

***PHARMACEUTICAL CGMPs
FOR THE 21ST CENTURY —
A RISK-BASED APPROACH***

FINAL REPORT

**Department of Health and Human Services
U.S Food and Drug Administration**

September 2004

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EXECUTIVE SUMMARY — KEY ACCOMPLISHMENTS

In August 2002, the Food and Drug Administration (FDA or the Agency) announced a significant new initiative, Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century, to enhance and modernize the regulation of pharmaceutical manufacturing and product quality — to bring a 21st century focus to this critical FDA responsibility. The initiative, which this final report describes in detail, was intended to modernize FDA's regulation of pharmaceutical quality for veterinary and human drugs and select human biological products such as vaccines. As part of this initiative, both the pharmaceutical, as well as the chemistry, manufacturing, and controls (CMC) regulatory programs were evaluated with the following objectives in mind.

- ◆ 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

Over the course of the 2 years, FDA released reports documenting its progress and plans. The first, issued on February 20, 2003, conveyed the initial accomplishments and listed the first steps toward achieving FDA's goals for a 21st century regulatory framework for pharmaceutical manufacturing. In September 2003, on the first anniversary of the initiative, FDA released its

second progress report and an outline of its implementation plan for achieving the objectives announced the previous year.

Early in the initiative, a number of multidisciplinary working groups were formed, comprising FDA experts from various areas of scientific and regulatory practice within FDA. These working groups have shaped the initiative during the past 2 years under the oversight of the FDA's current good manufacturing practice (CGMP) Steering Committee.

As a result of the diligent work of these groups, the FDA has completed its assessment of the existing CGMP programs. We assessed current practices as well as available new tools of enhancing manufacturing science. Our assessment helped us create a new framework for the regulatory oversight of manufacturing quality that is based on quality systems and risk management approaches. Our findings have put the Agency on a path to restructure its oversight of pharmaceutical quality regulation, thereby developing the product quality regulatory system of the future. The following remain our guiding principles:

- ◆ Risk-based orientation
- ◆ Science-based policies and standards
- ◆ Integrated quality systems orientation
- ◆ International cooperation
- ◆ Strong public health protection

Implementation of the envisioned new framework, the elements of which are explained in detail in this report, will require a highly educated and well-trained and integrated team of individuals throughout the FDA who use risk-based and science-based approaches for regulatory decision-making throughout the entire life-cycle of a product. We believe we have created a framework that will streamline the quality review of many products, allowing us to use our valuable resources in a more efficient manner. Our primary focus will remain the same: to minimize the risks to the public health associated with pharmaceutical product manufacturing.

To help implement this new framework in the coming years, the Agency has formed a ***Council on Pharmaceutical Quality***, which has been charged with policy development, coordination, and continuing change management, including the ongoing implementation of specific quality management systems within the FDA.

The following report explains the FDA's CGMPs for the 21st Century Initiative as well as the individual charges and achievements of the various working groups that have been involved in the initiative. The report also outlines our path forward in implementing the pharmaceutical quality regulatory system for the future. The report discusses in some detail various other documents that have resulted from work group activity. For example, a number of guidance documents have been developed that are being made available with this report, or will be available soon. We already have an extensive Web page on the CGMP initiative, and all of these documents, including this report, will be there, as they are made available.

Although a number of specific accomplishments have resulted from the CGMP Initiative, several key accomplishments are worth highlighting here.

❖ *ADOPTION OF QUALITY SYSTEMS MODEL FOR AGENCY OPERATIONS*

At the outset of the initiative, FDA conveyed its goal of bringing an integrated quality systems orientation to all Agency activities and programs. A specific goal was the development and implementation of a more systematic approach to regulating pharmaceutical quality, as well as more integration and collaboration among the different components of the Agency that are involved in pharmaceutical quality. The Quality Systems Framework Working Group, formed as a result of a restructuring of some the working groups at the 1-year mark of the initiative, developed such a model for the CGMP initiative, referencing key recognized external quality and risk management standards. During this past year, the Agency's Management Council — the highest management level group in FDA — reviewed the model and found it so impressive that they incorporated it into the FDA quality systems framework for application across the entire Agency. FDA will now be using a quality systems approach to improve the predictability, consistency, integration, and overall effectiveness of our entire regulatory operation. This quality systems model, now incorporated into the FDA Staff Manual Guide, *Quality Systems Framework for Internal Activities*, www.fda.gov/smg/vol3/2000/2020.html defines the essential quality elements to consider as part of any system that controls an internal FDA regulatory activity.

❖ *DEVELOPMENT OF QUALITY SYSTEMS GUIDANCE FOR CGMP REGULATION*

The Quality Systems Guidance Development working group considered what Agency guidance could be developed to encourage industry to implement the use of quality management systems and risk management principles. The Agency has released the results of this working group's efforts, the draft guidance for industry on *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations*. Once finalized, this guidance is intended to provide recommendations to the regulated industry on meeting the requirements of the Agency's CGMP regulations via a comprehensive quality systems approach, which encourages continuous improvement and risk management in the manufacturing of human and veterinary drugs, including human biological products. This guidance, when implemented, and other aspects of the initiative, (e.g., the pharmaceutical inspectorate), will work in concert with the new risk based pharmaceutical quality assessment system being developed by the Office of New Drug Chemistry (ONDC) within the Center for Drug Evaluation and Research (CDER).

❖ *IMPLEMENTATION OF RISK-BASED MANAGEMENT PLAN*

FDA has identified a risk-based orientation as one of the driving principles of the CGMP initiative. The progress outlined below reflects FDA's commitment to the adoption of risk management principles that will enhance the Agency's inspection and enforcement program, which is focused on protecting the public health.

- FDA's Strategic Action Plan

One year after the start of the CGMP initiative, FDA released the Strategic Action Plan for the Agency, *Protecting and Advancing America's Health*. The Agency's Strategic Plan identified efficient risk management as a key element. Efficient risk management requires using the best scientific data, developing quality standards, and using efficient systems and practices that provide clear and consistent decisions and communications for the American public and regulated industry. FDA has identified *efficient risk management* as the primary way to make the most effective use of Agency resources and address these challenges. This approach incorporates rigorous analysis to consistently identify the most important risks, and the use of a quality systems approach to designing, conducting, and evaluating FDA core business processes.

- Risk-based Model for Inspectional Oversight

The Agency has developed and will be piloting a risk-based model for prioritizing sites for manufacturing inspections. FDA publicly presented the highlights of this model on July 21, 2004, to the Manufacturing Subcommittee of the Pharmaceutical Science Advisory Committee. This model is explained later in this report and, in more detail, in the attached white paper.

- Ongoing Data Analysis

A complementary and ongoing approach to efficient risk management is an analysis underway by Professor Jeffrey Macher of Georgetown University and Professor Jackson Nickerson of Washington University, St. Louis. Using 13 years of data from more than 38,000 FDA inspections for more than 3,700 manufacturing facilities, their statistical analysis seeks to identify a wide variety of product-, process-, facility-, manufacturer-, and FDA-related factors that correlate with inspectional outcomes. Their analysis will be used to help refine the risk-based management of Agency resources.

- Part 11 Guidance

With the issuance in 2003 of the guidance for industry *Part 11, Electronic Records, Electronic Signatures — Scope and Application*, many barriers to scientific and technological advances were removed, and the use of risk-based approaches to managing computer systems is encouraged.

- Aseptic Processing Guidance

The final guidance for industry on *Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Process*, issued today, advocates a risk-based framework, underscoring the value of proactive approaches to ensure sterility. Among the sections of the guidance that address risk-based approaches are those relating to key roles played by personnel, design, environmental control, and media fills in an aseptic processing operation.

- ONDC Pharmaceutical Quality Assessment System

The Office of New Drug Chemistry (ONDC) within CDER has developed and is implementing a new risk-based pharmaceutical quality assessment system to replace its current CMC review process. This new system should reduce the need to submit manufacturing supplements and increase first-cycle approval of new drug applications, thereby making drug products available to patients in a timelier manner. The system should also encourage manufacturers to implement new technologies, such as process analytical technology, and facilitate continuous manufacturing improvements.

❖ *SCIENCE-BASED REGULATION OF PRODUCT QUALITY*

As pharmaceutical manufacturing evolves from an art to a science and engineering based activity, application of this enhanced science and engineering knowledge in regulatory decision-making, establishment of specifications, and evaluation of manufacturing processes should improve the efficiency and effectiveness of both manufacturing and regulatory decision-making. As a pillar of the initiative (and guiding principle), the Agency must ensure that science-based policies and standards form the foundation upon which product quality regulation is based. Because the American public is the ultimate customer of pharmaceutical manufacturing and because the public is often unable to judge the quality of a product, the goal of our regulatory system is to make sure that patients do not have to worry about the quality of their medicines.

We believe that using a scientific framework to find ways of mitigating risk while facilitating continuous improvement and innovation in pharmaceutical manufacturing is a key public health objective. Our shift from the current CMC review system to a new risk-based pharmaceutical quality assessment system within CDER's ONDC, explained in the section above, is one such example. This new system will encourage the implementation of new technologies, such as process analytical technology (PAT), and facilitate continuous manufacturing improvements via implementation of an effective quality system.

Quality and productivity improvement share a common element — reduction in variability through process understanding (e.g., application of knowledge throughout the product life-cycle). Reducing variability provides a *win-win* opportunity from both public health and industry perspectives. And, since 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 U.S. pharmaceutical manufacturing sector will be essential in the 21st century. The progress in the area of PAT and manufacturing science should prepare us well to meet the 21st century challenges.

- PAT team

The PAT Team and the Manufacturing Science Working Group have continued their collaboration and significant progress has been made in building consensus on the principles of manufacturing science and process understanding. The final PAT guidance

will issue soon, and the PAT team has completed its training. A significant support structure for the PAT guidance is evolving in the pharmaceutical community including the American Society of Testing Materials (ASTM) E55 committee on Pharmaceutical Applications of Process Analytical technology. Progress and next steps are described later in this report.

- International Collaborations

The FDA has increased its collaboration with international health and regulatory partners and will continue to actively collaborate with other regulatory authorities, in multilateral and international forums, to harmonize pharmaceutical quality standards or requirements to the fullest extent possible. Our active collaboration with other regulatory authorities as part of the International Conference on Harmonisation 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)¹ will continue. Agreement was reached last year by ICH to work on an internationally harmonized plan for developing a pharmaceutical quality system based on an integrated approach to risk management and science. FDA is developing bilateral and multilateral confidentiality agreements and specific information exchange agreements to facilitate these activities. Finally, the FDA is seeking membership in the Pharmaceutical Inspection Cooperation Scheme (PIC/S), a cooperative arrangement among health authorities whose purpose includes leading the international development, implementation, and maintenance of harmonized CGMP standards and quality systems of world-wide pharmaceutical inspectorates.

Accomplishments and specific achievements since 2003 related to the key accomplishments outlined in the above sections are discussed in detail in the following sections.

¹ The VICH is an international forum patterned after ICH that takes note of ICH experience in developing guidance related to veterinary medicinal products, including pharmaceuticals, biological products, and medicated premixes.

IMPLEMENTING THE FUTURE OF PHARMACEUTICAL MANUFACTURING REGULATION

FDA regulates pharmaceutical manufacturing to ensure that the drug supply in the United States is of consistently high quality. In the past, as a result of the many uncertainties in drug manufacturing, the FDA exercised extensive control over virtually every aspect of the manufacturing process. Consequently, pharmaceutical companies have often been reluctant to change their manufacturing processes and equipment because of perceived, and sometimes real, regulatory hurdles. In recent years, significant advances in manufacturing science, quality management systems, and risk management have taken place, yielding modern manufacturing tools that can be used to help ensure manufacturing quality. Such new tools enable manufacturers to detect, analyze, correct, and prevent problems and continuously improve their manufacturing processes. It has been the goal of the CGMP initiative to create a regulatory framework that will encourage pharmaceutical manufacturers to also make use of these modern tools, to facilitate the implementation of robust manufacturing processes that reliably produce pharmaceuticals of high quality and that accommodate process change to support continuous process improvement.

The quality management framework we have created has a number of elements. They are summarized in the following paragraphs.

Risk-Based Approaches

To keep pace with the many advances in manufacturing quality management and to enable the Agency to more effectively allocate its limited regulatory resources, the FDA is implementing a risk-based approach to regulating pharmaceutical manufacturing. The approach will be applied to the review, compliance, and inspectional components of FDA regulation.

The intensity of FDA oversight needed will be related to several factors, including the degree of a manufacturer's product and process understanding and the robustness of the quality system controlling their process. For example, changes to complex products (e.g., proteins, naturally derived products) made with complex manufacturing processes (or products that are less well understood from a manufacturing or quality attribute perspective) may need more regulatory oversight. Process changes with critical variables that have not been sufficiently defined (e.g., processes for many older products) may require the submission of additional data or comparability protocols. In other cases, changes in well understood processes could be managed under a firm's change control procedures. Additional factors in performing risk-based quality assessments include instances when manufacturing processes are crucial to the safety of the product (e.g., adventitious agent clearance, inactivation of live product) or when products serve a critical medical need or have a critical public health impact (e.g., products for the prevention of communicable diseases).

Other considerations, such as public health impact and the compliance status or compliance history of the manufacturer, will continue to influence the intensity of FDA oversight.

Beginning in the fall of 2004, FDA will begin using a risk-based approach for prioritizing domestic manufacturing site inspections for certain human pharmaceuticals. This approach will help the Agency predict where its inspections are likely to achieve the greatest public health impact. The frequency and/or scope of inspections will be reduced for firms that FDA determines have acquired sufficient process understanding and have succeeded in implementing effective quality systems approaches. We hope that this approach will create positive incentives for other firms to implement effective quality systems at their manufacturing sites.

At the same time, the Agency will continue to apply risk-based principles to the product quality review process (i.e., the product quality aspects of the investigational new drug (IND); preapproval chemistry, manufacturing, and controls (CMC); and postapproval supplement processes). FDA is expecting that these risk-based changes will facilitate continuous improvement in pharmaceutical manufacturing and improve availability of new drugs while increasing product quality and process efficiency.

The Office of New Drug Chemistry (ONDC), within CDER, is taking the first step toward establishing a new risk-based pharmaceutical quality assessment system to replace its current CMC review system. This new assessment system will focus on critical pharmaceutical quality attributes (chemistry, pharmaceutical formulation, and manufacturing processes as they relate to product performance) and their relevance to safety and efficacy. The new assessment system has the potential to reduce the regulatory burden in proportion to the manufacturer's efforts to achieve continuous improvement and manufacturing process optimization. FDA's regulatory strategies will be based on the degree to which an application reflects a manufacturer's understanding of manufacturing process, process control, and quality systems.

Quality Systems Approach

Best practices in quality management methods, particularly in other high-tech industries, have undergone significant progress since 1978 when the CGMP regulations were last updated. The FDA wants to ensure that its regulatory practices encourage similar progress in the pharmaceutical industry. The draft guidance for industry *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice*, issued today, describes a comprehensive quality systems model that manufacturers could use and highlights the model's consistency with the CGMP regulations for manufacturing human and veterinary drugs, including biological products. The guidance explains how manufacturers implementing such a comprehensive quality system can ensure that they comply fully with the CGMP regulations (21 CFR parts 210 and 211). This guidance is intended to serve as a bridge between the 1978 regulations and our current understanding of quality systems.

Enhanced Internal Regulatory Coordination

As mentioned during earlier updates, the FDA's product quality regulatory approach of the future will include a staff of highly trained individuals, known as the Pharmaceutical Inspectorate (PI), within the Office of Regulatory Affairs (ORA). These individuals will devote most of their time to conducting drug quality inspections of prescription drug manufacturers and other complex or

high-risk pharmaceutical operations. The PI will also conduct preapproval inspections and will continue to be trained on the latest science and manufacturing technology. Joint technical training sessions and creation of new mechanisms for collaboration among review, compliance, and inspectional personnel will allow FDA to enhance the consistency and sound scientific basis of its regulatory decisions. The PI will enhance the Agency's overall inspection program, which includes preapproval inspections conducted by CDER and CBER personnel for licensed biologics and Team Biologics, a program that includes a core team of highly trained individuals for biological product inspections.

International Collaboration

It is crucial that pharmaceutical quality standards or requirements be harmonized internationally to the fullest extent possible. The development of a global economy during the last few decades has had a profound effect on product development. To achieve its public health goals and leverage its resources, the FDA has increased its collaboration with international health and regulatory partners. Working together, international regulatory authorities have continued to harmonize their activities, especially in quality-related areas, and increased the sharing of regulatory information. Harmonizing scientific standards and assessments of drug product quality will promote technological innovation and, ultimately, enhance public health promotion and protection. The FDA will continue to actively collaborate 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). In November 2003, an agreement was reached by ICH to work on an internationally harmonized plan for developing a pharmaceutical quality system based on an integrated approach to risk management and science. FDA is developing bilateral and multilateral confidentiality agreements and specific information exchange agreements to facilitate these activities.

It is important to note that FDA will seek membership in the Pharmaceutical Inspection Cooperation Scheme (PIC/S), a cooperative arrangement between health authorities whose purpose includes leading the international development, implementation, and maintenance of harmonized CGMP standards and quality systems of world-wide pharmaceutical inspectorates. 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. FDA expects that its involvement with PIC/S will further increase opportunities for information sharing and facilitate steps toward harmonizing the interpretation and application of CGMP requirements.

Analysis of CGMP Requirements

As reported in the September 2003 announcement, FDA created a CGMP Harmonization Analysis working group to analyze internal and external CGMP requirements, including those related to quality systems. This working group performed a formal analysis of 21 CFR parts 210 and 211 against the GMPs of the European Union (EU), PIC/S, as well as other Agency CGMP

regulations to identify the differences and consider the value of adding or changing the current regulations. Upon completion of their analysis, the working group concluded that there are many more similarities than differences among the various regulations. Where differences exist, the working group found that they can often be explained by unique aspects of the specific product subject to the regulation. For example, the device quality system regulation (21 CFR 820.200) requires that procedures for performing servicing be established and maintained by the manufacturer, where appropriate, which is an activity unique to devices. The EU GMPs have explicit requirements for separate areas for maintenance workshops and weighing of materials, whereas 21 CFR 211.42(c) requires that operations be performed within specifically defined areas of adequate size.

Based on the working group's analysis, the Agency decided to take an incremental approach to modifying parts 210 and 211 while pursuing international harmonization through ICH and PIC/S. 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 and 211 both internationally and with other Agency regulations.

Keeping the key concepts in mind, the Agency intends to withdraw its ***1996 Proposed Rule: Current Good Manufacturing Practice: Amendment of Certain Requirements for Finished Pharmaceuticals*** and take a new look at the comments received on that proposal in the context of more recent scientific and technical advances and quality systems and risk management concepts.

FDA has also taken steps to clarify our approach to process validation, which was a subject of the 1996 proposal. Earlier this year, FDA published a revised compliance policy guide (CPG) entitled *Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval* (CPG 7132c.08, Sec.490.100). FDA intends to further address the validation aspects of the CGMPs by updating the 1987 *Guideline on Process Validation*, as announced on March 12, 2004. A draft revision for public comment will address the relationship between modern quality systems and manufacturing science advances to the conduct of process validation. We hope to issue this draft guidance in 2005.

Specific activities and achievements related to implementing the future of pharmaceutical manufacturing regulation are outlined in more detail in the following pages.

SPECIFIC ACHIEVEMENTS SINCE 2003 PROGRESS REPORT

In September 2003, the CGMP Steering Committee issued its second progress report. The following paragraphs outline achievements since 2003 as well as future plans, as appropriate, for the various working groups.

21 CFR Part 11 – Electronic Records Requirements

Consistent with the objectives of our CGMPs for the 21st Century Initiative, FDA has created a risk-based approach that manufacturers can use to comply with Part 11 electronic records requirements.

As a first step, FDA issued a draft guidance in September 2003, to clarify the scope and application of part 11 and describe several aspects of the regulation for which enforcement discretion can be exercised. Following the evaluation of public comments, the guidance for industry *Part 11, Electronic Records, Electronic Signatures — Scope and Application*, was finalized. FDA's next step was to publish a notice in the *Federal Register* on April 8, 2004, announcing its intention to amend part 11 and seeking the input from the public. The comment period for this notice closed on July 9, 2004. Although FDA had originally intended to have a public meeting on the subject, we have determined that the extensive written comments submitted to the docket provide an adequate basis for beginning the rulemaking process. All interested parties will have ample time to comment when the proposed amendment for part 11 is issued. It is expected that this proposed amendment will issue for public comment during 2005.

Next, we have issued a draft guidance for industry titled *Computerized Systems Used in Clinical Trials*. Once finalized, the guidance will replace the guidance of the same name issued in April 1999. This guidance is being revised to make it consistent with Agency policy as reflected in the part 11 final guidance. The draft revision reflects policy that also is consistent with the Agency's international harmonization efforts. The guidance provides recommendations about computerized systems that are used to create, modify, maintain, archive, retrieve, or transmit clinical data intended for submission to FDA. These data form the basis for the Agency's decisions regarding the safety and effectiveness of new human and animal drugs, biological products, medical devices, and certain food and color additives. Because the data have broad public health significance, they are expected to be of high quality and integrity.

A Technical Dispute Resolution Process for CGMP Disputes

The Dispute Resolution Working Group began developing dispute resolution procedures for CGMPs by holding a meeting with the related trade associations to solicit their concerns and suggestions regarding the current processes for raising and resolving disputes related to CGMP inspectional findings. This information supported the development of a draft guidance *Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP*, which

issued in August 2003. Once finalized, the document will 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.

This draft became the foundation for the launch of a 12-month *Dispute Resolution Pilot Program* that began on January 1, 2004, and is still ongoing. The Working Group has reviewed all of the comments submitted in response to the draft guidance and is closely monitoring the operation of the pilot program to help determine the value of the dispute resolution process and learn what changes might improve the guidance and its implementation.

Most recently, on September 8, 2004, the Working Group held a second meeting with interested trade associations to hear their thoughts on the pilot program and any final comments on the draft guidance. The Working Group will make appropriate modifications as it finalizes the final guidance on this subject, targeted for early 2005. Internally, the Working Group is completing the formation of the Tier II Panel, as outlined in the draft guidance, and establishing procedures for public disclosure of the substance of issues that are raised through the dispute resolution process.

Changed Procedures for Drug CGMP Warning Letters

FDA has revised its regulatory procedures for determining when to issue warning letters in response to noncompliance with CGMP requirements. Beginning in March 2003, all proposals to issue warning letters to human and animal drug and medicated feed manufacturers are reviewed by the centers with product jurisdiction and by the Office of the Chief Counsel. The final letter is issued by the recommending field office.

The centers' continued role in the process will ensure that adverse findings will be based on the best science available. We are enhancing communication and coordination between the field and centers with the goal of identifying possible program inconsistencies that can be resolved before a warning letter is issued.

In March 2004, the Agency completed an internal assessment of the content, consistency, and outcome of the Warning Letter recommendation process related to CGMP deficiencies for human and animal drug and medicated feeds. Overall, the assessment showed that the rescission of direct reference authority (i.e., ability of district offices to issue CGMP warning letters prior to center concurrence) added value to the CGMP warning letter process. Steps have been initiated to address the concerns noted in the assessment.

Finally, the ORA Office of Enforcement is leading an Agency-wide initiative to implement a quality system for overseeing the warning letter process.

Cooperation with International Regulatory Partners

As international cooperation has been one of the guiding principles of this initiative, FDA's international strategy to improve the quality of pharmaceutical products includes enhancement of

relevant international harmonization activities and increased sharing of regulatory information with counterpart authorities in other countries.

FDA believes that the harmonization of international scientific standards on drug product quality will promote technological innovation for enhanced public health promotion and protection. To facilitate this, CDER and CBER actively collaborate with other regulatory authorities via the International Conference on Harmonisation of the Technical Requirements for Registration of Pharmaceuticals (ICH). The Center for Veterinary Medicine (CVM) is a participant in a separate International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), an international harmonization process for animal drug products. CVM also attends ICH meetings to facilitate FDA harmonization for human and animal pharmaceutical drug products and gain knowledge for development of comparable guidelines in the VICH international harmonization process for animal drug products.

In November 2003, ICH agreed to work on a harmonized plan to develop a pharmaceutical quality system based on an integrated approach to risk management and science.

To implement its vision, ICH established two Expert Working Groups (EWGs) on pharmaceutical development. The first (ICH Q8 EWG) seeks to incorporate elements of risk and *quality by design* throughout the life-cycle of the product. The ICH Q8 EWG articulated the “desired state” for pharmaceutical manufacturing in the 21st century as:

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

The second working group (ICH Q9 EWG) is trying to better define the principles by which risk management will be integrated into decisions by regulators and industry regarding quality, including CGMP compliance. The outcome should be a risk management framework intended to lead to more consistent science-based decision-making across the life-cycle of a product. These two expert working groups work in parallel and exchange information on a regular basis.

Currently, ICH Q8 EWG is developing a guidance describing 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. The Pharmaceutical Development section will provide the Agency the opportunity to use the knowledge gained through both the application of scientific approaches and various risk management strategies to the development and review of a product and its manufacturing process. Pharmaceutical development information will help to reduce uncertainty with respect to critical variables, sources of variability, and their clinical relevance while improving FDA's ability to make risk-based decisions. In the current state, uncertainty during the review process 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 being spent debating issues related to acceptable variability, need for additional testing controls, 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.

The emerging 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) and 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

It is hoped that this document will reach ICH step 2 in November, 2004. ICH Q8 EWG is working closely with the ICH Q9 EWG to incorporate certain risk management principles in pharmaceutical development.

At the same time, FDA continues its active participation in the development of an internationally harmonized guidance on quality risk management by the ICH Q9 EWG. Since adoption of this topic by the ICH Steering Committee in November of 2003, EWG meetings were held in March and June of 2004. The next EWG meetings are scheduled for September 29, 2004, (via telephone) and November 2004. FDA believes that Q9 will encourage industry and regulators to increase the use of risk management tools to ensure drug quality. In addition, the development of harmonized guidance on this topic will improve the level of discourse, both within and among regulators and industry, concerning risk management tools and terminology.

While Q8 and Q9 continue to progress, ICH will begin to pursue Q10, a document that will cover life-cycle management for process and system control. Q10 is intended to promote postapproval improvements to manufacturing processes. This document will address current pressures felt by both regulatory authorities and industry with respect to postapproval changes. For the regulatory authority, there is a need to reduce the burden of supplement review and provide review oversight to only certain changes using a risk basis. For manufacturers, the regulatory process should not delay implementation of improvements in manufacturing processes once a product has been approved for marketing. In addition, it is hoped that manufacturers will also be more willing to use innovative solutions to resolve quality problems.

As already mentioned, to further advance its collaboration with international partners and strengthen its oversight of non-U.S. drug manufacturing sites that produce FDA-approved pharmaceuticals for Americans, FDA will be seeking membership in the Pharmaceutical Inspection Cooperation Scheme (PIC/S).

Science-Based Policies and Standards to Facilitate Innovation

1. *Aseptic Processing Guidance*

Today, the FDA has issued the final guidance for industry *Sterile Drug Products Produced by Aseptic Processing-Current Good Manufacturing Practice*. This guidance replaces the 1987 *Guideline on Sterile Drug Products Produced by Aseptic Processing*. The guidance recommends "building quality into products" through science-based facility, equipment, process, and system design for sterile drug manufacture. This guidance includes two central themes:

- Ensure robust product protection through adequate design and control of equipment and facilities
- Ensure that the operational and raw material inputs are predictable through adequate quality control and quality assurance

Sterile drug products are a major component in FDA's risk-based inspectional program. Through this guidance, FDA hopes to facilitate the application of good science and modern technology, and thus lessen or eliminate avoidable risks from aseptic operations. The adoption of better contamination prevention practices and a higher assurance of process consistency is expected to reduce the incidence of sterile drug manufacturing problems, thus facilitating the ongoing availability of these often therapeutically significant pharmaceuticals.

Consistent with the objectives of the initiative, the guidance encourages the adoption of new technological advances by the pharmaceutical industry. In particular, the guidance underscores the advantages that automation and isolation concepts offer in protecting the exposed sterile drug product during its aseptic manufacture. The guidance also encourages use of modern microbiological testing methods that are more accurate and precise. It also advocates a risk-based and quality system framework that stresses contamination prevention. In particular, risk-based approaches are covered in sections describing the roles played by personnel, design, environmental control, and media fills in an aseptic processing operation. Through this guidance, FDA hopes to facilitate the application of good science and modern technology, and thus lessen, or eliminate, avoidable risks from aseptic operations. The adoption of better contamination prevention practices and a higher assurance of process consistency is expected to reduce the incidence of sterile drug manufacturing problems, thus facilitating the ongoing availability of these often therapeutically significant pharmaceuticals.

2. *PAT Guidance and the PAT Team Approach*

This guidance, made available today, 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 the 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 errors
- Improving energy and material use and increasing capacity
- Facilitating continuous processing to improve efficiency and manage variability

By definition PAT brings a systems perspective to the design and control of manufacturing processes. Therefore, a systems approach was absolutely necessary 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 entire team 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 preoperational 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 have been removed, and the 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 the following.

- 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 the 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.

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 preoperational 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 PAT Framework is supported by the ASTM International Technical Committee E55: Pharmaceutical Applications of Process Analytical Technology

The pharmaceutical community was asked to take on responsibility for developing standards to support the introduction of innovative tools and technologies under the PAT framework. In this regard, ASTM International provided an excellent process to identify and develop standards in a timely manner using technical expertise in all relevant disciplines from the pharmaceutical community and other industrial sectors. The FDA's PAT team worked with ASTM International to establish the *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 International provides an opportunity to bring a strong engineering process control perspective and to learn from other industrial sectors that have used 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. Three subcommittees of E55 include PAT system management, PAT system implementation & practice, and PAT terminology. The standard E2363-04: Standard Terminology related to PAT was recently published. The PAT Team is represented on E55 committees with a goal to ensure that standards developed are aligned with the PAT guidance and acceptable to FDA.

The definition of PAT in the FDA guidance and ASTM E55 as well as 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. The next steps in the PAT process include:

- Following the issuance of the PAT guidance, workshops are planned in the three ICH regions.
- The PAT process will be incorporated into the FDA's quality system.
- FDA will continue to participate in the ASTM E55 Committee to support development of standards consistent with the PAT framework.
- We will help to strengthen the emerging support structure in scientific societies and association (e.g., AAPS, ISPE, IFPATMA, PDA, and others).
- CBER (as observer) and a Pharmaceutical Inspectorate member from Team-Biologics will join the PAT Steering Committee.
- The second PAT team will be selected (to include Office of Biotechnology, Compliance and ORA Team-Biologics CGMP Inspection staff).
- Teambuilding, training, and certification of the second team will begin.
- Invitations will be extended to Health Canada, Japan's Ministry of Health, Labour and Welfare (MHLW) and EMEA to participate in the second training program.
- We will share lessons learned and training materials with Health Canada, MHLW, and EMEA.

- The PAT team will continue its education and training.
- PAT Team and Team-Biologics will collaborate to identify best practices and lessons learned; recommendations will be sought on how to develop a team approach between Product Specialists and Pharmaceutical Inspectorate.
- We will seek out critical path research and research collaborations (academia and industry).
- Following the second PAT team training, we will expand the PAT program to include all Product Specialist and Pharmaceutical Inspectorate.

3. *Comparability Protocols*

To provide the most effective public health protection, FDA must determine how best to perform regulatory review based on its understanding of product risk and how best to mitigate such risk. In the past, FDA has depended on notification of postmarket manufacturing changes on all products without considering the extensiveness of change and risks associated. These notifications — supplements to approved NDAs, BLAs and ANDAs — are reviewed by CMC reviewers who in turn communicate with manufacturers on the suitability of the changes. Decisions on postmarket changes need to be made based on an understanding of the process and risks associated with the changes on the quality of the manufactured product. Knowing that a company has a scientific and technical understanding of its manufacturing processes and relationship to the specific manufactured product at the development stage enables the Agency to access risks and make decisions as to when and if additional information is needed before a postapproval manufacturing change is implemented.

The Changes Without Prior Review Working Group was established to look at various options for a systematic risk-based approach to the review process for post-approval manufacturing changes.

The working group focused mainly on establishing a mechanism for regulatory relief through the use of comparability protocol. A draft guidance *Comparability Protocols Protein Drug Products and Biological Products - Chemistry, Manufacturing, and Controls Information* was issued in September 2003, which describes recommendations for preparing and using predefined change evaluation plans, generally referred to as comparability protocols. A *comparability protocol* is a comprehensive, detailed, written plan that describes the specific tests and studies, analytical procedures, and acceptance criteria to be achieved to demonstrate the lack of adverse effect for a specified type of CMC change that may relate to the safety or effectiveness of the drug product. A reduced reporting category can be justified when a comparability protocol provides evidence that an applicant has a scientific and technological understanding of the drug, manufacturing process, controls, proposed change and potential effect of that change on the product quality. The use of a comparability protocol could allow an applicant to implement a CMC change without waiting for prior approval from FDA and therefore place a product in distribution sooner than without the use of a protocol. A comparability protocol may also provide a means to facilitate process improvement and/or process optimization. In some cases, a comparability protocol may provide a means to prevent or mitigate drug supply disruptions or shortages.

This guidance is currently being finalized to incorporate the tenets of the risk-based approach to ensuring reductions in postapproval manufacturing changes and to ensure that appropriate manufacturing science is incorporated in the decision-making processes.

The Agency will continue to incorporate up-to-date concepts of risk management and quality systems approaches. The Agency will also continue to identify opportunities for improving coordination between review and inspection activities to identify and implement opportunities for managing manufacturing changes without the need for prior FDA review or approval. The following opportunities are being considered.

- 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.
- Under the Manufacturing Subcommittee of the Advisory Committee for Pharmaceutical Science (ACPS), a working group will be formed to identify specific steps needed to move towards the desired state. The group will be asked to develop case examples to support the ICH Q8 document and CPG 7132c.08 and to illustrate the relationship between an adequate level of process understanding and regulatory flexibility to make changes without prior review.
- ACPS recommendations on regulatory flexibility for postapproval changes (e.g., reduce the need for prior review) will be considered for modifying the draft Comparability Protocol Guidance (for small molecules only).

Manufacturing Science – The Basis for Innovation and Continuous Improvement in Pharmaceutical Product Development

Continuous improvement is an essential element in a modern quality system. Its aim is to improve efficiency by optimizing a process and eliminating wasted efforts in production. Improvement efforts are carried out in a structured manner with appropriate predefined protocol and oversight. These efforts are primarily directed towards reducing variability in a process and product quality characteristics and are not for changing the fundamental design of a manufacturing process.

Generally the term *continuous improvement* is broadly used for all improvement efforts including those that result from *corrective 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.

In the current state corrective actions are the dominant mode for improvement and continuous improvement is difficult. The attached white paper entitled Pharmaceutical CGMPs for the 21st Century: Innovation and Continuous Improvement in Pharmaceutical Manufacturing examines the challenges for continuous improvement in the manufacturing process for pharmaceutical dosage forms. It is a combined report of the PAT team and the Manufacturing Science Working Group and provides a summary of their learning, contributions and proposed next steps for moving towards the desired state of pharmaceutical manufacturing in the 21st century.

It provides a systems view of the current system and describes the desired state and explains how the combined work products of the CGMP initiative are positioned to provide a comprehensive set of regulatory tools to facilitate the journey to the desired state. However, the challenge ahead is significant. At the end of the CGMP Initiative the pharmaceutical community has arrived at a cross-road; one path goes towards the desired state and the other maintains the current state. The path towards the desired state is unfamiliar to many while the current state provides the comfort of predictability. The Agency hopes the pharmaceutical community will choose to move towards the desired state.

Product Specialist on 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 Biologics). This principle was used to develop the PAT team. To accommodate specific objectives of the initiative and the need for a systems approach in the PAT team, team building and joint training and a certification process were developed. The entire team of CMC reviewers, CGMP investigators and compliance officers trained together on all aspects of PAT.

The PAT team building and training program identified several challenges. Of these the most critical challenge was that of organizational barrier (review/compliance/inspections). Team

building exercises and a joint training program were critical for overcoming the organizational barriers and communication challenges.

Lessons learned from the PAT team and Team-Biologics will be used for the Product Specialists on Inspection program. Team building and joint training opportunities will be created for CMC reviewers, compliance officers and investigators, including the Pharmaceutical Inspectorate on the work products of CGMP Initiative prior to initiation the Product Specialists on Inspection program.

Improved Integration of the Preapproval and CGMP Inspection Programs

To improve the integration of the preapproval and CGMP inspection programs, a memorandum of understanding (MOU) between CDER and ORA, signed on August 22, 2003, establishing the Pharmaceutical Inspectorate (PI) and defining the roles and relationships of CDER and ORA. The PI will be a staff of highly trained individuals within ORA who will devote most of their time to conducting drug quality inspections of identified pharmaceutical operations. The PI will also conduct preapproval inspections and participate in various other investigations that require their technical expertise.

The previously established Level III Drug Investigator Certification Board reviewed submission packets and selected 26 candidates for membership into the PI. The curriculum was established, and a course advisory group developed the first of several PI training modules, which were presented in August 2004. The next set of training modules will be delivered in January 2005, and a third set of training modules will be presented in mid-2005. In keeping with the effort to foster a close working relationship between the individuals in the field and individuals in CDER, CVM, and CBER; the staff of Center Compliance Offices and the review divisions participated in the initial training modules along with the ORA staff. The PI candidates will also go on temporary details to offices in relevant centers to gain a better understanding of the work of the different centers. These temporary details will allow for team building among the field PI candidates and center staff. The experience of ORA and CBER in the development and implementation of the Team Biologics Program has served to inform the development of the PI program.

To serve as a member of the PI, an investigator will have to obtain and maintain a Level III Drug Investigator Certification. The Level III Drug Investigator Certification signifies that an investigator is primarily working on highly complex drug inspectional work, has been endorsed by his or her district, and has been selected by the Level III Drug Investigator Certification Board. The investigator will receive extensive training on advanced technology in pharmaceutical manufacturing and complete a detail in the center.

Next steps for the PI are to define, under the risk-based quality management system, the process and procedures for interactions among the involved centers and the field offices and the role of the PI members in those interactions. This segment of the quality systems framework will be implemented in the involved centers and the field to ensure quality and consistency and regulatory effectiveness of inspections.

FDA has also taken steps to improve its preapproval inspection (PAI) program. In the September 2003 update, it was announced that an interim change had been made to Compliance Program 7346.832, Preapproval Inspections. That change eliminated mandatory categories for performing inspections and listed a smaller number of categories that should trigger inspections based on the risk and complexity of the product subject to the pending application. The plan for the next year is to revamp this entire program to further reflect the thinking that has been derived from the CGMP for the 21st Century Initiative, including means for better Agency communication from review to inspection on product design, identifying process issues that are most relevant to product design, and the use of center specialists on inspections.

Quality Management Systems

During the past 2 years, FDA has made significant strides in designing and implementing programs to encourage and manage the quality of pharmaceuticals with a more systematic approach. The value of systematic approaches has been embraced both within the Agency as well as by the industry at large. Some of the pivotal components of FDA's own achievements have been highlighted previously. Although all of the working groups that are a part of this initiative have some aspect of quality management or assurance in their plans, this has been the sole focus for several of the working groups.

The Quality Systems Working Group, formed at the launch of the initiative, was dedicated to enhancing the consistency and predictability of FDA's approach to production quality and safety assurance among our centers and field components. The Quality Systems Working Group completed its initial charge in the summer of 2003 and was then reformed into three new working groups (WGs): the Quality Systems Framework WG, the Quality Systems Guidance Development WG, and the CGMP Harmonization Analysis WG. In addition, two other related workgroups were formed: one for quality communications and another for quality systems implementation. The communications group was charged with developing a mechanism similar to CDER's *CGMP Notes* that, consistent with good guidance practices, can quickly communicate FDA decisions and interpretations related to CGMPs and FDA inspectional findings to FDA staff and the public to improve the quality of both pharmaceutical products and regulatory activities. The focus of the second group is coordination with the implementation of a quality program for FDA's Team Biologics, which is being implemented by the Team Biologics Operations Group. The achievements of these groups are discussed here.

1. Quality Systems Framework

The Quality Systems Framework WG has developed a standard quality systems framework that integrates and enhances the Agency's existing and planned internal quality programs. This quality systems framework was created to ensure quality and consistency of reviews, inspections, and other regulatory activities. The framework provides common vocabulary and required system elements. Elements include typical quality systems requirements, such as ensuring that there are process plans with written procedures; well-trained staff; record keeping and review; knowledge sharing and coordination; and continuous process and product evaluation and improvement.

The Quality Systems Framework for Internal Activities was approved by the FDA Management Council and incorporated into the FDA Staff Manual Guides to demonstrate executive commitment and to ensure Agency-wide implementation of quality systems approaches. To provide Agency-wide advice regarding the implementation of quality systems, the Management Council chartered a new subcommittee on July 1, 2004, the Quality Resource and Guidance Team (QRGT). The QRGT has developed a White Paper, *Defining the Customer in a Regulatory Agency* to assist FDA components in implementing internal quality systems. The Quality Systems Framework emphasizes customer identification as a critical step in developing quality awareness and quality system effectiveness.

In addition to the FDA quality systems work that is already underway discussed earlier, other important projects are being undertaken using the new FDA Quality Systems Framework:

- Warning Letters for CGMP-related issues
- Recalls
- Pharmaceutical Inspectorate
- PAT initiative

2. *Quality Systems Guidance Development*

The draft guidance *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations* is intended to provide recommendations on how to meet the requirements of the CGMP regulations while using a comprehensive quality systems approach to the manufacturing of human and veterinary drugs, including biological drug products.

This draft guidance provides a contemporary framework for implementing quality by design, continuous improvement and risk management in the drug manufacturing process. The guidance, along with the flexibility of the CGMP regulations, allows manufacturers to implement modern quality systems in their manufacturing operations in a manner that is tailored to their specific manufacturing environment. The resulting robust quality system may serve to lower the need for regulatory oversight, allowing for more efficient, focused inspections and less review oversight.

Quality principles are inherent in the CGMP regulations. However, the regulations do not fully delineate the means by which quality is achieved during the manufacture of pharmaceuticals. The *Quality Systems* guidance, once finalized, will describe a comprehensive quality systems approach to drug manufacturing that correlates closely with the regulatory requirements. The elements that make up this approach intertwine with the basic principles of CGMP and are instrumental to successful pharmaceutical development and manufacture. The draft guidance is consistent with Agency efforts to harmonize with international regulatory standards as well as to implement a modern quality systems approach for all medical products under FDA regulation.

A more uniform approach to quality systems will, in turn, facilitate our handling of issues raised when combining products (e.g., a drug with a device). Because we will be receiving applications on increasing numbers of combinations products, we have developed a draft guidance for

industry on *Current Good Manufacturing Practice for Combination Products*, a first step in standardizing and harmonizing quality requirements.

3. *GMP Harmonization Analysis*

As part of the initial announcement in 2002, FDA indicated that the CGMP regulations for pharmaceutical products (21 CFR parts 210, 211) “appear to provide a degree of flexibility to allow the Agency to shift the emphasis to a science-based, risk management approach.” However, the evaluation of comments from the May 1996 proposed drug CGMP amendments will continue, and consideration will be given to revising these regulations and others (e.g., 21 CFR 11) in the future.

The GMP Harmonization Analysis Working Group was charged with the challenging task to, “Perform a formal analysis of 21 CFR 210 and 211 against: EU GMPs, PIC/S and other CGMP regulations across the Agency,” the goal being “to call out the differences and benchmark against those to determine the value of adding to or changing the current 210 and 211 regulations.”

The working group, comprising members from CBER, CDER, CDRH, CFSAN, CVM, ORA and the Office of Combination Products, assigned the comparisons accordingly:

- CBER, CDRH, and ORA members compared 210/211 with 820
- CDER members compared 210/211 with the EU GMPs
- CVM members compared 210/211 with 226 and compared it looking the opposite way, from 226 to 210/211
- CFSAN members compared 210/211 with Juice HACCP while an ORA member compared Juice HACCP with 210/211.
- A CFSAN member also compared 210/211 with 110/111.

The working group determined that the EU GMPs and the PIC/S GMPs were virtually identical, in base requirements, although the EU GMPs are more comprehensive. Therefore, the working group decided to focus on the EU GMP comparison.

Upon completion of its assessment, the group concluded that there are many more similarities than differences among the various regulations, and, where differences do exist, they are often related to the commodity in question. Although a number of differences were identified between Parts 210/211 and the main EU GMPs, most were not considered substantive.

To reinforce the Agency’s decision stated earlier in this report, based on the analysis of this working group, FDA will take an incremental approach to modifying parts 210/211, while pursuing international harmonization through ICH and PIC/S. 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.

This working group will carefully consider comments on the draft Quality Systems guidance as well. The Agency believes those comments will provide an opportunity to better understand current industry practice in the area of quality systems. Although the Agency intends to withdraw the 1996 Proposed Rule: Current Good Manufacturing Practice: Amendment of Certain Requirements for Finished Pharmaceuticals, it will not abandon the important concepts presented in that proposal. The Agency will review those concepts in light of the many comments submitted to the proposed rule, more recent scientific and technical advances, and quality systems principles in going forward with rulemaking to incrementally modify parts 210/211.

4. *Process Validation*

We have begun updating our current thinking on validation under a Cross-Agency Process Validation workgroup led by CDER's Office of Compliance Coordinating Committee with participation from CDER, CBER, ORA and CVM. In March of this year, FDA began this process issuing a compliance policy guide (CPG) entitled *Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval* (CPG 7132c.08, Sec 490.100). The CPG stresses the importance of rational experimental design and ongoing evaluation of data. The document also notes that achieving and maintaining a state of control for a process begins at the process development phase and continues throughout the commercial phase of a product's life-cycle. The CPG incorporates risk-based approaches with respect to inspectional scrutiny; use of advanced technologies, and by articulating more clearly the role of conformance batches in the product life-cycle. The document clearly signals that a focus on three full-scale production batches would fail to recognize the complete story on validation.

5. *GMP/Good Guidance Practices*

On August 4, 2004, FDA implemented a new approach to providing timely guidance on CGMP-related questions on human, animal, and biological drug products. This approach will enable more widespread dissemination of CGMP information and provide more transparency of FDA policy concerning CGMPs. Guidance will be provided in a question and answer format. The first set of questions and answers can be found at <http://www.fda.gov/cder/guidance/cGMPs/default.htm>. New questions and answers will be provided as they arise. This resource is being co-sponsored by CDER, CVM, CBER, and ORA.

Agency guidance represents the FDA's current thinking on a specific topic ([21 CFR 10.115](#)). It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach can be used if the approach satisfies the requirements of the applicable statutes and regulations. Inquiries for information concerning a specific guidance document, should be directed to the originating office.

6. *Related Activities*

In conjunction with all of the CGMP activities, FDA hosted an internal seminar series for all FDA units involved in the regulation of pharmaceuticals. This series was entitled Quality Systems and Risk-Based Approaches and their Application to FDA Pharmaceutical Product Quality Regulation. Over a 4-month period, six seminars were presented that addressed quality systems and risk management approaches. Speakers at the seminars were leaders from industry, academia, and other government agencies who have had extensive experience in the quality and risk arenas. The seminars were designed to be informative and to stimulate thoughts about implementing quality systems within the Agency and how the Agency might add risk-based components to their regulatory structure. Approximately 130 FDA staff and managers attended the presentations in person at an FDA location while several hundred more viewed the presentations from remote sites served by satellite video.

The presentations described the process of implementing quality systems to build a quality organization, the inclusion of risk-management approaches, and variation risk management (VRM), an approach aimed at allocating organizational resources to achieve maximum impact on manufacturing quality. The presentations focused on the key elements needed to implement quality systems successfully and to maximize the benefits. A follow-up survey of participants resulted in the series receiving very high ratings and requests for and suggestions for additional speakers on related topics in the future.

Risk Management — Risk-Based Inspection Site Selection

This working group's development of the previously discussed risk-based model will assist the Agency in further prioritizing domestic manufacturing sites for human drug CGMP inspections. The model is intended to help the Agency predict where its inspections are likely to achieve the greatest public health impact. In addition, the model should assist the Agency in creating positive incentives that reduce the frequency or scope of inspectional oversight for firms that FDA determines have acquired sufficient process understanding and implemented effective quality systems. FDA intends to begin pilot implementation of the model for certain pharmaceuticals regulated by CDER beginning next month. The risk-based model will serve to supplement, where appropriate, other risk-based inspection programs used within the Agency.

Team Biologics²

In the September 3, 2003, second CGMP initiative progress report, FDA listed several initiatives underway by the Team Biologics Operations Group as a result of its in-depth evaluation of the Team Biologics Program, which was designed to review, assess, and improve the program. At the time the CGMP initiative was initiated in August 2002, the Team Biologics Operation Group had completed its evaluation of the Team Biologics Program and had begun to implement several initiatives. The Team Biologics initiatives fully complement the CGMP Initiative's goals and efforts.

² Although Team Biologics is not a working group under the Initiative, its activities and accomplishments are included in this section as they fully complement the CGMP Initiative.

Since the second progress report, much has been accomplished to enhance and improve the Team Biologics Program. For example, Team Biologics has implemented a revised charter that formally adopts a quality systems management framework, improves processes for communication and coordination between headquarters and the district offices, and further integrates product specialists into the program. In addition, on an interim basis, the Team Biologics program has expanded to include the CDER for those biological therapeutic products that were transferred in October 2003. Other significant developments resulting from the evaluation include:

- A quality policy has been developed and adopted.
- Enhanced risk based work planning principles are being implemented.
- The standardized training and qualifications of Core Team members is being strengthened to, among other things, help ensure consistency in regulatory application, with additional training programs of Core Team investigators and Center Product Specialists scheduled for October 2004.
- Metrics are being developed to further assess the impact of the Team Biologics Program on industry and to measure success.

The Team Biologics Operations Group also will be assisting the CDER/ORA Pharmaceutical Inspectorate and PAT Team in developing and implementing quality management systems to provide consistency throughout the program areas.

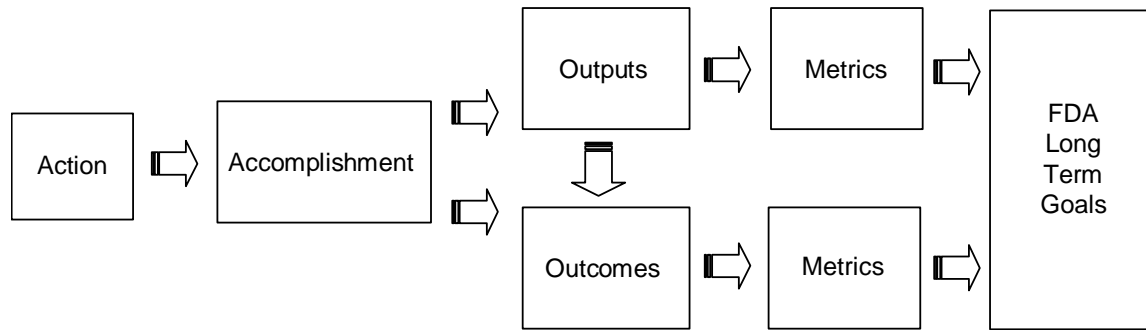
Evaluation of the Initiative

Under the cGMP Initiative, we have spent the past two years assessing what is needed to enhance and modernize the regulation of pharmaceutical manufacturing and product quality. As we now begin the implementation phase of the initiative, we are also putting in place a plan for evaluating the impact on manufacturing and drug quality.

Business school professors Dr. Jackson Nickerson of Washington University in St. Louis, and Dr. Jeffrey Macher of Georgetown University are conducting research that will be helpful to our evaluation of this initiative. A large part of their work involves identifying factors that predict manufacturing performance in pharmaceuticals. This will complement FDA's work on improving the inspection process, including its risk-based site selection model and training an inspectorate on how to best identify risks to pharmaceutical quality.

FDA will also conduct its own evaluation studies. The Agency will explore and identify relationships between FDA actions and accomplishments under the CGMP Initiative, and subsequent improvements in public health. Examples of such actions and accomplishments are: the adoption of quality systems by industry; the use of risk factors to select inspection sites; and the review of the warning letter process. The studies will attempt to link such activities to their impact on regulated industry and on public health-related outcomes (e.g., improvement in drug quality). FDA also plans to validate the CGMP Initiative's contributions to the Agency's long-term goals and mission.

Conceptual Framework of Evaluations



The study will be done in two phases—planning and implementation. The Planning phase will involve deciding which components of the cGMP Initiative to evaluate by: 1) identifying the actions and accomplishments of each cGMP working group to date; 2) determining the feasibility of evaluating their impact on public health issues; and 3) prioritizing them, based on feasibility and resources, and selecting which to evaluate. The Planning phase will be completed in the fall of 2004.

In the second phase, implementation, we will conduct some or all of the evaluations selected and prioritized in Phase I, to determine possible impacts on regulated industry, product quality, and public health.

In addition, as FDA implements quality systems programs, an ongoing evaluation will be incorporated into those programs.

PLAN FOR MEETING THE NEEDS OF TOMORROW

To continue the important work already underway, as well as to achieve the new goals that have evolved from the CGMP Initiative, FDA is restructuring its oversight of pharmaceutical quality regulation. To this end, the Agency is instituting an Agency-wide *Council on Pharmaceutical Quality* that will be charged with policy development and implementation, leadership, and oversight, including the ongoing implementation of internal quality management systems relating to drug quality regulation. The Council will oversee and assist with the shift from the assessment and evaluation phase, which has occurred over the past two years, to the implementation phase. Although the initiative began two years ago as the Pharmaceutical CGMPs for the 21st Century, the Agency believes that this title does not accurately reflect all that has been accomplished, nor the goals and objectives as we move forward, as all aspects of pharmaceutical quality are involved.

The following are among the steps to be included in the next phase of the initiative under the leadership of the Council on Pharmaceutical Quality:

- ◆ Develop additional guidance on quality systems for pharmaceutical manufacturing so that the Agency's goal to enhance and modernize the regulation of pharmaceutical manufacturing and product quality is met.
- ◆ Continue development of the risk-based pharmaceutical quality assessment system that will replace the current CMC review system to remove hurdles to continuous improvement following drug approval.
- ◆ Revise the 1987 industry guideline on Process Validation to include 21st century concepts, including risk management and a life-cycle approach.
- ◆ Continue to explore and formalize risk-based tools to enhance FDA's regulatory oversight.
- ◆ Refine the CGMPs and meet our harmonization (internal and international) goals.
- ◆ Continue timely communication of our current thinking on various quality issues to the public to facilitate compliance with FDA requirements.
- ◆ Further enhance FDA's own quality systems (including more mechanisms to facilitate communication within the Agency).
- ◆ Continue and expand on opportunities to integrate science-based policy and standards into our product quality regulatory approach.