality agreements and specific information exchange agreements, while reaching out in other ways to collaborate with its international partners

APPENDIX 4
INVESTIGATIONAL CLINICAL SUPPLIES WORK GROUP

Chairs: Joe Famulare and Chris Joneckis
Project Manager: Vacant

Members: Monica Caphart, CDER, John Dietrick, CDER, Joe Famulare, CDER, Chris Joneckis, CBER, Laurie Norwood, CBER, Walt Brown, ORA, Guraig Poochikian, CDER, Chiang Syin, CBER, Dan Takefman, CDER, Brenda Uratani, CDER, Keith Webber, CDER, Paula McKeever, OC, Peter Beckerman, OC, Rachel Berman, OC

Background
In response to comments from regulated industry and academic/clinical developers, FDA recognized that application of the CGMP regulations, as described in 21 Code of Federal Regulations CFR 211, is not always relevant for the manufacture of clinical investigational drug products. Furthermore, FDA’s current approach of employing enforcement discretion in applying CGMPs at 21 CFR 211 was not acceptable to manufacturers of clinical investigational drug products because of the concern of the legal liability to comply with all of the GMP regulations specified in 21 CFR 211. In response to this and internally-driven needs for clarification, the Agency recognized the need to develop specific GMPs for investigational products. FDA elected to address the progressive nature of CGMPs in drug development for a wide variety of manufacturing situations and product types by providing appropriate guidance for compliance with CGMPs starting with Phase 1 studies.

Goal(s) and Tasks
- Evaluate applicability of CGMP (21CFR 211) to production of drug product for Phase 1 studies
- Develop an appropriate course of action to clarify CGMP for manufacture of drug substances and drug products used in Phase 1 clinical trials
- Issued Draft Guidance INDs - Approaches to Complying with CGMPs for Phase 1 Drugs (DRAFT); currently evaluating docket comments
- Issued a proposed rule for exempting production of most drug products used in Phase 1 clinical trials from following 21 CFR 211; currently evaluating docket comments
- Develop an appropriate course of action to clarify CGMP for manufacture of drug substances and drug products used in Phase 1 clinical trials

APPENDIX 5
MANUFACTURING SCIENCE AND CONTINUOUS IMPROVEMENT WORK GROUP

Chair: Mohbeh Nasr
Project Manager: Christine Moore

Members: Diana Amador, ORA, William Bargo, CVM, Andrew Chang, CBER, Jon Clark, CDER, Robert Coleman, ORA, John Dietrick, CDER, Douglas Ellsworth, ORA, Raafat Fahmy, CVM, Joseph Famulare, CDER, Frank Holcombe, CDER, Mai Huynh, CVM, Chris Joneckis, CBER, Diana Kalolitis, ORA, Steven Kozlowski, CDER, See Yan Lam, CDER, Grace McNally, CDER, Elaine Morefield, CDER, Elise Murphy, ORA, Guraig Poochikian, CDER, Vilayat Sayeed, CDER, Chris Watts, CDER, Keith Webber, CDER, Mansoor Khan, CDER

www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm128080.htm
### APPENDIX 6

#### PART 11 - ELECTRONIC RECORDS REQUIREMENTS WORK GROUP

**Chair:** Joe Famulare  
**Project Manager:** Diane Hanner  
**Members:** Beers Block, Patricia; Carvajal, Ricardo; Doleski, Joseph (David); Druckman, Michael; Elder, David K.; Epstein, Laura; Famulare, Joseph; Fitzgerald, Brian; Gallant, David; Gatling, Bob; Goldstein, Jennifer; Hanner, Diane; Henriksen, Erik N; Liensch, John; Loreng, Joan; Mednick, David; Murray, John F.; Sims, Margaretta; Smith, George; Thomas, Audrey A; Thomas, Jennifer; Toelle, Vemon D; Wyn, Sion; Zabriski, Margaret A; Ziyad, JoAnn

**Background**  
As an outgrowth of its quality initiative for human and animal drugs, and biologics, FDA continues to re-examine Part 11 as it applies to all FDA regulated products.  
Part 11 regulations provide criteria for acceptance by FDA, under certain circumstances, of electronic records, electronic signatures, and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures executed on paper. These regulations, which apply to all FDA program areas, were intended to permit the widest possible use of electronic technology, compatible with FDA's responsibility to protect the public health.

**Goal(s) and Tasks**

- Promulgate the final regulation and publish the final companion guidance

### APPENDIX 7

#### PHARMACEUTICAL QUALITY STANDARDS WORK GROUP

**Chair:** Helen Winkle  
**Project Manager:** Chris Watts  
**Members:** Buehler, CDER, Jon Clark, CDER, Joseph Famulare, CDER, Rick Friedman, CDER, Frank Holcombe, Jr, CDER, Chris Joneckis, CBER, David Kelly, OC, Steven Kozlowski, CVM, Donald Marlowe, OC, William Marnane, CVM, Steve Niedelman, ORA, Charles O'Brien, CVM, Guiragos Poochikian, CBER, Herman Schoenemann, CVM, Chris Watts, CDER, Keith Webber, CDER, Helen Winkle, CDER

**Background**  
This work group was formed to develop and implement a process for evaluating and facilitating the use of standards related to pharmaceuticals and pharmaceutical manufacturing.

**Goal(s) and Tasks**

- To oversee FDA's process for acceptance of pharmaceutical-associated standards  
- To review proposals from United States Pharmacopeia (USP) and other standards-setting groups (e.g. flexible monograph) and access the potential impacts of such proposals on implementation of the Initiative  
- To make recommendations to the CPG regarding policies to encourage the use of standards

### APPENDIX 8

#### PROCESS ANALYTICAL TECHNOLOGY WORK GROUP

**Chair:** Helen Winkle  
**Project Manager:** Chris Watts  
**Members:** Ali Afnan, CDER, Patricia Alcock, ORA, Dennis Bensley, CVM, Jon Clark, CDER, Doug Ellsworth, ORA, Joe Famulare, CDER, Frank Holcombe, CDER, Chris Joneckis, CBER, Steve Kozlowski, CDER, Moheb Nasr, CDER, Chris Watts, CDER, Keith Webber, CDER, Helen Winkle, CDER

**Background**  
The goal of the PAT Framework is to understand and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design.

A desired goal of the PAT Framework is to design and develop processes that can consistently ensure a predefined quality at the end of the manufacturing process. Such procedures would be consistent with the basic tenet of quality by design and could reduce risks to quality and regulatory concerns while improving efficiency.  
- Gains in quality, safety and/or efficiency will vary depending on the product and are likely to come from: 1) reducing production cycle times by using on-, in-, and/or at-line measurements and controls; 2) preventing rejects, scrap, and re-processing; 3) real-time release; 4) increasing automation to improve operator safety and reduce human error; 5) facilitating continuous processing to improve efficiency and manage variability using small-scale equipment (to eliminate certain scale-up issues) and dedicated manufacturing facilities, improving energy and material use, and increasing capacity.

**Goal(s) and Tasks**

- Develop and implement second round of PAT training - Agency-wide (CBER, CDER, CVM, ORA)  
- Develop and implement training for all CMC Reviewers  
- Continue to support innovation in pharmaceutical development, manufacturing, and quality assurance

### APPENDIX 9

#### PROCESS VALIDATION WORK GROUP

**Chairs:** Brian Hasselbach and Grace McNally
Goal(s) and Tasks

- Revise 1987 guidance to incorporate lifecycle concept
- Issue as final Level 1 guidance to industry

### APPENDIX 10
QUALITY SYSTEMS CONTINUOUS IMPROVEMENT WORK GROUP

**Chairs:** Robert Saussville and Joseph Famulare  
**Project Manager:** Patrick Quinn  

**Members:** Diane Alexander, CBER; Diana Amador, ORA; Dennis Bensley, CVM; Monica Caphart, CBER; Chris Joneckis, CBER; June Liang, CVM; Patricia Maroney-Benassi, ORA; Sherry Purvis-Wynn, ORA; Michael Smedley, CDER; Joe Famulare, CDER; Robert Saussville, CBER; Patrick Quinn, CDER

**Background**
The Quality System Development Work group (QS work group) is responsible for comparing the current CGMP regulations, which call for specific quality management elements, to other existing quality management systems. The QS work group mapped the relationship between CGMP regulations (parts 210 and 211 and the 1978 Preamble to the CGMP regulations) and various quality system models such as the Drug Manufacturing Inspections Program (i.e. systems-based inspectional program), the Environmental Protection Agency's Guidance for Developing Quality Systems for Environmental Programs, International Standards Organization (ISO) Quality Standards, other quality publications, and experience from regulatory cases.

**Goal(s) and Tasks**

- Publish and finalize a guidance on Quality Systems approach to the CGMP Regulations

### APPENDIX 11
OFFICE OF REGULATORY AFFAIRS PHARMACEUTICAL INSPECTORATE QUALITY MANAGEMENT SYSTEMS TASK FORCE

**Chair:** Susan Setterberg  
**Project Manager:** Eileen Cole  

**Members:** Susan Setterberg, ORA; Helen Wilkine, CDER; Kristen Anderson, CVM; Chuck Edwards, ORA; Douglas Ellsworth, ORA; Kristen Evans, CDER; David Horowitz, ORA; Yvett Johnson, ORA; PHI-DO; June Liang, CVM; Patricia Maroney-Benassi, ORA; Nancy Rolli, ORA; NJ-DO; John Thorsky, ORA; SW/KAN-DO; Chris Watts, CDER; Faye Wei, CVM

**Background**
The Office of Regulatory Affairs (ORA) task force was established to develop a quality management system for the Pharmaceutical Inspectorate (PI). The prime focus is to identify issues relating to developing a quality management system, ensure interaction between reviewers and inspectors, make more information available on the PI, and discuss how the PI will be used in the future.

**Goal(s) and Tasks**
Create an environment that ensures quality, consistency, and regulatory effectiveness of inspections so that the reviewers and investigators have the same common goals

- Reviewed and drafted internal documents to increase ease of contact and communication between segments of FDA involved in review and regulatory oversight of drug products
- The MOU (Memorandum of Understanding) between CDER and ORA is being evaluated and will be expanded to cover CVM/CBER.
- Set up an Interaction Work Group to look at work process design, interactions with generic product reviewers, new drug product reviewers, veterinary medicine product reviewers, and consider the role of GMP

### APPENDIX 12
QUALITY SYSTEMS IMPLEMENTATION WORK GROUP - RECALLS

**Chairs:** David Elder and Carl Draper  
**Project Manager:** Patricia Maroney-Benassi  

**Members (Recall QS Project Team):** Anna Marie Kempic, Office of Chief Counsel; Dorothy Miller, Office of Crisis Management; Catherine McDermott, OER/OPA; Media Relations Staff, Isadore Steinh, OER/OPA; Website Mgt. Staff, Len Valenti, OIASI/International Programs, Dianne Murphy, OIASI/Pediatric Therapeutics, Mark Kramer, OIASI/Combination Products, Laura Hieronymus, CBER; Lavonia Huff, CDER; Frances Benedict, CDRH; Lilane Brown, CDRH; Cecilia Woyniak, CFSAN; Barbara Rodgers, CVM; Glenn Peterson, CVM; Bradford Stone, ORA; Mei Szymanski, ORA/Enforcement, Sherrie Krolczyk, ORA/Southwest Region

**Background**
One goal of the FDA quality Initiative is to integrate quality systems and risk management approaches into existing agency programs. The Initiative’s members (CBER, CDER, CVM, and ORA) agreed with the Center for Devices and Radiological Health (CDRH) and Center for Food Safety and Applied Nutrition (CFSAN) to develop agency-wide quality system implementation of two specific projects focused on recalls and warning letters.

**Goal(s) and Tasks**

- Develop and document an agency-wide process map showing all actors, interactions, and major procedural steps
- Identify quality metrics: the process control points that result in the quality product and measures of the product that demonstrate quality
- Recommend continuous improvement projects such as uniform procedures or best practices to be performed either within the QS Implementation Project or separately

### APPENDIX 13
QUALITY SYSTEMS IMPLEMENTATION WORK GROUP - WARNING LETTERS

**Chairs:** Carl Draper and David Elder  
**Project Officer:** Valerie Valley  

**Project Manager:** Vacant  

**Members:** Joy Dawson, Office of Chief Counsel; M. Dianne Murphy, Office of Pediatric Therapeutics; Mark Kramer, Office of Combination Products; Rosie Whitcraft, Office of the Chief Information Officer; Fred Sadler, Office of Management Programs; Anita Richardson, CBER; Frances Benedict, CDRH; Lilane Brown, CDRH; Deborah Autor, CDER; Leslie Bel, CDER; Lesley Frank, CDER; Judith Gushue, CFSAN; Michael Hackman, CVM; James Kewley, ORA/Field

**Background**
One of the Agency’s goals is the integration of quality systems and risk management approaches into existing Agency programs and processes. The Warning Letter process was identified as a quality system candidate because of its significance in achieving industry compliance and in emphasizing the importance of timeliness, consistency, and legal sufficiency in the final work product.

**Goal(s) and Tasks**

- Recommend continuous improvement projects such as uniform procedures or best practices to be performed either within the QS Implementation Project or separately
- Develop high level and detailed component process maps showing the routing in each organization within the scope of the project
- Recommend best practices and identify quality metrics
- Identify processes for improvement, both concurrently with the ongoing project and for continual improvement

**APPENDIX 14**

**RISK MANAGEMENT WORK GROUP**

**Chair:** David Horowitz, Deborah Autor  
**Project Manager:** Vacant

**Members:** John Gardner, CDER, Brenda Wang, CDER, Vincent Zenger, CDER, Suzanne Barone, CDER, Karen Kirchberg, CDER, Nicholas Buhay, CDER, George Smith, CDER, Jon Clark, CDER, Vilayat Sayeed, CDER, Charles Gray, CVM, Meyer Slobotsky, ORA, NJ-DD, Mandalla Torez-Itzarry, ORA, Stephen Soura, ORA, NEW-DO

**Background**

The group was initially formed to explore opportunities for applying risk-based approaches to prioritize and focus the various activities performed by FDA concerning the oversight of GMP requirements. The group then concentrated its efforts on developing and implementing a quantitative model to prioritize inspections of drug manufacturing facilities. The highest priority sites selected by the model are counted toward the agency's annual performance goal for high-risk human drug inspections under the Government Performance Results Act. The work group developed and implemented the expert elicitation survey, which gathered data from agency experts to identify and weigh factors associated with (1) maintaining manufacturing process control and (2) vulnerability to cross-product or environmental contamination. The group also participated in drafting the white paper that described how the model would be piloted in FY '05 and in implementing that pilot. The work group next devoted its attention to improving and continuing implementation of the model. Significant advancements in FY '06 included data quality improvement efforts carried out by the field; the inclusion on data from Field Alert Reports associated with facilities; and on therapeutic risk categories associated with products.

**Goal(s) and Tasks**

- Running the risk management site selection model and communicating the output to the field.

**APPENDIX 15**

**DISPUTE RESOLUTION WORK GROUP**

**Chairs:** David Horowitz and Helen Winkle  
**Project Manager:** Ted Sherwood

**Members:** Mike Rogers, ORA, Walt Brown, ORA, Doug Ellsworth, ORA, Mary Malarkey, CBER, Anita Richardson, CBER, Albi D'Sa, CDER, John Dietrick, CDER, Teddi Lopez, CDER, Jorge Christian, CVM, Mary Leadbetter, CVM

**Background**

The Agency acknowledged concern expressed by the pharmaceutical industry that disputes related to scientific and technical issues may arise during FDA inspections of pharmaceutical manufacturers to determine compliance with CGMP requirements or during the Agency's assessment of corrective actions undertaken because of such inspections. As these disputes may involve complex judgments and issues that are scientifically or technologically important, it is critical to have procedures in place that will encourage open, prompt discussion of disputes and activities leading to their resolution. The Agency also realized that industry uses the outcomes of inspections as tools to prepare for future inspections. Therefore, the Agency recognizes the importance of reporting the proper inspection outcomes. At the onset, it was clear that formal procedures for raising disputes to ORA and Center levels were lacking.

**Goal(s) and Tasks**

- Issue a guidance for Industry; The Guidance: Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP issued January 11, 2006. The intent of this document is to provide guidance to manufacturers of veterinary and human drugs, including human biological drug products, on how to resolve disputes of scientific and technical issues relating to CGMP requirements.

Please note: This Work Group completed its task and is no longer active.

**APPENDIX 16**

**PHARMACEUTICAL RESEARCH MANUFACTURING COLLABORATION**

Conducted under an arrangement with Professor Jeff Macher of Georgetown University and Professor Jack Nickerson of Washington University, St. Louis; the Council received results generated from statistical analyses of data comprised of CDER, ORA and Industry data metrics.

These statistical analyses derived from two phases of the Professors' Pharmaceutical Research Manufacturing Project (PRMP). The first phase involved working with the FDA to collect and compile data from FDA internal databases. Based on this data, the project developed risk-based statistical models to assess the probability of a facility being chosen for inspection, to evaluate the effect of investigator training and experience on the probability of investigational outcomes as well as individual investigator effects on the probability of investigational outcomes, and to identify characteristics of facilities and firms that correlate with the likelihood of noncompliance. A preliminary report was delivered to the FDA on January 28, 2005.

The second phase of the PRMP focused on collecting and analyzing data from 42 pharmaceutical manufacturing facilities of 19 manufactures. Preliminary results were presented to FDA on February 17, 2006. While results from all 27 statistical analyses were presented in the report, five consistent findings were identified. First, the adoption of information technology by manufacturing facilities corresponds to higher manufacturing performance metrics. Second, the locus of decision rights, especially with respect to deviation management, affects performance metrics. Decision rights located closer to the shop floor generally improve manufacturing performance metrics.

Third, facilities engaged in contract manufacturing generally correspond to worse performance metrics. Fourth, the use of process analytic technology tools generally, although not in all instances, corresponds to worse performance metrics. This correspondence, however, does not imply causation, which means that these tools may be adopted because of poor performance metrics instead of generating poor performance. Finally, the scale and scope of the manufacturing facility have a complex interplay with manufacturing performance as both a benefit and a detriment to performance depending on the metric of interest and the type of production process.

Next steps involve the Professors working with CDRH to develop a risk-based assessment tool. This tool will be implemented by the FDA to plan inspections based on a facility's risk profile.

**APPENDIX 17**

**WORKSHOPS**

**AAPS WORKSHOP ON PHARMACEUTICAL QUALITY ASSESSMENT - A SCIENCE AND RISK-BASED CMC APPROACH IN THE 21ST CENTURY**

**Co-sponsored with FDA and ISPE, October 5 - 7, 2005, North Bethesda, Maryland**

**Summary**

600 scientists and regulators from industry and government agencies around the world gathered to discuss concerns, make suggestions, and engage in challenging debate about the U.S. Food and Drug Administration's new science and risk-based pharmaceutical quality assessment system. The new assessment system is based on principles designed to facilitate regulatory flexibility, thereby allowing for a more efficient drug approval process without compromising product quality and efficacy. FDA's vision is to empower industry scientists to create development parameters, called "Design Space," using quality risk management principles and prior knowledge. Operating within a given product's "Design Space" assures a more efficient review process and eliminates the need for multiple submissions, which often slows down the drug approval process and delays the research from reaching its final and most important audience, the patient. The workshop planning committee consisted of the following individuals:

The basic format of the workshop was three morning plenary sessions that incorporated talks on Pharmaceutical Quality in the 21st Century, A New Pharmaceutical Quality Assessment System (PQAS), Understanding Key Terms, Quality by Design (QbD), Utilization of Comprehensive Quality Overall Summary (QOS) in CMC.
Submission and Review, Innovation and Continuous Improvement, and Challenges and Opportunities in Drug Development, Manufacturing, and Regulations. The plenary sessions were enhanced by breakout sessions and case studies on days 1 and 2 and an animated panel discussion on day 3.

University of Rhode Island (URI) Conference

UNIVERSITY OF RHODE ISLAND (URI) CONFERENCE ON CMC – 21ST CENTURY CHEMICAL MANUFACTURING AND CONTROLS STRATEGIES
Co-sponsored with FDA October 17 - 18, 2006, Reston Hyatt, Reston, Virginia

Summary
The U.S. Food and Drug Administration (FDA) and the University of Rhode Island (URI), College of Pharmacy co-sponsored a workshop on the progress the FDA has made on the 21st Century Initiative since the final report. This event included discussions with the Director of each CMC review Office in CDER and the Director of the Office of Testing and Research. Details of specific efforts to better meet Critical Path Industrialization goals where provided.

FDA wanted to provide an open dialogue with the pharmaceutical industry in order to provide new critical information to them for leveraging advantages available in the Critical Path Industrialization and CGMPs for the 21st Century Initiatives. This venue provided an audience to focus on the implementation of these initiatives in areas specific to commercial manufacturing and the interaction of OPS and CGMP.

AAPS WORKSHOP ON PHARMACEUTICAL QUALITY ASSESSMENT - A MODERN RISK-BASED APPROACH
Co-sponsored with FDA and ISPE, February 28- March 2, 2007, Bethesda North Marriott Hotel and Conference Center, North Bethesda, Maryland

Summary
This workshop was a follow up to the PQRI/FDA Workshop on A Drug Quality System for the 21st Century held in April 2003. It was being planned under the auspices of the Council on Pharmaceutical Quality at FDA and was co-sponsored with the American Association of Pharmaceutical Scientists and the International Society of Pharmaceutical Engineers. The 2-1/2 day program was intended to present progress on FDA's pharmaceutical quality initiatives. Furthermore, the workshop allowed regulated industry, other stakeholders, and the public to comment on progress made and to provide input to facilitate implementation of a common vision for pharmaceutical manufacturing in the 21st century. Among topics addressed: pharmaceutical development, chemistry, manufacturing and controls (CMC), manufacturing and quality operations, good manufacturing practices (GMP), quality systems and quality assurance. Over 500 scientists and regulators from industry and the FDA attended the workshop. The plenary sessions and the breakout sessions provided a number of recommendations which are now being reviewed by FDA and incorporated into current thinking.

APPENDIX 18
PHARMACEUTICAL INSPECTORATE TRAINING PROGRAM
A significant milestone was reached on FDA's progress under the Pharmaceutical Inspectorate program during the past year. Fourteen of FDA's experienced investigators became the initial members of the Pharmaceutical Inspectorate upon completion of Level III certification. In addition, one CDER employee achieved Level II certification. With this achievement, FDA's systematic effort began to produce its expected results towards constantly upgrading the scientific, technical and regulatory knowledge base and skill sets of its field investigators.

FDA's Level III Drug Investigator Certification Board and its Course Advisory Group comprised of experienced members from CDER, CVM, and ORA have now established a well-structured program towards further enhancing the work efficiency of FDA's Drug Investigators. For the first cohort of PI members, a three-weekdidactic training was conducted at FDA's ORA University. The PI curriculum and the didactic courses consisted of topics such as:

- Regulation of Pharmaceutical Quality in relation to FDA's mission of protecting and promoting the health of our citizens
- Risk Management and strategies used to determine product risk and their impact on public health
- Advanced Quality Systems and approaches used to build, assess, and maintain quality of pharmaceutical products that FDA regulates
- Discussion of emerging concepts and state-of-the art principles of applied pharmaceutical science, including causes of product variability
- Discourses on well-established and developing technologies used in the manufacturing, testing, and distribution of pharmaceutical products
- Extensive group interaction among FDA's product quality evaluation personnel consisting of Center reviewers, researchers, compliance officers, and field investigators about science-based and risk-based techniques and procedures used in the inspection of firms that manufacture CDER and CVM regulated products.

After the didactic courses, each candidate participated in a four-week visit to CDER and CVM Offices responsible for the assessment of product quality and regulatory compliance, according to FDA's "Detail Rotation" program.

Each of our Level III Drug Investigators who are now members of the Pharmaceutical Inspectorate commented that it was a rewarding experience for them to go through the entire PI training program. They described the PI program to be very useful in our effort to increase efficiency of FDA's operations through extensive interaction between application review, site inspection programs, and monitoring of pharmaceutical manufacturers' compliance to applicable regulations. Because of the highly valued nature of the Pharmaceutical Inspectorate training they received, almost every investigator has recommended that the Agency should consider offering many elements of the Level III Drug Investigator training in the earlier phases of a Drug Investigator's training, for further improving FDA's capabilities to protect and promote public health. The Council will consider implementing their suggestions.

APPENDIX 19
QUALITY BY DESIGN GRAPHIC

APPENDIX 20
ACRONYMS USED
AAPS: American Association of Pharmaceutical Scientists
BLA: Biologics License Application
CBER: Center for Biologics Evaluation and Research
CDER: Center for Drug Evaluation and Research
CDRH: Center for Devices and Radiological Health
CFR: Code of Federal Regulations
CFSAN: Center for Food Safety and Applied Nutrition
CGMP: Current Good Manufacturing Practices
CMC: Chemistry, Manufacturing and Controls
CRADA: Cooperative Research and Development Agreement
CVM: Center for Veterinary Medicine
DFS: Division File System
DHHD: Division of Human Resource Development, Office of Resource Management, Office of Regulatory Affairs
EIR: Establishment Inspection Reports
FDA: Food and Drug Administration
FMD: Field Management Directives
ICH: International Conference on Harmonization
IND: Investigational New Drug
ISO: International Standards Organization