Quality Management Plan for the Chemistry Manufacturing and Controls Review Process

Final, September 13, 2007

Neptune and Company, Inc.

Submitted by: Dean Neptune, Kevin Hull, Daniel Michael, Kelly Bennett, Kristen Lockhart

FOREWORD

Quality is defined as a measure of a product's or service's ability to satisfy the customer's stated or implied needs (Staff Manual Guide (SMG) 2020). *Quality Systems* (also called Quality Management Systems) are formalized business practices that define management responsibilities for organizational structure, processes, procedures, and resources needed to fulfill product/service requirements, customer satisfaction, and continual improvement (SMG 2020). There are many quality process improvement models that take this approach, including the plan–do–check–act cycle included in SMG 2020. Quality Systems are typically documented and managed by means of *Quality Management Plans (QMPs).*

This QMP presents the Quality System for the Chemistry Manufacturing and Controls (CMC) review process in the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER). The Quality System presented in this document is based on a quality improvement philosophy that embodies a "process approach." This approach is a systematic identification and management of the processes employed within an organization throughout the product development lifecycle, and particularly the interactions between such processes. The process approach systematically links the *inputs* provided by suppliers to the *processes* implemented during CMC reviews, and ultimately to the *outputs* delivered to customers. In the case of the CMC Review Quality System, the process is the CMC review process, and the product is the CMC review memorandum and recommendations that capture the scientific judgment of the reviewer(s) in supporting a decision, typically regarding regulatory actions to be taken based on the submission.

This QMP describes a set of quality components, elements, and tools applicable to the overall Quality System and lifecycle of the CMC review process, including the organizational structure for implementing the Quality System. Some of the tools offered as part of the Quality System will need to be developed (such as customer expectations and work specifications), while others (such as training programs) are already in use within part or all of CBER and CDER. In cases where one or more of the quality tools identified in this QMP are found to already exist, they should be reexamined to determine if they should be further refined. As the Quality System matures, additional tools will likely be developed as other opportunities and related tools for quality improvement within the CMC review process are identified. In addition, tools described here will be subject to continuous improvement as experience is gained in their implementation. This kind of feedback is critical to ensuring that the quality system is long-lived, and not viewed as a quick-fix, short-lived phenomenon.

The Quality System presented in this QMP consists of five components:

1) Quality System framework,
2) Planning,
3) Conduct of CMC reviews,
4) Evaluation and improvement, and
5) Infrastructure.

Each of these components is supported by elements and quality tools, which are described in each section of the report. A brief overview of each component and its associated elements and quality tools is presented below.

1) The Quality System framework explains how the Quality System will be defined and documented in the QMP and related documents. The QMP serves as an umbrella document that lays out the overall Quality Policy for the CMC review process and explains the Food and Drug Administration's (FDA) strategy for instituting quality management principles within the CMC review process in CBER and CDER. Quality Implementation Plans (QIPs) will be developed by CBER and CDER, building on this QMP. The QIPs developed by each organization will document specific approaches and priorities for Quality System implementation. The QIPs are expected to evolve as new quality tools are developed, and new priorities are identified. For the Quality System to be effective, CBER and CDER employees need to understand their roles and responsibilities for the implementation of the QS. The framework section presents the overall organizational structure for the Quality System and emphasizes the importance of commitment by all parties to the success of the Quality System. As each person demonstrates commitment to implementing the Quality System, it is also important to recognize the efforts of those individuals.

2) In order to facilitate the implementation of the Quality System, considerable thought must go into planning the resources that must be available in order for reviewers to be prepared to review a submission and for sponsors to provide better submissions. This second component addresses the need to identify customers and elicit expectations in order to define work product specifications. It also discusses the need to develop, keep current, access and use quality tools such as regulations, guidance, policies, internal resource materials, training and mentoring programs, career development, continuing education, and quality performance metrics.

3) The third component covers the processes that take place during the conduct of CMC reviews, including scoping, primary review and secondary review. The "scoping" process involves an initial screening technical evaluation of the sponsor's submission to help focus the CMC review process. The next step is conduct of the CMC review by the primary reviewer. In an important sense, the entire CMC review Quality System exists in order to support the conduct of the review process. Mid-cycle reviews and peer reviews are also discussed as part of the conduct of primary CMC reviews. Other tools that support the conduct of the primary CMC reviews include internal and external communication procedures, secondary/supervisory reviews, and a reporting system for performance metrics.

4) The CMC review process as well as the Quality System itself are targets for continual evaluation and improvement. Technical Audits and Process Audits provide mechanisms to evaluate the CMC review process from both a technical content and organizational process perspective. These audits assist in documenting what is happening in the process at that time and how well it is accomplished. Audit findings provide input to continual improvement of both the CMC review process and the Quality System. Employees' performance with respect to their roles in implementing the Quality System is also important to evaluate.

5) The infrastructure component of the Quality System consists of three systems that are needed to support the CMC review process: project management, document control and information management. In order to efficiently manage staff workload for the conduct of the CMC reviews, a project management system will be used to track the status of the reviews and, ideally, the issues that may be associated with each review. A document control system is

important for tracking documents related to this Quality System and to the CMC review process. The relevance of FDA's Information Management System to operation of the Quality System is also discussed in this section of the QMP.

The CMC Review Quality System is one manifestation of ongoing quality-related initiatives in CBER and CDER. It is designed for flexibility, with the anticipation that CBER and CDER organizations will adopt and adapt the elements that best integrate with their other Quality Systems and management structure and priorities. It is also anticipated that implementation of this Quality System will take place over several years and will be dependent on available resources and staff commitment, especially management.

Instituting a quality system is an evolutionary process; expecting radical or revolutionary changes as a result of this system is not realistic. It is critical in the implementation of this Quality System to focus on the end goal, which is to establish a Quality System that will improve the CMC review process and resulting work products. The QMP and related documents are not themselves the end goal. They are tools to help improve the quality of the CMC review process, including attributes such as efficiency, effectiveness, consistency, and transparency, as well as scientific soundness and completeness of the work products. The QMP and QIPs will be considered living documents, will be reviewed on a regular schedule, and will be updated to ensure they remain relevant.

CONTENTS

1.0 INTRODUCTION 1

1.1 Overview of the CMC Review Process in CBER and CDER 1

1.2 Context/Purpose of the Quality Management Plan 3

2.0 PROGRAM MISSION AND QUALITY POLICY 5

2.1 Mission 5

2.1.1 FDA 5

2.1.2 CDER 5

2.1.3 CBER 5

2.2 Quality Policy 6

3.0 QUALITY SYSTEM OVERVIEW 9

4.0 COMPONENT 1: QUALITY SYSTEM FRAMEWORK 11

4.1 Documentation of the Quality System 11

4.2 Organization-Specific Quality Implementation Plans for the CMC Review Quality System 12

4.3 Organizational Structure for implementing the Quality System 13

4.3.1 Office of the Commissioner 13

4.3.2 Center for Biologics Evaluation and Research 14

4.3.3 Center for Drug Evaluation and Research 18

4.4 Staff Commitment and Engagement 21

4.5 Senior Management Commitment and Engagement 22

4.6 Recognition of Employee Contributions 22

5.0 COMPONENT 2: PLANNING 24

5.1 Customer Expectations and Work Product Specifications 24

5.1.1 Process to Identify CMC Review Customers 24

5.1.2 Customer Briefing 25

5.1.3 Elicitation Process 25

5.1.4 Work Product Specifications 26

5.2 Regulations, Guidance and Policies Affecting Sponsors 27

5.2.1 Written Regulations, Guidance and Policies Affecting Sponsors 27

5.2.2 External Web Site 28

5.3 Internal Resource Materials 28

5.3.1 Internal Web Sites 29

5.3.2 Internal Policies and Procedures 29

5.3.3 Templates with Instructional Materials 29

5.3.4 Case Studies 30
5.3.5 Training Materials 30
5.3.6 Compilation of Precedents 31
5.3.7 Compilation of Comments to Sponsors 31
5.3.8 Scoping Guide 31
5.4 Training 32
5.4.1 Training-Needs Assessment 32
5.4.2 Training Plans 32
5.4.3 Training Curriculum Development 33
5.4.4 Tracking System 34
5.4.5 Evaluation Tools 34
5.5 Mentoring 35
5.5.1 Process for Selecting Mentors 35
5.5.2 Mentor Training 35
5.5.3 Mentor Resource Materials 35
5.5.4 Mentoring Process 35
5.5.5 Feedback on the Mentoring Process 36
5.6 Career Development and Continuing Education 36
5.7 Quality Performance Metrics 37
5.7.1 Process for Developing Performance Metrics 38
5.7.2 Documentation of Metrics 38

6.0 COMPONENT 3: CONDUCT OF CMC REVIEWS 39

6.1 Initial Scoping of Submissions 39
6.2 Conduct of Primary CMC Reviews 39
6.2.1 Systematic Use of Internal Resource Materials 40
6.2.2 Mid-Cycle Reviews 40
6.2.3 Peer Reviews 40
6.3 Internal Communication Procedures 40
6.3.1 Process for Identifying Internal FDA Communication Procedures Needed for CMC Reviews 41
6.3.2 Methods of Communication within an Organization 41
6.3.3 Communication Procedures with Other CMC Review Groups 41
6.3.4 Communication Procedures with Other Discipline Review Divisions 42
6.3.5 Team Reviews 43
6.3.6 Communication Procedures for the Offices of Regulatory Affairs and Compliance 43
6.4 External Communication Procedures 43

6.4.1 Process for Identifying External Communication Procedures 44
6.4.2 Communication Procedures 44
6.5 Secondary/Supervisory Reviews 45
6.5.1 The Secondary Review Process 45
6.5.2 Tools to Support Secondary Reviewers 46
6.5.3 Procedure for Resolving Conflicting Review Conclusions 46
6.6 Performance Metrics Reporting System 47
6.6.1 Periodic Reports 47
6.6.2 Annual Report 47

7.0 COMPONENT 4: EVALUATION AND IMPROVEMENT 49
7.1 Technical Audits 49
7.2 Process Audits 50
7.2.1 Planning for Process Audits 50
7.2.2 Conducting Process Audits 51
7.2.3 Audit Follow-Up 51
7.3 Continual Improvement of the CMC Review Process 51
7.3.1 Analyze the Current Process 51
7.3.2 Identify the Issues/Problems 52
7.3.3 Develop Solutions to the Issues/Problems 52
7.4 Continual Improvement of the Quality System 53
7.5 Incorporating Quality Issues Into Employee Performance Evaluations 54

8.0 COMPONENT 5: INFRASTRUCTURE 55
8.1 Project Management System 55
8.2 Document Control System 55
8.3 Information Management System 56

ACRONYMS

510k	510(k) Premarket Notification
ANDA	Abbreviated New Drug Application
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CMC	Chemistry Manufacturing and Controls
FDA	Food and Drug Administration
HHS	Health and Human Services
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IDP	Individual Development Plan
IMS	Information Management System
IND	Investigational New Drug
MaPPs	Manual of Policies and Procedures[1]
NDA	New Drug Application
OGD	Office of Generic Drugs (CDER)
ONDQA	Office of New Drug Quality Assessment (CDER)
OPS	Office of Pharmaceutical Science (CDER)
PMA	Premarket Approval Application
QIP	Quality Implementation Plan
QMP	Quality Management Plan
QRGT	Quality Resource and Guidance Team
RLD	Reference Listed Drug
RPM	Regulatory Project Manager
SMG 2020	Staff Manual Guide 2020
SOPPs	Standard Operating Procedures and Policies[2]

[1] Applicable only to CDER

[2] Applicable only to CBER

1.0 INTRODUCTION

This Quality Management Plan (QMP) presents the Quality System[3] that has been developed to support the Chemistry Manufacturing and Controls (CMC) review process in the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER). It consists of five components (framework, planning, conduct of CMC reviews, evaluation and improvement, and infrastructure) that are made up of quality elements and tools applicable to the CMC review process.

This QMP is built for flexibility, so that CBER and CDER can each implement the CMC Quality System in ways that are appropriate for their respective purposes. They will do so by

- defining their quality-related needs and understanding their customers'[4] needs,
- identifying the set of new and existing quality tools that will meet those needs,
- documenting their organizational approach and compiling available tools in an organization[5]-specific Quality Implementation Plan (QIP), and
- adding new tools and resources to the QIP as they are developed.

In this way, the Quality System in both Centers will mature over time as each organization moves toward the development, documentation, and implementation of an appropriate set of quality tools[6].

1.1 OVERVIEW OF THE CMC REVIEW PROCESS IN CBER AND CDER

CMC reviews in CBER and CDER are conducted by Food and Drug Administration (FDA) scientists[7], along with other disciplines, to help evaluate the safety, purity, potency, strength, and efficacy of biologics[8], chemical entities, combination products, and/or devices. CBER staff mainly review submissions for biologics while CDER staff mainly review submissions for chemical entities. However, biologics and chemical entities can both be reviewed at each Center.

---

[3] *Quality System*—formalized business practices that define management responsibilities for organizational structure, processes, procedures, and resources needed to fulfill product/service requirements, customer satisfaction, and continual improvement (SMG 2020).

[4] *Customer*—a person or organization (internal or external) that receives a product or service anywhere along the product's life-cycle (SMG 2020).

[5] "Organization" within this document refers to a defined group within FDA, for example, a Center or an Office.

[6] Quality tools can be defined as the techniques, procedures, and methods that constitute a Quality System.

[7] "Scientists" as used in this document also encompasses engineers and other technical specialists that perform CMC reviews.

[8] Biologics include products such as vaccines, plasma derivatives, blood and blood products, as well as cell and gene therapies.

The CMC review includes, as applicable, examination of raw and/or source materials, components, drug substance and/or product formulation, sterility, manufacturing processes and controls, stability, and some facility information such as potential for cross-contamination of the product, for example. A comprehensive, scientific evaluation of a submission is performed by highly trained specialists to determine if the submission adequately addresses the appropriate requirements for the product phase in the lifecycle, from development to post-marketing.

There are several types of submissions that require CMC reviews:

- Investigational New Drug Application (IND),
- New Drug Application (NDA),
- Biologics License Application (BLA),
- Abbreviated New Drug Application (ANDA),
- Post-marketing Supplement,
- Annual Report,
- Investigational Device Exemption (IDE),
- 510(k) Premarket Notification (510k), and
- Premarket Approval Application (PMA).

IND applications are submitted to the FDA for regulatory action, such as entering into clinical trials with a product[9]. NDAs and BLAs are submitted for approval to market a product after undergoing appropriate demonstrations of efficacy and safety, including clinical trials. ANDAs are applications for the marketing of generic drugs. For approval of significant post-marketing changes to the manufacturing process, post-marketing supplements are submitted. Annual reports may contain minor post-marketing manufacturing changes. An IDE allows an investigational device to be used in a clinical study. A PMA or 510k, depending on the class of device, must be submitted for approval to market a medical device.

For any regulatory action, the submission from a sponsor[10] should address a critical set of elements relevant to the product and its phase in the product lifestyle. These may include product quality attributes and specifications, manufacturing controls, information to establish performance requirements, and determination that the sponsor's manufacturing process is controlled or validated such that the product can continue to be produced consistently within established requirements. Based on this information, the reviewer recommends one of the following regulatory actions:

- allow the sponsor to proceed with the clinical study, approve the submission, approve clearance of a submission (for devices),

[9] For simplicity, the term "product" is used throughout the rest of the document to refer to biologics, chemical entities, combination products and/or devices.

[10] A "sponsor" for purposes of this document is defined as any entity that provides a submission.

- put the clinical study on clinical hold, communicate non-approval of a submission, or
- specify what additional information is needed.

CMC reviews are one type of discipline review conducted on a sponsor's submission. Clinical, pharmacological, statistical, and toxicological are examples of other discipline reviews that may be conducted, depending on the product being reviewed and the type of submission. Ultimately, information obtained from all of the review disciplines is assimilated and a decision on the submission is made and communicated to the sponsor.

1.2 CONTEXT/PURPOSE OF THE QUALITY MANAGEMENT PLAN

This QMP addresses the requirements of FDA's Staff Manual Guide 2020 (SMG 2020) *Quality System Framework for Internal Activities*, which describes a Quality System as "a set of formal and informal business practices and processes that focus on customer needs, leadership vision, employee involvement, continual improvement, informed decision making based on real-time data and mutually beneficial relationships with external business partners to achieve organizational outcomes." SMG 2020 is the product of a subcommittee established in response to FDA's "*Pharmaceuticals for the 21st Century – A Risk-based Approach*" initiative. The subcommittee based SMG 2020 on the international standard ANSI/ISO/ASQ Q9001-2000: *Quality management systems – Requirements*, among other standards.

The main purpose of SMG 2020 is to provide a framework whereby FDA organizations can develop Quality Systems applicable to their internal work products[11] and services. This QMP establishes such a Quality System for the CMC review process carried out in CBER and CDER organizations.

"Quality" is a term that is meaningful only in the appropriate context. For manufacturing, the context is generally that of the customer's needs and expectations for the performance of a product. For data collection and analysis efforts, it is best viewed in terms of fitness or adequacy for specific, well-defined uses of data, such as the ability to answer specific questions or support specific decisions with an acceptable degree of uncertainty. For the CMC review process, quality is related to the demonstrated ability to routinely perform CMC reviews resulting in science-based recommendations or determinations that appropriately manage risk and meet internal (FDA) and external (Congress, the public, sponsors) expectations.

The overall goal of the Quality System is to establish business practices that define responsibilities and set the stage for continual improvement of the CMC review process in CBER and CDER. The CMC review process is a long-established process with a solid framework and a successful record, but, like any operation, the CMC review process has the potential for improvement. Previous analyses have pinpointed concerns about issues such as the efficiency, consistency, and transparency of CMC reviews. This QMP has

[11] *Work product*—the intended results of activities or processes (SMG 2020; modified).

been created with those issues in mind and has been designed to accomplish the following goals:

- **Optimize performance practices** and results across CBER and CDER organizations;
- **Facilitate communication** across the organizations and with stakeholders[12];
- Share best practices for review and use of scientific information to **enhance work products** within the organizations; and
- Serve as a mechanism for **understanding and managing performance** of CMC review and support staff in CBER and CDER, in part by establishing a framework for and implementing technical audits, process audits, and continual improvement activities.

The development and implementation of the CMC Review Quality System will be a gradual process, with yearly priority setting to focus the allocated resources on the most crucial elements of the Quality System as determined by CBER and CDER and documented or referenced in the QIPs.

[12] *Stakeholder*—an individual or organization having an ownership or interest in the delivery, results, and metrics of the quality system framework or business process improvements (SMG 2020).

2.0 PROGRAM MISSION AND QUALITY POLICY

This section quotes existing relevant FDA vision and mission statements and also presents a Quality Policy focused specifically on the CMC review process.

2.1 MISSION

2.1.1 FDA

The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

2.1.2 CDER

The Office of Pharmaceutical Science (OPS) is the Super Office in CDER under which CMC reviews of drug products are performed in the Office of Generic Drugs, the Office of New Drug Quality Assessment, and the Office of Biotechnology Products. The OPS vision is to be an international champion and leader in regulatory application of contemporary scientific knowledge of design, development, manufacture, and clinical performance of pharmaceutical and biotechnology products.

The mission of OPS is to ensure timely availability of high quality drug products to the U.S. patients through

- effective and efficient scientific assessment of relevant pharmaceutical and biotechnology information in regulatory submissions, and
- facilitating those scientific and technological innovations that improve understanding of product performance, quality and efficiency of development, manufacturing, and quality assurance processes.

2.1.3 CBER

The Center for Biologics Evaluation and Research uses sound science and regulatory expertise to

- protect and improve public and individual health in the U.S. and, where feasible, globally;
- facilitate the development, approval of, and access to safe and effective products and promising new technologies; and
- strengthen CBER as a preeminent regulatory organization for biologics.

CBER's mission is to ensure the safety, purity, potency, and effectiveness of biological products including vaccines, blood and blood products, cells, tissues, and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury. Through this mission, it also helps to defend the public against the threats of emerging infectious diseases and bioterrorism.

2.2 QUALITY POLICY

The Quality Policy statement for the CMC Quality System can be considered a written expression of the overall intentions and directions for CBER and CDER regarding quality, including objectives for quality and commitment to quality. It communicates what CBER and CDER feel are the most important quality concerns/issues related to the CMC review process.

This Quality Policy was developed through a series of briefings and elicitations with a wide range of CBER and CDER CMC review staff[13]. The information obtained was used to create a draft Quality Policy statement, which was then reviewed and revised to accommodate comments from middle and senior management. The resulting Quality Policy was approved by the OPS and CBER Directors for incorporation into this QMP.

***The Quality Policy*:**

FDA is committed to supporting the development, implementation, and continual improvement of a Quality System designed to address the Agency's CMC review activities in CBER and CDER through collaboration of Management and Technical Staff. The intent of the CMC Review Quality System is to

- *build quality management into the CMC review process;*
- *foster a culture that embraces the need for the CMC review process and the resulting review products to meet new priorities and challenges as well as address the complexity and diversity of existing issues;*
- *develop and utilize meaningful, transparent, and objective metrics[14] that can be used to assess the CMC review process and associated products and to determine progress towards meeting the missions, goals, and objectives of CBER, CDER, and FDA;*
- *encourage all CMC review staff to participate in the continual improvement of the CMC review process by establishing effective methods for providing input, incorporating suggestions, and sharing "best practices" implemented within FDA and from other organizations; and*
- *encourage improvements that measurably enhance the quality and consistency of CMC review processes and products.*

[13] CMC review staff includes CMC reviewers, managers, and supervisors.

[14] *Metric*—specific data selected as an indicator (SMG 2020).

CBER and CDER senior management will support the creation and maintenance of a Quality System, communicate the importance of this system to the CMC review staff and their customers, and maintain an effective and productive CMC work force for its implementation. This, in part, will be accomplished by

- *hiring and maintaining qualified scientists/engineers with the skill-sets necessary to conduct CMC reviews;*
- *providing CMC review process training, mentoring, professional development, and constructive feedback;*
- *helping CMC review staff to understand and be accountable for their roles in the Quality System and for the technical basis of their review recommendations;*
- *recognizing the contribution and value of the CMC review and support staff; and*
- *supporting infrastructure, including information management technologies, which will enable access to historical and precedent setting documents.*

CMC reviews conducted by FDA scientists will

- *assure the safety, purity, potency, strength, and effectiveness of products;*
- *facilitate scientific and technological innovations and access to safe and effective products;*
- *be based on the current and evolving understanding of the science and technology related to the products and manufacturing processes regulated by FDA;*
- *reflect the current legal and regulatory framework;*
- *be completed and documented on a timely basis consistent with FDA goals;*
- *maintain appropriate ethical standards during all phases of the review process;*
- *incorporate a risk-based approach throughout the CMC review process;*
- *result in clear, concise communication of complex technical information; and*
- *be consistent with historical precedents and current practices and policies as appropriate, but allow acceptable alternative approaches with accompanying rationale.*

Mechanisms to improve and simplify communication related to the CMC review process will be documented and/or developed and implemented so that

- *cross-center, cross-office, and cross-division communication is encouraged;*
- *communications with sponsors are efficient, effective, and timely;*
- *CMC reviewers work in a collaborative manner; and*

- *CMC reviewers demonstrate respect for their colleagues' opinions and positions.*

FDA will develop and maintain, or refine existing, information management systems (IMS) that support the CMC review process. They will be

- *user friendly;*
- *highly searchable;*
- *readily accessible; and*
- *able to protect sponsors' proprietary information and data.*

Quality System tools will be developed and/or refined by CMC managers and technical staff with input from their customers. The tools may include

- *a process to elicit customer expectations;*
- *objective metrics to measure CMC review quality;*
- *internal resource materials, including review templates with instructions and case studies;*
- *training on the use of internal resource materials for conducting CMC reviews;*
- *guidances, manual of policies and procedures (MaPPs), standard operating procedures and policies (SOPPs); and*
- *workload management tools.*

Periodic technical and process audits will be conducted by qualified and experienced personnel to evaluate the CMC review process and products through

- *involving CMC review staff in the preparation for and conduct of audits;*
- *sharing results of reviews and audits with the organization reviewed and appropriate managers;*
- *using findings to evaluate the adequacy of existing policy, procedures, and guidance;*
- *tracking and communicating any process improvements and corrective actions, and determining effectiveness of such corrective actions; and*
- *soliciting customer comments.*

3.0 QUALITY SYSTEM OVERVIEW

The CMC Review Quality System consists of five major components as depicted in Figure 3.1.

1. Component 1 is the overall **framework** for the Quality System. This component is discussed in Section 4.
2. Component 2 focuses on **planning** and includes a number of quality tools that together lay out the customer expectations and define the process for conducting a CMC review to meet those expectations. Planning is discussed in Section 5.
3. Component 3 covers the processes that take place during the **conduct** of CMC reviews, including the initial scoping, use of templates, internal reviews, and communication protocols. This component is addressed in Section 6.
4. Component 4 addresses **evaluations and improvement** and is discussed in Section 7.
5. Component 5 addresses the underlying **infrastructure**, including information technology, and is discussed in Section 8.

Each component of the Quality System is integrally linked to the whole, and all components included in this QMP will themselves be subject to a continual quality improvement process.

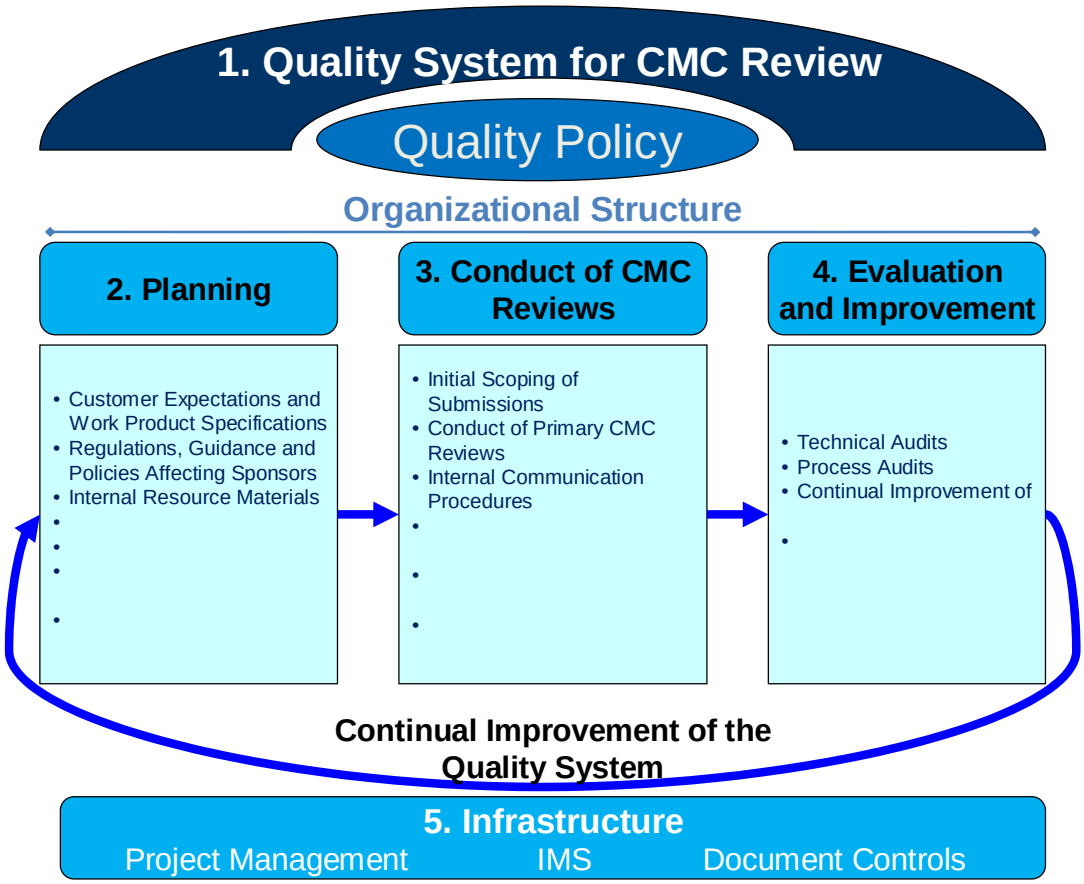

Figure 3.1. CMC Review Quality System Diagram

4.0 COMPONENT 1: QUALITY SYSTEM FRAMEWORK

The overarching framework for the CMC Review Quality System is captured in this QMP. This section explains how the Quality System will be defined and documented. Since CMC reviews are carried out in two separate Centers, CBER and CDER, the QMP establishes a requirement for QIPs to be developed within each Center, tiered to this QMP. In addition, this section summarizes the organizational roles and responsibilities in each Center for implementing the components of the Quality System.

4.1 DOCUMENTATION OF THE QUALITY SYSTEM

Purpose: To provide a reference document for implementing the Quality System.

This QMP serves as an umbrella document that explains FDA's strategy for instituting quality management principles within the CMC review process in CBER and CDER. This QMP incorporates input from a wide range of CBER and CDER scientists engaged directly in the CMC review process as primary reviewers, secondary reviewers, specialty consultants, line management, and senior management. This input was sought through one-on-one interviews, questionnaires, focus group meetings, and discussions and reflects the evolving nature and inherent complexity of the CMC review process. Information from the review of existing documents (guidance, templates, policies, and procedures) was also incorporated into this QMP.

The QMP documents the organizational structure for implementing the Quality System and considers the CMC review activity as a process that generates specific work products. The final work product generated from the CMC review process is a document (e.g., the CMC review) that captures the scientific judgment of the reviewer(s) in supporting a decision, typically regarding regulatory action to be taken based on a submission.

The QMP addresses components of planning, conduct, evaluation and continual improvement, and infrastructure associated with the CMC review. The QMP identifies appropriate Quality System elements and proposes specific quality tools that together will constitute the Quality System. It also explains the requirements for QIPs that will be put in place to implement this QMP. The QMP and QIPs will be considered living documents that will be reviewed on a regular schedule and will be updated to ensure they remain relevant.

Recognizing that some elements described in this QMP are currently in place, this document is meant to describe the complete set of elements comprising a comprehensive Quality System for the CMC review process. The QMP is designed to build on best practices, facilitate new management initiatives and scientific paradigms, and provide CMC review teams with a systematic set of essential resources/tools for the CMC review process. The process of developing this Quality System has identified some new tools that, along with existing tools, will help FDA to address quality concerns and improve the confidence that CMC review products will meet customer expectations and be based on the latest scientific knowledge and risk management principles.

4.2 ORGANIZATION-SPECIFIC QUALITY IMPLEMENTATION PLANS FOR THE CMC REVIEW QUALITY SYSTEM

Purpose: To tailor the overarching CMC Review Quality System to meet organization-specific needs in CBER and CDER and to document how these organizations will implement Quality System elements.

This QMP establishes the overall framework for the CBER and CDER CMC Review Quality System. However, the diversity of priorities, practices, and needs across and within CBER and CDER means that it is not possible to apply any Quality Management Plan as a "one-size-fits-all" system that is completely applicable throughout both Centers. The comprehensive set of general quality elements and tools described in this QMP is designed with the expectation that it will be fine-tuned and prioritized to meet the needs of individual CBER and CDER organizations. Each organization requires the flexibility to implement quality tools (such as training materials or review templates) that address its specific circumstances.

Both CBER and CDER will create and maintain Quality Implementation Plans, or QIPs, formally tiered to and based on this QMP[15]. The QIP specifies quality-related roles within the organization and lists the organization's priorities for Quality System tool development and implementation. Part of the QIP also serves as the organization's annual Quality System report. QIPs will consist of two parts:

- Part 1 presents the organization's overall approach to implementing the Quality System, including a description of specific quality roles, responsibilities, authorities, and accountability; a mapping of current quality tools that apply to each of the five components discussed in the QMP (Figure 3.1); and a list of tools to be developed in the future along with priorities for implementation. Initially, the QIP will compile the existing set of quality tools such as templates, training modules, and procedures. The QIP should cite, but need not replicate, information contained in this QMP or other documentation. Part 1 will evolve over time as the Quality System matures and new tools are developed and documented in the QIP. Initially, Part 1 of the QIPs will be approved annually along with Part 2. After a comprehensive set of quality tools is documented and implemented, Part 1 of the QIPs will be reviewed and updated on an as-needed basis, at a minimum every five years. QIPs will be approved by the CBER Director or OPS Director (or their designees).
- Part 2 is the organization's Quality System Annual Report and Work Plan. It will feature a description of the previous year's accomplishments as well as planned activities for the upcoming year. It will be updated annually (e.g.,

[15] For CBER, a single QIP will be developed at the Center level. For CDER, separate QIPs will be developed at the Office level.

each October) and submitted for approval by the OPS Director or CBER Director (or their designees).

4.3 ORGANIZATIONAL STRUCTURE FOR IMPLEMENTING THE QUALITY SYSTEM

Purpose: To define organizational roles, responsibilities, authorities, and accountability related to the Quality System.

For a Quality System to be effective within an organization, all staff will need to grasp the importance and scope of the system, understand the Quality Policy, and perhaps most importantly, understand their specific roles and responsibilities. This section provides an overview of the roles and responsibilities for implementing the Quality System at higher levels in the organization. QIPs developed within CBER and CDER may include more detailed roles, responsibilities, authorities, and accountability of the scientists and support staff within their organizations.

Figure 4.1 shows that the CMC Review Quality System will be managed separately within the two major Centers. Quality tools that are relevant to both Centers may be shared, and communication across Centers will encourage sharing of best practices. In addition, the Quality Resource and Guidance Team (QRGT) will maintain an awareness of the CMC Review Quality System and will serve as one resource for FDA-wide guidance and policy issues related to Quality System development and implementation.

4.3.1 Office of the Commissioner

Quality Resource and Guidance Team

Responsibilities include the following:

- Maintaining an awareness of the CMC Review Quality System
- Reporting on quality issues to the Management Council
- Serving as a resource for FDA-wide guidance and policy related to Quality System initiatives

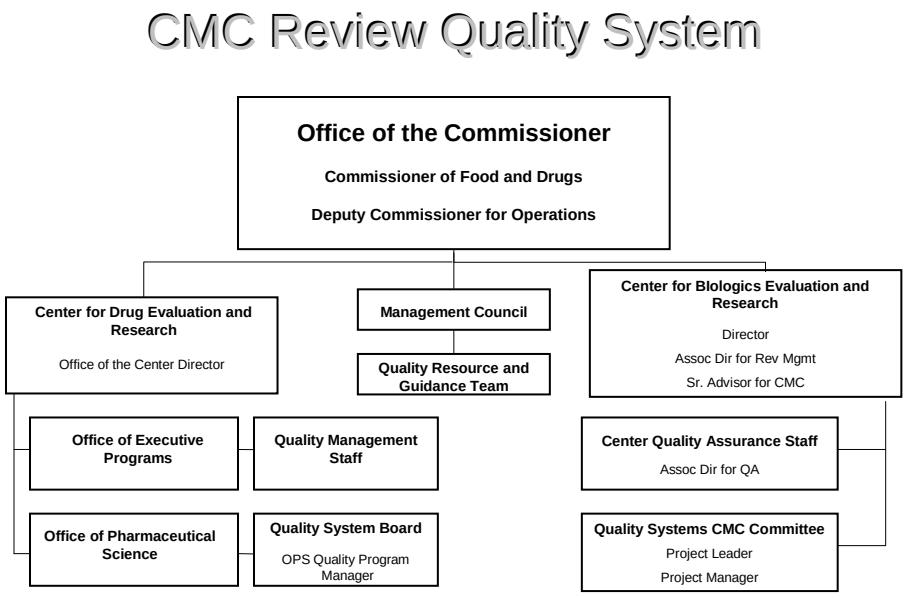

Figure 4.1. Quality Organizational Structure for the CMC Review Quality System

4.3.2 Center for Biologics Evaluation and Research

CBER Director

The CBER Director is responsible for providing leadership and ensuring senior management commitment to the CMC Quality System. Responsibilities include the following:

- Approving the QMP
- Approving the QIP
- Appointing the Quality Systems CMC Committee Project Leader
- Appointing Senior Management Champion(s) to act on his behalf

Quality Systems CMC Committee Project Leader

The Quality Systems CMC Committee will be led by a Project Leader with technical CMC expertise and knowledge of Quality Systems with assistance from a Project Manager. Responsibilities include the following:

- Chairing the Quality Systems CMC Committee and coordinating Committee activities
- Serving as a change agent by championing the implementation of the QMP

- Deploying/rolling out the Quality System with assistance from the Quality Systems CMC Committee
- Coordinating with Review Management Staff, the CBER Quality Assurance Staff, the CMC Coordinating Committee, the Review Management Coordinating Committee and any other committees as needed
- Recommending resource allocation with input from the Quality Systems CMC Committee
- Coordinating with QRGT to keep the FDA Management Council aware of CMC Review Quality System efforts
- Drafting the Center's QIP together with the Quality Systems CMC Committee
- Coordinating the development and tracking of performance metrics in conjunction with CBER Quality Assurance Staff
- Communicating metric performance and audit results to the Quality Systems CMC Committee
- Performing the lead role in developing centralized quality tools for use throughout CMC organizations within CBER
- Coordinating the elicitation, organization, and documentation of customer expectations; promoting harmonization of customer expectations related to CMC review work products
- Developing an audit plan, with input from the Quality Systems CMC Committee and CBER Quality Assurance Staff, that contains a description of who will conduct audits, how frequently audits will be conducted, how results will be reported, and how corrective actions will be tracked
- Managing in collaboration with the CBER Quality Assurance Staff and Quality Systems CMC Committee the conduct and review of Technical Audits
- Advising and communicating with the Center Director, Associate Director for Review Management, Associate Director for Quality Assurance, Senior Advisor for CMC Issues, and other senior management including Office Directors, on the CMC Quality System including reporting the results of audit findings, metric performance, and other activities

Quality Systems Project Manager

Responsibilities include the following:

- Serving as a change agent by championing the implementation of the QMP within the Center
- Supporting the Project Leader and Quality Systems CMC Committee in executing assigned responsibilities
- Coordinating activities needed to implement the CMC Quality System at a Center level

- Maintaining documentation of the Quality System, including assisting in developing and maintaining content related to Quality System tools

Quality Systems CMC Committee

A CBER-wide Quality Systems CMC Committee will consist of a Quality Systems CMC Committee Project Leader, experienced reviewers and first-line supervisors, representative(s) of the CBER Quality Assurance Staff, and additional individuals from other CBER Offices as needed. Responsibilities include the following:

- Serving as a change agent by championing the implementation of the QMP within their Office
- Deploying/rolling out the CMC Quality System in conjunction with the Project Leader
- Coordinating issues related to Quality System components, including determining gaps in existing tools, prioritizing the development of planning, implementation, evaluation, and continual improvement tools
- Developing aspects of the quality toolbox[16] that will be utilized by all CBER Offices; this includes assembling and organizing current or existing quality tools as well as developing new quality tools
- Contributing to the development of the CBER QIP tiered to this QMP
- Conducting a training-needs assessment and providing input on training requirements, including developing core and advanced curricula in conjunction with CBER training staff
- Establishing procedures for internal and external communication as part of the CMC review process
- Contributing to the continual improvement of the Quality System
- Serving as advisors for quality issues and reporting status of Quality Systems activities to Office including Office Directors
- Collaborating with the CBER Quality Assurance Staff on recommending Technical and Process Audits and the conduct and review of Technical Audits
- In conjunction with CBER Quality Assurance Staff, creating metrics and a metric reporting system
- Conducting periodic evaluations of the Quality System and preparing updates to the QMP as needed and at least on a five-year cycle
- Making recommendations, together with the Project Leader, to the Center's Associate Director for Quality Assurance, Associate Director for Review Management, and Senior Advisor for CMC Issues with consultation from

[16] The term "toolbox" in this context refers to a set of quality tools that forms the CMC Review Quality System.

other senior management as needed on major activities (e.g., audit recommendations, metric development, tool development and implementation), with a final determination made by these individuals or CBER Director as appropriate for the activity

CBER Office Directors

Responsibilities include the following:

- Appointing representatives to the CBER Quality Systems CMC Committee
- Championing Quality System implementation within the Office
- Nominating individuals to serve as technical auditors on a rotating basis subject to approval of the Project Leader
- Holding staff accountable for Quality System implementation and incorporating quality roles (as specified in the Center QIP) into personnel performance plans
- Receiving briefings on a routine basis to stay informed about the status of key Quality System tools, audit findings, and corrective actions
- Advocating the Quality System by communicating the Quality Policy and recognizing outstanding performance by staff within the Office related to implementation of the Quality System

Center Quality Assurance Staff

Responsibilities include the following:

- Planning and conducting independent[17] process audits of the CMC Review Quality System
- Collaborating with the Quality Systems CMC Committee on the conduct and review of Technical and Process Audits of the CMC review process within CBER
- Providing briefings and reporting audit results to the Center's Associate Director for Quality, Associate Director for Review Management, and Senior Advisor for CMC Issues, who together will keep the CBER Director and other senior management apprised of findings as well as follow-up actions
- Serving as a resource to the Quality Systems CMC Committee, Project Leader, and Project Manager by providing broader Center perspective on quality issues
- Appointing a member to serve on the Quality Systems CMC Committee

[17] Independent in this context refers to audits conducted by parties not affiliated with the organization that is being audited.

4.3.3 Center for Drug Evaluation and Research

Office of Executive Programs, Quality Management Staff

Responsibilities include the following:

- Planning and conducting independent process audits of the CMC Review Quality System
- Collaborating with the Quality Program Manager on the conduct and review of Technical and Process Audits of the CMC review process within CDER
- Serving as a resource to the Quality Program Manager by providing broader Center perspective on quality issues
- Appointing a member to serve on the Quality System Board

Office of Pharmaceutical Science

The CMC Review Quality System for CDER resides within OPS. A single Quality Program Manager will be assigned to oversee CDER's CMC Review Quality System.

OPS Director

The OPS Director is responsible for providing leadership and ensuring senior management commitment to the CMC Quality System. Responsibilities include the following:

- Approving the QMP
- Approving the QIPs
- Appointing the OPS Quality Program Manager
- Identifying and positioning a Senior Management Champion

OPS Quality Program Manager

The Quality System Board will be led by a Quality Program Manager with technical CMC expertise and knowledge of Quality Systems. Responsibilities include the following:

- Chairing the Quality System Board
- Serving as a change agent by championing the implementation of the QMP
- Deploying/rolling out the Quality System with assistance from the Quality System Board
- Recommending tasks, priorities, etc. for the Quality System
- Prioritizing and scheduling deployment
- Communicating efforts
- Advising the OPS Director on the CMC Quality System

- Coordinating with QRGT to keep the FDA Management Council aware of CMC Review Quality System efforts
- Drafting the OPS level QIP and incorporating input from the Quality System Board
- Coordinating the development and tracking of performance metrics, which includes
  - communicating metrics required by OPS Management to the Quality System Board,
  - creating and maintaining a metrics reporting system, and
  - reporting results to the OPS Director.
- Performing the lead role in developing centralized quality tools for use throughout CMC organizations within CDER
- Reviewing QIPs and advising the OPS Director
- Coordinating with the Quality System Review Board about the need, scope, and conduct of audits
- Coordinating the elicitation, organization, and documentation of customer expectations; promoting harmonization of customer expectations related to CMC review work products
- Managing independent audits and collaborating with CDER Quality Management Staff on the conduct and review of Technical and Process Audits
- Developing an audit plan, with input from the Quality System Board, that contains a description of who will conduct audits, how frequently audits will be conducted, how results will be reported, and how corrective actions will be tracked
- Conducting periodic evaluations of the Quality System and preparing updates to the QMP on a five-year cycle

Quality System Board

The OPS Quality System Board will consist of the OPS Quality Program Manager, Quality Implementation Leaders from OPS Offices, and a representative from the Office of Executive Programs Quality Management Staff. Responsibilities include the following:

- Deploying/rolling out the CMC Quality System in conjunction with the Quality Program Manager
- Coordinating issues related to Quality System components, including prioritizing the development of planning, implementation, evaluation, and continual improvement tools
- Determining which quality tools will be developed or coordinated at the OPS (Super Office) level versus the Office level

- Developing aspects of the quality toolbox that will be utilized by all OPS Offices within CDER; this includes assembling and organizing current or existing quality tools as well as developing new quality tools
- Establishing or selecting quality metrics and incorporating those required by OPS Management; communicating required metrics to lower Offices
- Conducting a training-needs assessment and providing input on training requirements, including core curricula
- Overseeing the implementation of CMC training, including formal tracking
- Establishing procedures for internal and external communication as part of the CMC review process
- Contributing to the continual improvement of the Quality System
- Serving as an advisory board for quality issues
- Ensuring consistency in how each Office addresses quality responsibilities
- Developing and maintaining content related to Quality System tools on an internal web site; keeping links to documents, precedents, and databases current
- Developing data bases that include searchable precedents
- Collaborating with Quality Management Staff on the conduct and review of Technical and Process Audits

OPS Office Directors

Responsibilities include the following:

- Championing Quality System implementation within the Office
- Appointing Quality Implementation Leaders
- Holding staff, including Quality Implementation Leaders, accountable for Quality System implementation; incorporating quality roles (as specified in the Office QIP) into personnel performance plans
- Endorsing Office-specific QIPs and submitting for OPS Director (or designee) approval
- Receiving briefings on a routine basis to stay informed about the status of key Quality System tools, audit findings, and corrective actions
- Advocating the Quality System by communicating the Quality Policy and recognizing outstanding performance by staff within the Office related to implementation of the Quality System

Quality Implementation Leaders

Responsibilities include the following:

- Drafting the QIP for the Office and spelling out Quality System roles and responsibilities, for example:
  - Division Directors,
  - Branch Chiefs,
  - Lab Chiefs,
  - Team Leaders,
  - Liaisons,
  - Review Scientists, and
  - Administrative Staff.
- Developing Office-specific quality tools and metrics
- Identifying CMC review resource material needs and priorities
- Serving as members of the Quality System Board
- Tracking performance against metrics and providing reports to the Quality Program Manager
- Developing an audit plan with a description of who will conduct the audits, how frequently audits will be conducted, how results will be reported, and how corrective actions will be tracked
- Ensuring Office-level implementation of the Quality System
- Overseeing the use of quality tools

4.4 STAFF COMMITMENT AND ENGAGEMENT

Purpose: To demonstrate that the organization must change to have a successful Quality System

A cultural change is a fundamental part of embracing a comprehensive Quality System. The CMC Review Quality System will be successful if senior managers, scientists, and other staff involved in the CMC review process put forth their best efforts to implement the system. Developing a QMP will not by itself result in any positive change in an organization. Quality management, to be successful, requires a significant investment on the part of the organization. This investment starts with learning, but includes a lot of hard work, self-scrutiny, careful analysis, and development of resource materials. It also requires a workforce open to change, willing to learn and incorporate new ideas and approaches, willing to develop and track quality metrics, and open to feedback from customers as well as auditors.

4.5 SENIOR MANAGEMENT COMMITMENT AND ENGAGEMENT

Purpose: To demonstrate to CMC review staff that the Quality System is important to senior management.

Lessons from industrial leaders, including the pharmaceutical industry, over the past two decades have shown that, time and time again, quality programs lacking senior management commitment and support do not yield the benefits of those that are fully embraced. For this Quality System to work, senior managers must own the Quality System. They must believe in and promote the Quality Policy.

To lead the CMC review community in this change, senior managers will need to demonstrate commitment to the Quality System. Without continuing senior management support, the Quality System may be viewed only as a short-lived phenomenon. Given the level of effort involved, and the fact that cultural change is part of the equation, Quality System implementation will need to be gradual and deep-rooted. Senior Managers will need to help prioritize the development and deployment of the overall plan and actively demonstrate that fully implementing the CMC Review Quality System will result in the achievement of the goals and rewards FDA is seeking.

Specific, tangible evidence of senior management commitment includes

- placing a priority on Quality System components;
- committing staff resources and funding to implement and maintain the Quality System;
- maintaining an awareness of the overall system, quality metrics, and results of audits; and
- informing people throughout CBER and CDER about the initiative, its status, and its importance.

4.6 RECOGNITION OF EMPLOYEE CONTRIBUTIONS

Purpose: To communicate to personnel that their efforts in implementing the Quality System are recognized and appreciated.

Management must recognize CMC review staff efforts in supporting the Quality System. Recognition should occur in a manner that is more frequent and more public than during the annual performance review cycle[18]. When senior managers publicly acknowledge contributions of others, three things are accomplished: the individuals singled out get positive feedback for their actions, other CMC review staff learn about the actions of their peers, and senior managers demonstrate their interest and support for the Quality

[18] Meetings of large groups (such as all-hands meetings or division meetings) are a common place to show employee appreciation with tangible recognition, such as awards, certificates, and placards. Announcements in newsletters, postings, or other publications are also mechanisms for recognizing employees to a larger audience.

System. Because of this, it is important to determine highly visible ways to reward CMC review staff for outstanding work on a regular basis.

5.0 COMPONENT 2: PLANNING

5.1 CUSTOMER EXPECTATIONS AND WORK PRODUCT SPECIFICATIONS

Purpose: To identify CMC review customers; to engage CMC review customers to better understand and, to the extent possible, harmonize expectations related to the CMC review work product generated on their behalf; to develop CMC review work product specifications.

Customers of the CMC review need to be identified and their expectations elicited and refined to develop a set of CMC review work product specifications (discussed in Section 5.1.4). With a well-defined set of review work product specifications, one can then evaluate one aspect of the quality of the CMC review by determining if the product meets or exceeds customer expectations – a commonly used definition for the term "quality."

5.1.1 Process to Identify CMC Review Customers

CMC reviews and/or the recommendations based on the CMC reviews generated by CBER and CDER are used by a diverse group of customers. In many cases, the reviewers' supervisors are the highest-priority customers. However, it is important to identify and recognize other customers and their individual needs. If this cannot be achieved in one attempt, a hierarchy or prioritization among the customers can be established and one can focus first on meeting the needs and expectations established as higher priorities. Meeting lower-priority customer needs may be attempted, to the extent that needs can be met without affecting the efficiency or cost of the review process. Through continual improvement, overall customer satisfaction can be achieved.

As a starting point, the following examples of customers internal to CBER and/or CDER have been identified:

- Other CMC reviewers
- Discipline reviewers (other than CMC) of INDs, NDAs, BLAs, PMAs, 510(k)
- Secondary and tertiary supervisory reviewers
- Regulatory Project Managers
- Other Managers and Supervisors
- Office Directors
- Offices of Compliance and Regulatory Affairs, including Field Investigators
- Reviewers of generic drug applications (ANDAs), who would benefit from well-documented reviews of the reference listed drug (RLD), along with communication to the original sponsors

Customers external to FDA have also been identified:

- Members of the public, both as consumers of pharmaceutical products and as taxpayers
- Congress
- Sponsors
- The medical community

5.1.2 Customer Briefing

Prior to eliciting input from CMC review customers on their expectations for the CMC review product, briefings to educate the customer base may be beneficial. These briefings can help CMC review customers see the advantages of harmonizing expectations and developing a core set of requirements that will meet most, if not all, customers' needs. The briefing could discuss the disadvantages and implications of divergent expectations. For example, when discipline review divisions have divergent expectations, reviewers may have to spend time tailoring each CMC review to each division's particular set of expectations. This individual tailoring of each review work product can result in inefficiencies in the review process and inconsistencies in the review work product. An advantage of having a consistent CMC review work product is more efficiency in the secondary, or supervisory, CMC review process.

Having divergent or completely unique expectations is not the same as customers having specific requirements that go beyond the core requirements. For example, requirements specific to a product class might be identified. The briefing would recognize this and set the framework for customers to think in terms of core and specific requirements.

5.1.3 Elicitation Process

Obtaining customer expectations is a critical part of any Quality System. One process for accomplishing this task involves using an elicitation process to determine both technical and non-technical expectations for the CMC review work product. This elicitation process can be in the form of a survey, questionnaires, facilitated meeting, focus group meetings, one-on-one interviews or other mechanism determined by the parties implementing this process. In addition to core expectations that should be common to all CMC reviews, customers can also be asked to identify those requirements that are unique to their specific needs. If an alternative process to a facilitated meeting is used, consideration should be given to creating a setting that will be conducive to gathering input from all priority customers.

CMC review expectations may include, for example, a list of questions that reviews must address, the format for the review work product, procedures to alert customers of significant findings, the role customers want CMC reviewers to play on the review team, and/or procedures to communicate internally and externally with sponsors. These expectations could then be organized and prioritized (based on customers' input on which

expectations are most and least important) to develop a common set of CMC review work product specifications, discussed in Section 5.1.4 below.

Given the diversity of CMC review customers, the elicitation process is likely to result in documentation of some divergent needs. In addition to core expectations that should be common to all CMC reviews, customers can also be asked to identify those requirements that are unique to their specific needs. For example, review needs will vary if one is

- a lead reviewer using the reviews to support decisions on whether to recommend approval of a new product;
- a secondary reviewer performing a supervisory review of the initial CMC review; or
- a reviewer of a generic drug application (ANDA) who may wish to use the CMC review for the innovator's product to understand what manufacturing issues were important during the initial approval of the product.

It will be important to evaluate customers' needs and determine which needs can be fulfilled considering various factors such as legal requirements and regulatory obligations (e.g., protection of confidential commercial information).

After establishing a focused, refined set of customer expectations, customers will be asked to supply their perceptions of how well the current CMC review process and work products are meeting their expectations. By obtaining these perceptions, CBER and CDER will have an understanding of how well the current work products produced by CMC reviewers are addressing customers' needs. This input will help to establish a basis for evaluating the adequacy of existing planning tools, identify gaps in the current CMC review process, and establish quality metrics associated with the CMC review work product. Over the long run, periodically surveying customers and providing opportunities for feedback about how well the CMC review process is meeting their needs will help to assess progress associated with this Quality System.

5.1.4 Work Product Specifications

Work product specifications, including those obtained from elicitations, should be documented. Work product specifications can be divided into several categories, for example, format, level of detail, and technical content of the CMC review memorandum. CMC review work product specifications should reflect customer needs and be written in a manner that facilitates assessments such as secondary/supervisory reviews and independent audits. For example, the technical content of the review should meet minimal standards, including accuracy, clarity, and transparency. Developing a comprehensive set of work product specifications that incorporate all CMC review customers' needs is the first critical step in implementing the CMC Review Quality System.

5.2 REGULATIONS, GUIDANCE AND POLICIES AFFECTING SPONSORS

Purpose: To improve review efficiency and effectiveness by obtaining submissions that facilitate CMC review.

Regulations, guidance and policies directly affect the process sponsors use to interact with the FDA, provide submissions for review, and get positive regulatory actions (e.g., ability to conduct a Phase I study, approval for new products or changes to existing products). In turn, the way that sponsors assemble the information for review directly affects both the efficiency and effectiveness of CBER's and CDER's analyses. Therefore, the development of regulations, guidance and policies affecting sponsor submissions is considered a fundamental part of the CMC Review Quality System. It is important to understand the differing role of regulations, guidance, and policy, and recognize that the impact of each on the Quality System and review process will be variable.

Guidance is explicitly *not* intended to be treated as a requirement, legal or otherwise. However, given the tremendous amount of resources expended by industry to obtain FDA's approval, many sponsors use guidance to address CMC issues in an attempt to get their products through the review process as efficiently as possible. When new guidance is developed, CBER and CDER may consider providing process-oriented instructions, along with tools (such as a standard format) for how information is presented. If followed by the sponsor, these items may lead to improved review efficiency.

FDA uses policies to communicate both internally and externally about CMC review issues. Many policies affecting CMC submissions and reviews can be accessed via the Internet and provide sponsors with a better understanding of what CBER and CDER consider important and how they conduct business. As new ways of doing business are developed to keep pace with the times, new or revised policies will be needed.

5.2.1 Written Regulations, Guidance and Policies Affecting Sponsors

Periodically, the existing set of regulations, guidance and policies available to sponsors and CMC reviewers will be evaluated and possibly revised, replaced, or withdrawn. International Conference on Harmonisation (ICH) guidance documents and standards developed through Standards Development Organizations and other organizations may complement, augment, or in some instances replace guidance issued by FDA to sponsors. Sponsors are encouraged to utilize risk management processes that focus on establishing acceptable quality controls for the steps of manufacturing. Sponsors should also demonstrate they have a clear understanding how modifying quality controls affects individual product quality and the ability to efficiently manufacture efficacious, consistent, and safe products.

Submissions represent a wide variety of products, and thus the steps in the manufacturing processes may vary greatly from product to product. Accordingly, guidance will need to continue to offer flexibility in data and information requirements and will need to consider the acceptable risk and benefit to the ultimate users of the product. Therefore, it is not conceivable that one acceptable "recipe" for submissions or CMC reviews can be

established. Instead, the focus should be on the correct instrument that helps sponsors understand the scientific questions that CBER and CDER will be evaluating and the type, extent, and possibly format of sponsor documentation related to these questions.

Using guidance as intended can:

- minimize the request for additional data and information needed for CMC reviews;
- provide a common process by which data will be generated for the CMC review process; and
- expedite CMC reviews when fully implemented.

5.2.2 External Web Site

FDA maintains public web sites that provide access to many relevant regulations, policies and guidance documents. Continued use and improvement of these web sites as a means of disseminating current guidelines, updates, and announcements to sponsors and CBER and CDER scientists, is critical and considered an integral part of the overall Quality System. It may be beneficial to consider having users register to access the regulations, guidance or policies on the web site and then send automated emails to these users when changes, additions, or deletions occur. Through augmentations such as this, sponsors are more likely to know what CBER and CDER are expecting, and submissions are more likely to be organized in a way that improves the ability to efficiently and effectively complete CMC reviews.

5.3 INTERNAL RESOURCE MATERIALS

Purpose: To provide information to reviewers to aid in the review; to incorporate management initiatives into the CMC review process in an objective, consistent, and documented manner.

This section describes internal documentation of the process for performing CMC reviews, coupled with tools such as templates with instructional materials designed to support those involved in the CMC review process. The internal resource materials described in this QMP will explain the systematic approach CBER and CDER will use to perform CMC reviews. These documents will also provide material against which audits can be performed.

There is a distinction between internal resource materials and formal guidance. Formal guidance must go through a comprehensive review and approval process prior to dissemination, since the documents are aimed not only at internal reviewers, but also at sponsors and other members of the public. Resource materials intended only for internal use do not need to go through the same review process as formal guidance, but do have to be reviewed for quality and updated to remain current. While internal resource materials may be subject to a Freedom of Information Act request, their primary intent is to be of direct use to the CMC reviewers. Internal resource materials may be evaluated to

determine if they should go through the rigorous process to allow them to be placed on external sites to facilitate product development.

Listed below are specific internal resource materials. However, others may be developed by or already exist in CBER and CDER organizations.

5.3.1 Internal Web Sites

Web sites that provide CMC review staff access to internal resource materials will be enhanced to ensure quality tools are readily available to CMC reviewers. These web sites will be mutually accessible by appropriate staff in both Centers to provide for cross-pollination of quality tools and ideas and to improve information sharing between Centers. Significant updates to the web sites, such as when guidance documents are added or retracted, or information on a new management initiative is available, will be widely advertised among the CMC community. Direct links will be provided to relevant FDA or ICH guidance documents, standards, internal training materials, and internal resource materials including templates, instructions, policies, and procedures. Currently, many tools exist in isolated pockets and the web sites will make these readily available across organizations. In addition, when other resource materials become available, such as systems to track CBER and CDER precedents or communications with sponsors, they should be readily accessible.

5.3.2 Internal Policies and Procedures

CBER and CDER management issue written statements to prescribe policies, responsibilities, and/or procedures that are to be applied during the conduct of daily operations. In CBER, the statements are referred to as Standard Operating Procedures and Policies, or SOPPs. In CDER, these statements are called the Manual of Policies and Procedures, or MaPPs.

5.3.3 Templates with Instructional Materials

Review templates provide a systematic format for presenting review findings. Well designed templates that reflect the current understanding of critical attributes of CMC reviews and are well integrated with sponsor submissions will be identified, developed or updated for each Center. Many benefits have been ascribed to the use of templates, such as ensuring completeness of the review and reducing the variability in where a given topic may be found in the review. Since CMC reviews require extensive scientific analysis and judgment, instructions on the use of templates will avoid misinterpretation of their intended meaning, and prevent excessive cutting and pasting of material from the sponsor's submission.

Internal instructional materials that are linked to a template are intended to provide CMC reviewers with insights into how to approach their technical review, what important questions they should be asking as they perform their review, and other technical issues that they may need to be aware of as they perform their work. Science-based, process-oriented instructions can help reviewers grasp what is expected of them in terms of both

content and format. Instructions are not intended to be prescriptive. Instead they are intended to promote good science, get reviewers thinking about how to critically evaluate product issues, and provide a "user-friendly" means of documenting findings.

While these documents have existed historically, or are currently available in isolated groups, they are likely to require updating or rewriting to incorporate new technical issues, paradigms, guidance, policies, and procedures. These documents are an important internal resource and can be made accessible to all CMC reviewers (e.g., via the internal web site). To ensure they are used properly, they should clarify upfront what types of issues or product classes they are intended to address in addition to stating which aspects are likely to be widely applicable.

5.3.4 Case Studies

Case studies can be a powerful tool for training CMC reviewers and, therefore, have been identified as an important tool for the CMC Review Quality System. Case studies are real or constructed examples of CMC reviews that incorporate regulations, guidance, policies, procedures, precedents, and other internal resource materials to illustrate approaches to CMC issues. Case studies must be kept up to date to remain relevant. They should reflect CBER and/or CDER management initiatives for improving the submission and review process. Given the diversity of product classes and CMC issues, a determination needs to be made as to how many different case studies are needed.

One approach is to develop case studies using a team approach, based on fictitious, yet realistic, submissions. Another approach is to utilize real examples from review situations that raise novel approaches or key elements for discussion, and discuss the rationale and approach used or potential alternative approaches that could be taken. The most relevant case studies will likely integrate technical, scientific, and regulatory elements in a manner consistent with the CMC Quality System. It is important that the examples be extensively developed and reviewed, possibly to include comments from key customer groups, prior to adoption. The case studies should consider well-defined customer expectations, and should exemplify all key planning tools that are relevant (e.g., internal resource materials such as templates with instructions). Once developed, case studies can be used in training courses or posted on the internal web site to clarify the intended meaning of guidance, policy, or procedures. If new procedures are developed over time, it may be possible to modify the case study to illustrate the use of the new procedures.

5.3.5 Training Materials

Materials developed in support of training for CMC reviewers are likely to include formal presentations, workbooks, examples or case studies, on-line video lectures, and other types of instructional videos such as tours of manufacturing plants. These materials, once developed, are extremely valuable internal resource materials and can be made accessible using the internal web site. By this means, CMC reviewers can maintain an awareness of which training modules are up to date and which have been replaced and should be viewed again to maintain awareness of the latest information. See Section 5.4 for further information on training.

5.3.6 Compilation of Precedents

Reviewers need to maintain knowledge of the set of formal and informal policies and guidelines applicable to the conduct of CMC reviews. This includes an awareness of precedents established on an ongoing basis so reviewers can help ensure consistency in how CMC issues are handled within CBER and CDER. Precedents are defined as ways in which issues have been handled historically in CMC reviews as well as decisions made by CBER and/or CDER management on how to address certain topics. CBER and CDER organizations will develop a formal process for documenting and communicating precedents relevant to that organization. The process will include a way to identify and include new precedents that have emerged from recently completed CMC reviews.

5.3.7 Compilation of Comments to Sponsors

Another quality tool that will help ensure consistency in CBER and CDER and help identify areas for improvement is a compilation of questions and comments transmitted to sponsors. CMC review organizations may elect to develop a data base that can be used to compile these comments. Reviewers and supervisors will access this compilation to see how communications of CMC issues have been worded to sponsors in the past, helping to ensure consistency in communications from FDA, as appropriate. Analysis of these data bases may also pinpoint common issues and/or deficiencies in sponsor submissions. This could help identify opportunities for improvement in FDA's CMC guidance system and communication processes.

5.3.8 Scoping Guide

Reviewers can use a scoping guide upon receipt of a submission to help set the stage for a CMC review process that is both efficient and effective. Scoping guides would address the preliminary review of each category of submission routinely received by an organization. The guides will describe the organization's approach to addressing issues such as the following:

- From a risk management perspective, what are the key questions presented by this submission? What elements of the submission are the risk drivers, and what assumptions made by the manufacturer will be most sensitive from the CMC review perspective? This will vary dramatically by product class and by CBER/CDER organization.
- What information should be provided to or requested from other FDA organizations that will play a role? For instance, what questions should be brought to the attention of facility investigators at an early stage, so they can be incorporated in the inspection?
- In addition to the CMC review, what other disciplines need to be represented in this review, and what early steps need to be taken to assure that representatives of those disciplines will be available when the time comes?

- What policies, guidance documents, or other resources are particularly relevant to this review? Are there any anticipated difficulties in obtaining access to these resources?
- Are there important precedents of which the review team should be aware? These may include recent FDA policy pronouncements that will have a bearing on the review, or the results of prior reviews of products that are similar to the current one.
- Are there any questions that should be transmitted to the sponsor at the outset of the review process?

5.4 TRAINING

Purpose: To ensure CMC review staff have the necessary skills to effectively accomplish their work; to ensure staff understand their Quality System responsibilities and requirements.

Training is a central component of the CMC Review Quality System because it provides the CMC review staff with instructions and insights necessary to fulfill their roles. Training directly related to the CMC review process is beneficial, in addition to more general training on the Quality System and the regulatory framework within which FDA must operate. It is vital to the CMC review process that CMC review staff are provided core training applicable to all reviewers within an organization to help ensure a consistent basis for conducting reviews. Training in addition to the core curricula will be provided depending on the type of review performed. Many of the quality tools described in this QMP will be incorporated in the curricula, and training materials (both hard copy and on-line) will become references for reviewers. All CMC review staff will need to adhere to established training requirements.

5.4.1 Training-Needs Assessment

In order for a training program to be effective, the goals of the training program must be clearly defined. A training-needs assessment, also referred to as a job-task analysis, provides a systematic way to evaluate the type and level of training required for the personnel involved in the CMC review process to meet these goals. Examples of possible goals include training related to Quality System requirements, regulations, procedures, Information Management Systems, and instructions specific to CMC reviews. Time is a valuable resource, so the training-needs assessment should also take into consideration how to prioritize the needs if only a limited amount of training time is available to the CMC review staff.

5.4.2 Training Plans

Program Level Training Plan

A Program Level Training Plan must be developed that documents and specifies the training requirements for CMC review staff according to their roles and responsibilities.

FDA-wide requirements as well as the Center- or Office-specific training requirements will be identified in the Training Plan, and will reflect the output of the training needs assessment. This Plan will document core curricula for CMC reviewers, utilizing Agency established Competencies and Learning Pathways, as well as identify additional training needs for new CMC reviewers, specialized training specific to each product class, and ongoing training for experienced CMC reviewers. The Plan for new staff will include a core set of training that will be integrated into the employees' responsibilities upon starting employment. Core training must be completed in a timely manner.

Individual Development Plans

Individual Development Plans (IDPs) should be developed for each individual, using the Program Level Training Plan as a starting point. Direct supervisors and mentors will be actively involved in the development of these IDPs. The individual plans will spell out types of training, in addition to the Program Level training, that are recommended and a timeline for obtaining this training. The IDPs will be revisited during annual reviews.

IDPs for experienced reviewers will be aimed at ensuring everyone has been exposed to the latest training materials and content. Training plans for experienced reviewers will include topics such as training on the latest management initiatives, guidances, internal resource materials, and scientific and technical information.

When appropriate, training workshops could be designed with experienced reviewers in the same classes with less experienced reviewers. This approach promotes interaction and communication among CMC review staff and allows experienced reviewers to share their experiences on the topic(s) being presented with less experienced reviewers.

5.4.3 Training Curriculum Development

In order for CMC reviewers to have access to appropriate training, training curricula must address issues that are relevant to CMC reviewers, including topics related to current management initiatives. Additional training courses may be developed as needs are identified. Training curricula will need to be appropriately targeted for the experience level of the trainee, and address issues that are relevant to the trainee's position. All phases of the review process—scoping, detailed evaluation, communication, and documentation of findings—will be addressed through the training curricula.

Various forms of training materials and presentations may be used to provide the training curriculum in a form that supports the topic of the training. The training courses should be designed to facilitate attendance as much as possible. Training presentations may be in the form of on-line training, classroom settings, formal workshops, seminars, or required reading. The instructor for a training session should be highly qualified (e.g., having in-depth experience with the subject matter) in order for the training to be well received. If possible, all formal courses should be recorded and stored electronically so that students can retrieve sessions they attended and staff members who were unable to attend a course can access the material they missed.

Training materials in support of the curricula may include, but are not limited to, slides, speaker notes, handouts, case studies, exercises, web-based interactive presentations, and videos (e.g., a tour of an industrial facility). To maximize their utility, all training materials could include instructions for the course instructors, including speaker notes, references, and lists of materials or special needs such as access to the internal FDA web sites. Incorporating a modular approach in training materials helps maximize their flexibility and longevity. Each module could present material related to a specific topic and could easily be updated to reflect the latest developments, such as new guidance, internal resource materials, etc.

5.4.4 Tracking System

The Health and Human Services (HHS) Learning and Competency Modules of the HHS Learning Management System will be used to document competencies, skill gaps and training that pertain to each person involved in the CMC review process. In addition, a local tracking system within each organization may be used to document the completed training requirements for all CMC review staff so a current list of each person's training status will be available when needed.

5.4.5 Evaluation Tools

Self-evaluation Tool

CMC review staff members should have the opportunity to see how well they understand and are implementing their training, including that related to their role in the Quality System. Self-evaluation tools, such as interactive multiple choice questionnaires, allow individual staff to answer questions related to their roles in the Quality System and their job. Immediate feedback tells the CMC review staff if they are providing correct answers. Incorrect answers could provide a link for the CMC review staff to look up information on the topic of the question.

Training Evaluation

Evaluations of the training courses allow trainees to assess how well the training courses are providing support to their work. Training evaluations should be conducted at three levels when possible. At the first level, an evaluation tool would be developed to provide valuable feedback to CMC review management so they can evaluate the usefulness of the training as well as identify other areas where training may be needed. It also allows the trainee to provide input for continual improvement of the training program. The evaluation may be presented in a form such as a survey for staff to fill out after training courses have been completed. At the second level, learning evaluations would be conducted after training through post-tests. On-line courses could have embedded evaluation questions as well as a post-test. The third level of evaluation, transfer of training, would be measured by conducting a post-course survey of performance one to three months following training.

5.5 MENTORING

Purpose: To facilitate development of less experienced reviewers, and to provide a point of contact for answering new reviewers' questions.

The CMC mentoring program discussed here involves coaching skilled scientists on how to conduct a good CMC review. Due to the technical complexity of CMC reviews and the uniqueness of each CMC submission, mentors play an important role in CMC reviewer training. Mentors facilitate training by providing assistance to reviewers in applying the knowledge obtained during training courses, such as instructing reviewers on how to use internal resource materials. Mentors also provide on-the-job training by answering questions reviewers may have during the conduct of reviews. The mentoring role is highly beneficial to the success of CMC review programs. It should be recognized as an integral part of a reviewer's work and taken into consideration when evaluating performance. The process of selecting and training mentors, mentoring, and evaluating mentors will be documented and followed to ensure the mentoring process is conducted as consistently as possible.

5.5.1 Process for Selecting Mentors

To enhance the success of the mentoring program, CMC reviewers with relevant experience who have gained the respect of their colleagues will be encouraged to serve as mentors. Supervisors should not be mentors for the CMC reviewers whom they supervise. Mentors with good communication skills are more likely to be effective than those without. A person can be an accomplished reviewer but a poor mentor if the dialogue with the mentee is not constructive. In order for mentors to see the role as worthwhile, credit will be given for time spent mentoring so it is not considered a nuisance that detracts from a reviewer's other responsibilities.

5.5.2 Mentor Training

Training for mentors, customized to the CMC Review Quality System, ensures mentors know their responsibilities, have resources to assist the mentoring process, and put mentoring in context with and integrate it with other forms of training. Training is discussed in detail in Section 5.4.

5.5.3 Mentor Resource Materials

A compilation of reviewer internal resource materials (templates, instructions, case studies, etc.) will be used by the mentor to show the reviewer the utility of each resource in the context of conducting a review. Another useful tool is a list of topics to be covered during the mentoring process.

5.5.4 Mentoring Process

An established mentoring process allows for an objective evaluation of a mentor's performance. Mentoring can occur individually and/or in small groups. Advantages of

small group mentoring include efficient use of the mentor's time and the ability for mentees to hear questions and issues raised by other reviewers.

5.5.5 Feedback on the Mentoring Process

A feedback tool, such as a comment form, will enable reviewers to provide feedback on their experiences with mentors and/or the mentoring process. Obtaining feedback allows for the evaluation of the success of the mentoring process and implementation of improvements as needed. Issues to be considered when designing a feedback tool include the timing and frequency of eliciting feedback, and which personnel will have access to the feedback results.

5.6 CAREER DEVELOPMENT AND CONTINUING EDUCATION

Purpose: To keep CMC review staff up to date on topics related to CMC reviews; to provide greater flexibility in work assignments by expanding each reviewer's knowledge base.

Providing CMC review staff with opportunities for career development and continuing education contributes to the maintenance of a work force that has the necessary skill set to review CMC submissions involving the latest technology and science, including those related to manufacturing. CMC reviewers need to be exposed to emerging technologies and science so they are well versed in the issues and are prepared to discuss proposals during review activities, including product development meetings.

There are many mechanisms for providing CMC review staff with opportunities to increase their knowledge base. Examples of continuing education events are conferences, seminars, workshops, professional meetings, and scientific journals. Examples of career development opportunities are rotational assignments, details, and professional development assignments such as academic research appointments.

Journals are more economical than other types of continuing education and should be made available to all CMC review staff because they are often necessary to execute review activities. Conferences, seminars, and professional meetings are also important so CMC reviewers have opportunities to interact with other scientists in the field and stay abreast of the latest developments in their areas of expertise.

Rotational assignments, details, and professional development assignments for CMC reviewers are types of career development that could be considered for implementation. Allowing CMC reviewers to rotate assignments, along with other necessary requirements (e.g. training), could potentially increase the flexibility of the CMC review work force by providing reviewers the opportunity to develop expertise in another area of CMC review. By broadening a reviewer's capabilities, he/she could be moved from a Division/Branch with a lighter workload to one receiving more submissions during a given time period. This could also facilitate the continuation of operations in the event of a declared public health emergency (e.g., responding to a pandemic influenza outbreak or bioterror event).

Direct supervisors and mentors should be actively involved in recommending career development and continuing education opportunities for reviewers. CMC review staff should participate in at least one continuing education event annually. Processes and procedures for requesting career development and continuing education opportunities should follow established Agency and Center procedures

5.7 QUALITY PERFORMANCE METRICS

Purpose: To identify key aspects of the CMC review process and work products that can be objectively evaluated on an ongoing basis.

Measurement is fundamental to the management and operation of a Quality System; if you are not measuring a process, you are not managing it either. A metric in the context of the CMC Review Quality System is a measurement that reflects a particular CMC review work product or process characteristic. The establishment of appropriate performance metrics is difficult in the case of a complex scientific endeavor such as the CMC review process. For instance, even though there are basic topical commonalities in the reviews of all NDAs and BLAs, the reality is that each industry submission is different, and therefore each CMC review poses unique challenges that would not be adequately assessed by a "one-size-fits-all" approach to performance measurement.

In crafting performance measures for the CMC review process, one should avoid blurring quantity and quality by focusing exclusively on easily countable "production statistics" such as the number of reviews completed or the number of work hours required to complete a review. The desired goal is to devise a set of metrics that authentically cast light on the quality issues related to scientific and regulatory concerns that are at the heart of CMC reviews.

Performance metrics will generally fit into one of three categories:

Output measures are designed to evaluate efficiency. These include the "production statistics" mentioned above, and should not be the entirety of a set of metrics. But output measures (e.g., number of submissions reviewed) should be considered, because they can provide helpful insights that illuminate quality issues, not from a perspective of establishing quotas or assigning blame, but from a perspective of identifying potential process improvements.

Product quality measures are designed to evaluate the work product itself, and relate back to program/project effectiveness. Product quality metrics encompass both technical and non-technical aspects of the work product. Technical product quality measures may include scientific soundness and thoroughness of a review (e.g., whether it has clearly addressed the risk management issues associated with a submission). These technical metrics may be useful to CMC review staff directly involved in generating the CMC review product. Clinicians and other customers may assume that the CMC reviews are technically thorough and scientifically sound and so may be more concerned with non-technical metrics. These can include ease of use, clarity and transparency of the work

product. Measures of overall effectiveness, consistency and customer satisfaction (see Section 5.1) are other examples of product quality measures.

Process quality measures are designed to evaluate and track the procedures used to generate a product. Feedback on these metrics can be extremely helpful in conjunction with product quality measures to identify possible causes of deficiencies, and possible targets for process improvements (which are often process simplifications).

5.7.1 Process for Developing Performance Metrics

Specific performance metrics for monitoring the quality of the CMC review process and work products will be developed by CBER and CDER organizations[19]. Performance metrics will be influenced by several factors such as the category of review typically performed by that organization (e.g., IND, NDA, BLA, and/or supplement), product class, etc.

Metrics of each type discussed in Section 5.7 could initially be identified or developed, in part, by means of an elicitation process. This process would involve participation by selected managers and experienced CMC reviewers and take into account the perspectives and expectations of CMC review process customers as described in Section 5.1. Participants would be asked to consider from their perspective how they can distinguish an excellent review from a poor or unacceptable review. Attributes of each would be identified and categorized. A core set of metrics that reflects attributes of a scientifically sound review as well as attributes identified as important to management would then be documented. Additional metrics can be added that embody customer requirements.

It is likely that some metrics will be more easily measured than others. It would be valuable to evaluate metrics from this perspective, select a subset to begin to measure, and test their usefulness in a pilot study. The value of information obtained could be evaluated based on the pilot implementation and the set of metrics revised accordingly.

The CMC performance metrics will be reevaluated when this QMP is updated or more frequently if indicated by the CBER Quality Systems CMC Committee, the CDER Quality System Board or Quality Program Manager.

5.7.2 Documentation of Metrics

Performance metrics will be clearly described and each organization will document how metrics are tracked, how often metrics will be summarized and evaluated, and by whom.

---

[19] The CBER Quality Assurance Staff and Quality System CMC Committee are responsible for developing metrics in CBER. Metrics for CDER will be developed in part by OPS Management, and in part by the Quality System Board and Offices.

6.0 COMPONENT 3: CONDUCT OF CMC REVIEWS

6.1 INITIAL SCOPING OF SUBMISSIONS

Purpose: To facilitate early identification of and address issues that will be important to the review process; to initiate required contacts with other FDA staff or organizations; to help determine at the outset what guidance documents, precedents, etc. are applicable to the review.

Once a sponsor's submission has been received and administratively accepted by FDA, the first step in the conduct of CMC reviews should be to carry out an initial screening technical evaluation of the sponsor's submission, or "scoping." Scoping sets the stage for a CMC review process that is both efficient and effective. The purpose of scoping is to help the reviewer identify issues that will be important to the review process, initiate required contacts with other FDA staff or organizations, and determine at the outset what guidance documents, precedents, etc. are applicable to the review. This process may occur at the same time as an initial assessment of a submission such as a determination of sufficiency for review (e.g., refusal-to-file).

The complexity and formality of scoping depends on the type of submission. INDs and supplements may require minimal scoping, depending on the complexity of the submission. Section 5.3.8 describes questions that may form a basis for scoping.

Some scoping activities can be conducted by supervisors, some by members of a review committee, and some issues can be addressed by the primary CMC reviewer. Some organizations have scoping of a submission performed by experienced senior reviewers who are assigned the task of performing an initial "triage"[20] of an incoming submission. Any organization that adopts a scoping role, especially for a submission with multiple CMC reviewers, will formalize it by means of an official role description that documents the responsibilities, authorities, and limitations associated with this function. The lines of communication between the initial senior reviewer and the subsequent primary reviewer of the submission must also be clarified. The organization will assess the performance of this role on a routine basis and identify any recommended revisions to the role description or to its implementation.

6.2 CONDUCT OF PRIMARY CMC REVIEWS

Purpose: To conduct CMC reviews in a transparent, consistent, and efficient manner.

This step addresses the main focus of the CMC review process, which is the actual conduct of the CMC review by the primary reviewer (or team if applicable). The entire CMC Review Quality System exists in order to support this step. Every tool described in

[20] For instance, in the Office of New Drug Quality Assessment (ONDQA) in CDER, this role is routinely assigned to a Pharmaceutical Assessment Lead, who takes a first look at an NDA in an effort to assure that fundamental issues are identified and preliminary requests for assistance or information are initiated.

the Framework, Planning, Conduct, Evaluation, and Infrastructure components is meaningful to the degree that it benefits the work of the primary reviewer, and ultimately enhances the quality of the completed review.

6.2.1 Systematic Use of Internal Resource Materials

The development of internal resource materials was described in Section 5.3. These resource materials come into use during the conduct of the review. An important concern at this point is to use the resource materials in a fashion that maintains consistency and transparency in the CMC review process. Each organization's QIP should convey the strategies, policies and procedures for the systematic use of internal resource materials. It is important to appropriately capture the salient information from the implementation of the internal resource materials to support continual learning and improvement.

6.2.2 Mid-Cycle Reviews

Mid-cycle reviews can be a useful tool in assuring satisfactory progress toward the successful completion of NDA, BLA and ANDA reviews. Mid-cycle reviews represent an opportunity for the various discipline review staff involved in reviewing a submission (e.g. CMC, clinical, statistical, project management) to assure that a review is on track, that communication with sponsors is being conducted satisfactorily, and that all key technical issues with a submission have been identified and are being resolved.

In cases where a formal mid-cycle review is not necessary, it is still possible for CMC review organizations to conduct internal mid-cycle reviews, using the results of the initial scoping described in Section 6.1 as a starting point.

6.2.3 Peer Reviews

Peer reviews are used as an opportunity for FDA staff to discuss and get feedback on issues that have been raised during a review. It is preferable for a peer review to occur before a CMC review has been completed. The CMC reviews that undergo peer review will be selected by appropriate management and will be chosen based on whether the review contains interesting or unique issues that would benefit from broader discussion. Peer reviews will not be required for all reviews and will be scheduled when resources and time are available.

6.3 INTERNAL COMMUNICATION PROCEDURES

Purpose: To facilitate interaction with other FDA organizations with a role in the CMC review process; to ensure communication of facility inspection issues and results.

Well-defined procedures for communication within the FDA can help to ensure that information needed for completion of CMC reviews is obtained in an efficient, consistent and reliable manner. These procedures will assist in directing questions from other FDA organizations to the appropriate CMC review staff member. Well-defined communication procedures also ensure that information obtained during CMC reviews is disseminated to

other FDA organizations that require the CMC review input to complete their work (e.g., facility investigators), or whose work quality will be improved by CMC review input.

Specific groups for which internal communication procedures should be developed are described below. However, each CMC review organization will potentially identify other FDA entities for which communication procedures need to be developed or enhanced. Each procedure should clearly define how a CMC reviewer, manager, and/or other staff member should contact the organization to obtain or disseminate the information to be communicated.

6.3.1 Process for Identifying Internal FDA Communication Procedures Needed for CMC Reviews

Prior to developing procedures, the scenarios requiring internal FDA communication on CMC review issues need to be identified. This identification process could include obtaining input from CMC review staff in order to determine the organizations for which communication procedures should be developed, and what particular issues these procedures should address. Methods for communicating within an organization and between groups[21] should be identified for the CMC review process as well as for the rest of the product's lifecycle.

6.3.2 Methods of Communication within an Organization

Communication within CBER and CDER organizations is essential for ensuring reviewers understand the "current thinking" and practices regarding CMC issues addressed by their organization, as well as management and policy issues. This communication could occur during periodic meetings or by formal documentation of management's policy regarding a new CMC issue, for example.

Other communications within an organization can help reviewers learn from previous CMC reviews. For example, if there is an adverse event report due to CMC issues for a product, this could be communicated back to the primary reviewer of the submission and a lessons-learned meeting could be held to discuss reasons the adverse event may have occurred.

6.3.3 Communication Procedures with Other CMC Review Groups

Communication procedures with other CMC review organizations are important so that CMC reviewers can efficiently obtain information from CMC reviewers in other FDA organizations that may have information on topics relevant to the CMC review in question[22],[23].

---

[21] Groups may include other CMC Review organizations, clinical review divisions, applications divisions, Office of Regulatory Affairs, or Office of Compliance.

[22] For example in CBER, an Office of Cellular, Tissue and Gene Therapies reviewer may have a question about a topic (e.g., manufacturing or testing for a class of vectors) in a submission, and needs to contact the Office of

6.3.4 Communication Procedures with Other Discipline Review Divisions

Communication procedures with other discipline review divisions, such as clinical, pharmacology and toxicology, and statistical, would benefit those in CMC review organizations that interact with other discipline reviewers and managers. Members of CMC review divisions interact with members of other discipline review divisions about a range of topics ranging from administrative issues such as review schedules, deadlines, and status of submissions to scientific issues discovered during the course of the reviews.

Scientific issues discovered during the review of other discipline-specific portions of the submission may need input from, or have the potential to affect, the CMC review of the submission. Likewise, issues discovered during review of the CMC part of the submission may need input from, or have the potential to affect, other discipline-specific portions of the submission. One example of this is narrow therapeutic index drugs, where the ratio of the concentration of the toxic dose to the therapeutic dose is close to 1. In these types of drugs, slight variations in the product produced during manufacturing may greatly affect the toxicity of the drug product. The CMC reviewer should be alerted to this issue as soon as possible (i.e., during the initial review or scoping exercise) when reviewing the submission so relevant sections can be carefully addressed and results communicated back to the clinical reviewer. The protocol would clearly address how to alert the other party of the issue(s), as well as how to communicate the relevant review findings associated with the particular issue(s). Having consistent communication protocols ensures these issues are communicated in a timely manner.

In CDER, some CMC review organizations interact with many clinical review divisions and there is the potential for each clinical division to have a different method for communicating with CMC reviewers. This should be avoided to the degree possible, because it is inefficient for a CMC reviewer to have to refer to each clinical division's protocol before attempting to communicate regarding CMC review issues. It is important to elicit expectations from and harmonize expectations across the clinical divisions for communication procedures as discussed in Section 5.1. With one set of harmonized expectations, a single procedure can be developed for interaction with clinical review divisions, thus increasing review efficiency.

Vaccine Research and Review reviewer to discuss if the same issue was covered and, if so, how the issue was resolved.

[23] For example in CDER, an Office of Generic Drugs (OGD) CMC reviewer may have a question about a manufacturing topic in a submission, and needs to contact the ONDQA CMC reviewer to discuss if the same issue was covered in the reference listed drug (RLD) NDA and, if so, how the issue was resolved. In this case, the communication procedure should discuss exactly what information the ONDQA reviewer can give the OGD reviewer while still protecting proprietary information. With a formal communication procedure, all ONDQA and OGD reviewers would have a common understanding of how these proprietary issues should be handled.

6.3.5 Team Reviews

Team reviews provide the opportunity for internal communication between discipline reviewers and management in a branch, division or office. Team reviews help to make all involved aware of issues that a specific file raises and how they were resolved. These sessions are typically held on a recurring basis, prior to action being taken on multiple submissions. They provide both managers and reviewers the opportunity to discuss differing approaches to an issue to reinforce current expectations and precedents and to identify emerging issues that require further follow-up. In contrast to other reviews, team reviews typically cover several submissions, discuss multiple issues and may identify issues that need further resolution through an extended presentation and/or discussion on a specific topic.

6.3.6 Communication Procedures for the Offices of Regulatory Affairs and Compliance

As the review of the CMC portion of a submission is closely tied to facility inspections, CMC reviewers would benefit from good communication procedures with facility investigators to ensure CMC issues that need to be addressed during inspections are communicated. Also, issues that arise during a facility inspection could be communicated to the CMC reviewer so the reviewer can determine the impact the issue has on the CMC review.

6.4 EXTERNAL COMMUNICATION PROCEDURES

Purpose: To clearly define methods for use by CMC review staff when communicating with sponsors and other parties outside of the FDA.

Well-defined communication procedures with parties external to the FDA will be developed or reevaluated, including procedures for interactions between CMC review staff and sponsors for product development, approval, and post-approval communications. These procedures will help ensure that methods of communication are predictable and, as a result, more efficient. When communication procedures are not available, or are not consistent within a CMC review organization, the review process is potentially not as efficient because CMC review staff time is unnecessarily spent trying to determine how to communicate with other parties, and other parties' time is unnecessarily spent trying to determine how to communicate with the CMC review staff.

Each CMC review organization will identify entities external to FDA for which communication procedures need to be developed (e.g., sponsors, Environmental Protection Agency, Department of Agriculture, the Department of Health and Human Services, the Department of Homeland Security). Each procedure should clearly define how a CMC reviewer, manager, and/or other staff member should contact the party to obtain or disseminate information.

6.4.1 Process for Identifying External Communication Procedures

Before developing external communication procedures, the scenarios for which procedures need to be developed should be identified. This identification process should include obtaining input from the CMC review staff as to which communication procedures need to be developed and what particular issues they should address. Input could also be elicited from other discipline review divisions.

Potentially, lead reviewers or managers will have differing preferences for how CMC reviewers should communicate with sponsors. Consistent procedures have the potential to make communication with a sponsor more efficient, as long as the procedures themselves are not arduous.

Communication procedures between CMC reviewers and sponsors might be developed for interactions regarding

- general questions about products that are not associated with a submission;
- product development prior to an IND submission (also known as pre-IND);
- discussions before the submission of BLAs/NDAs, supplements, annual reports, and post-approval changes; and
- information/questions that arise during the course of the review of a submission.

6.4.2 Communication Procedures

When developing communication procedures, the methods used by reviewers to contact the parties external to FDA and document the contact will be addressed, as well as methods for receiving and directing inquiries to the appropriate CMC staff member for response. The procedures will include consideration of all forms of communication including, but not limited to, phone conferences, faxes, and e-mails.

It is important to facilitate the most direct and efficient communication possible between the CMC reviewer and the sponsor. Direct communication is important because CMC issues may be very technical and complex, so that details could be misinterpreted when communicated through people other than CMC reviewers. Also, communicating with the sponsor through more than one person potentially decreases the efficiency of the review process. For example, if a CMC reviewer has a question for the sponsor but has to communicate this issue by way of the Regulatory Project Manager (RPM), the reviewer has to wait until the RPM is available and has time to resolve the issue. However, this must be balanced with situations when there is the need for all relevant members of the team to participate in the communication.

Procedures should also be documented that describe the conduct of meetings with a single sponsor, such as pre-IND meetings, and multiple sponsors, such as workshops or training sessions put on by FDA that explain what is desired in a submission.

6.5 SECONDARY/SUPERVISORY REVIEWS

Purpose: To ensure the primary review was conducted and documented appropriately.

Secondary reviews, also called supervisory reviews, are an important tool for ensuring the quality of CMC reviews. Secondary[24] reviews differ from audits discussed in Sections 7.1 and 7.2 primarily because secondary reviews occur prior to the release of the CMC review work product (the CMC review document and associated recommendations).

The ultimate goal of the primary and secondary reviewer is the same—to ensure the CMC review will result in safe, effective manufacturing of products consistent with all applicable FDA regulations, policies, and guidance. Secondary reviews are performed by supervisors or other more senior reviewers bringing another perspective to the review, as well as the experience and expertise of having been through many reviews of differing types and complexities. Depending on the submission, additional reviews, sometimes by more senior reviewers or managers may also be performed on the CMC review work product.

6.5.1 The Secondary Review Process

The secondary review process may vary according to the organization in which it is performed. As a result, each organization needs to document the objectives of and processes used to perform secondary reviews. This documentation will provide secondary reviewers with clear instructions for how to perform the secondary review, as well as provide a defined process against which audits can be conducted.

The documentation should include how, under what circumstances, and how often secondary reviewers should interact with primary reviewers. These determinations can be made by eliciting input (perhaps in a confidential manner) from primary reviewers, secondary reviewers, and management to determine what aspects of the current process they feel are working well and what recommendations they have for improvements. Depending on the findings of these elicitations, the secondary review process can be modified as needed, and a plan put in place to evaluate how well the modified process is working down the road as discussed in Continual Improvement, Section 7.3.

In order to clearly define the secondary review process, one must understand what the objectives of the secondary review are and what process steps are used to reach those objectives.

Examples of potential secondary review objectives include

- a review for accuracy, transparency, clarity, logic, and non-sequiturs;
- a spot check of portions of the review where the secondary reviewer may have a differing perspective or set of concerns;

[24] For simplicity, secondary, tertiary, quaternary, and supervisory reviews will be referred to as secondary reviews in the text.

- a separate summary of the CMC review bringing the most pertinent facts to the customers of the review;
- a supplement to the review that adds policies and facts that were perhaps not readily available to the initial reviewer;
- a check to ensure that all precedents established by CBER and/or CDER in previous reviews were followed, or an explanation provided for any divergence from precedents;
- a list of questions or issues to the primary reviewer to address or consider in completing the review;
- a marked-up copy recommending edits for consideration by the primary reviewer; and/or
- a dissenting review if the secondary reviewer disagrees with the primary reviewer, with the intent to submit both the primary and secondary review for consideration to the person(s) ultimately in charge of deciding the approvability of the submission.

6.5.2 Tools to Support Secondary Reviewers

There are a number of tools that can be used to support the secondary reviewer and ensure the completeness of the review package. These include the following:

- Aids, such as check lists, to assist in determining completeness
- Searchable data bases
  - Internal to FDA—these should include precedents, previous reviews, as well as content related to guidance and internal resource materials
  - External to FDA—these should include guidance, policies, procedures, and other information that provides sponsors with a clear understanding of how CBER and CDER would like to see material presented
- Internal Resource Materials (see Section 5.3), including
  - Internal web site with links to current guidance, policies, and procedures
  - Templates and instructional materials
  - Case studies
  - Training modules

6.5.3 Procedure for Resolving Conflicting Review Conclusions

There may be instances in which the secondary reviewer comes to a different conclusion than the primary reviewer about the evaluation (e.g., approvability) of the submission. For these situations, a procedure needs to clearly document how the conflicting conclusions will be handled. In order to have consistency in the process, a procedure can be developed or referenced that will address whether the secondary reviewer's conclusion should be documented and forwarded to the supervisor, whether the primary and

secondary reviewer should try to come to a common conclusion through discussions, or another mechanism.

6.6 PERFORMANCE METRICS REPORTING SYSTEM

Purpose: To keep all interested parties informed of the status of measured performance.

Section 5.7 addressed the establishment of Quality System performance metrics as a planning activity. Once established, these metrics become the operational definition of whether the CMC review process is meeting its quality goals on a continuing basis. For performance metrics to be a meaningful tool, they ought to be sustained by a formal and visible reporting system that documents how the organization is succeeding with respect to quality. To the extent that this routine reporting process provides managers and staff with ongoing "real-time" information on what is going well and what might be an opportunity for correction or improvement, this process can be viewed as a type of quality control. To the extent that reporting occurs subsequently, too late to affect the quality of individual products, it can be viewed as input to the evaluation and continual improvement component described in Section 7.

6.6.1 Periodic Reports

CBER and CDER organizations will prepare periodic reports on the organization's performance with respect to established metrics. The organization will be responsible for developing the format of this report and the process for collecting data. The report could be posted on the FDA intranet so it is accessible to all interested parties within FDA.

6.6.2 Annual Report

Each organization's QIP (discussed in Section 4.2) will include a section that provides a summary and analysis of the organization's status with respect to its performance metrics.

This page intentionally left blank.

7.0 COMPONENT 4: EVALUATION AND IMPROVEMENT

Technical Audits (Section 7.1) and Process Audits (Section 7.2) provide mechanisms to analyze the CMC review process from both a technical content and organizational process perspective. These audits assist in documenting what is happening in the process at the time and how well it is accomplished.

7.1 TECHNICAL AUDITS

Purpose: To periodically evaluate the technical content of a subset of CMC review documents, including the underlying scientific bases for reviewer recommendations.

Technical Audits of CMC review documents will be performed periodically to serve as one type of quality evaluation of the CMC review process. Technical Audits, in contrast to secondary reviews, are a form of quality assessment used to periodically evaluate the technical correctness of CMC review documents. These audits will be performed by a CMC reviewer, a team of reviewers or a subject matter committee not involved in producing the CMC review document being audited. Results from the Technical Audits will be used to help determine the adequacy of the CMC review process, internal resource materials supporting the process, and the corrective actions needed, if any, to ultimately improve the CMC review product.

Due to the technical complexity of CMC review subject matter, the auditor(s) must have the technical expertise, regulatory expertise, and other skills required to evaluate the CMC review document. Depending upon the scope, the audit may be best accomplished by multiple individuals using a team approach.

A process for conducting Technical Audits of CMC review documents will be developed by CBER and CDER and documented for use by the auditors. The Technical Audit will include reviewing the sponsor's submission to determine if all the elements required in the CMC review document have been accurately addressed and communicated. Technical Audits should include a determination as to whether

- the review document has been written in an accurate, clear, and transparent manner, with scientific bases for conclusions provided in the document;
- all submission deficiencies have been identified and communicated clearly for inclusion in the transmittal letter to the sponsor;
- FDA policies and regulations have been followed; and
- CMC review issues are addressed in a manner consistent with FDA precedent or, if not, a clear explanation has been provided; if no precedent exists, the auditor determines if management has been alerted to the potential need to set precedent on the issue.

The results of the Technical Audits will be documented and provided to the primary reviewer(s), secondary reviewer(s), and appropriate levels of management. They will

then determine if corrective actions need to be taken to improve the quality of the CMC review process and, therefore, product, as discussed in Section 7.3.

7.2 PROCESS AUDITS

Purpose: To evaluate whether the CMC review process is being implemented according to applicable systems and procedures.

This section addresses another category of audits that is important to the Quality System: independent audits of the *processes* by which CMC reviews are being carried out. Process Audits focus on the work activities carried out during the CMC review cycle, to evaluate whether they are being done according to applicable systems and procedures.

As described in Section 7.1, Technical Audits require detailed knowledge in the particular science and subject matter pertinent to a given submission, and thus can be performed only by a qualified and recognized individual, often someone within the same organization. On the other hand, Process Audits focus on work activities and their documentation, and are best performed by independent parties. Thus Process Audits are best managed at the Center level or at a level where they are independent of the organization being audited.

This QMP and QIPs tiered to this document constitute the set of processes and work activities against which Process Audits can be performed. A Process Audit may address one CMC review or a set of CMC reviews within a given organization. It may be an overview of the entire set of processes and work activities, or it may focus on one or more specific topics, e.g., the demonstrated use of internal resource materials or implementation of the CMC training plan.

7.2.1 Planning for Process Audits

Each year the Centers will develop a Process Audit work plan[25] and schedule, listing the audits to be conducted that year and the specific topics to be audited, and assigning a Lead Auditor for each. This information will be added to the annual update to the organization's QIP. The Lead Auditor will be a qualified auditor designated by the Center Quality Staff or Quality Management Staff. Depending on the scope and complexity of the audit, the Lead Auditor may operate alone or as the head of an Audit Team.

[25] For CBER, this work plan will be recommended by the Center's Quality Staff with input from the Quality System CMC Committee and the Director of the organization that is being audited. The work plan will be approved by the Director of Quality, Director of Review Management and the Senior Advisor for CMC issues. In CDER, this work plan will be endorsed by the Director of each organization that is the focus of an audit, and will be approved by the Quality Program Manager.

7.2.2 Conducting Process Audits

Prior to conducting the audit, the Lead Auditor will prepare a checklist or questionnaire that is directly based on the applicable procedures or work activities to be audited. This audit instrument will be reviewed by the Quality Program Manager or Project Leader for any input, and will be provided to the audited organization prior to the start of the audit.

Audits will include interviews with involved staff and review of relevant documents to evaluate if the process step(s) under review have been conducted. The audit instrument will be completed as the audit proceeds. At the conclusion of the audit, the Lead Auditor will conduct an exit briefing for the management of the audited organization.

All audits will be documented in a formal audit report to be reviewed and approved by the Quality Program Manager or Project Leader.

7.2.3 Audit Follow-Up

It is important for the CBER Quality Assurance Staff or Project Leader, and the CDER Quality Program Manager, to maintain a system for tracking and resolving any issues identified by the audits. These may be issues specific to the particular CMC review or organization that was the focus of the audit, or they may be broader issues prompting systematic follow-up, e.g., a policy clarification, a revision of this QMP or a revision of the organization's QIP.

7.3 CONTINUAL IMPROVEMENT OF THE CMC REVIEW PROCESS

Purpose: To identify and implement process improvements that enhance the quality and consistency of the CMC review process.

The Quality System described in this document embodies an organizational commitment to continual improvement of the CMC review process (as shown in Figure 3.1). Even after the Quality System is well developed, the feedback and improvement cycle needs to continue. In order to identify future areas for improvement in the CMC review process, the process will continue to be analyzed carefully through systematic oversight, and feedback will be received from both customers and reviewers to identify new issues and solutions to address these issues.

7.3.1 Analyze the Current Process

Technical Audits (Section 7.1) and Process Audits (Section 7.2) provide mechanisms to analyze the CMC review process from both technical and management perspectives. These audits assist in documenting what is happening in the process at that time and how well it is being done. The results can be used to identify areas for improvement in the CMC review process. In addition to the use of audits, the CMC review staff can provide suggestions on how to improve the quality or efficiency of the review process from their unique perspective using various mechanisms designed to obtain candid feedback from

CMC reviewers. This feedback may reflect what is going well in the CMC review process, as well as ideas about what could be improved.

Identification of customer needs is a part of the Quality System. As discussed in Section 5.1.3, customers could be asked how well the current CMC review process is meeting their needs and where deficiencies are perceived. This input could be used as a basis to periodically assess how well their needs are being met and to determine ways the process can be improved to better meet customer expectations. This does not need to be an activity that must await a formal audit, but can be revisited on a routine schedule to ensure that customer needs are being addressed, whether the issues observed are unique to a portion of the reviewers or endemic to the Office or Center.

Over time, customer needs, or their ability to express their needs, may change. Changes that result in improvements in the review products over time will become routine, and new expectations will arise. By periodic assessment of customer satisfaction, and determining new requirements, the CMC review process can continue to improve and evolve.

Quality performance metrics, as described in Section 5.7, will be used in the assessment of the CMC review process. These metrics will provide regular feedback as to how well the CMC review process is doing from both a productivity and quality point of view. If key metrics are showing slow progress in improvement, this may point to something in the process that is not working as well as it should, and this type of feedback can then be used to work on improving that process.

7.3.2 Identify the Issues/Problems

The input from internal and external parties involved in the CMC review process and analysis of performance metrics should yield a list of issues that would benefit from further evaluation. Input may be submitted through written documentation or oral communication. Each issue needs to be linked to a particular group that is capable of providing further input on the topic.

Each issue that is identified through a source or metric has a reason behind its existence. In some cases the issue has a particular root cause such as a type of barrier that is not allowing the CMC review staff to perform their job better. By understanding the correct root cause, the solutions are more likely to be effective.

7.3.3 Develop Solutions to the Issues/Problems

If root causes of issues and barriers to better performance in the CMC review process are not identified, it will be difficult to develop potential solutions that will work to improve the process. Because multiple issues may exist, a formal process may be needed to prioritize which issues to address. A team or focus group approach can be used to concentrate on developing particular solutions for an issue. To be effective, the focus group will need to involve the people who will be participating in the implementation of

the solution that is decided upon, including the CBER Quality System CMC Committee and the CDER Quality System Board.

Once a solution has been evaluated by the focus group, the group will identify metrics that can be tracked and used to determine whether or not the solution is effective. The metrics will be carefully chosen so they will reflect improvements directly related to the original issue and the solution being implemented. Information from these metrics can put in place the structure for continual improvement of the action/solution taken.

After the implementation of the solution has begun, the metrics will be monitored on a regular basis. The metrics will reveal whether or not the objectives of the solution are being met. If the objectives are not being met, then the team will review the results and determine areas for improvement. It is possible the solution is not being implemented correctly, the solution is not a good choice, or the solution focuses on resolving the wrong problem.

This philosophy follows the traditional quality improvement approach of plan-do-check-act, as described in SMG 2020.

7.4 CONTINUAL IMPROVEMENT OF THE QUALITY SYSTEM

Purpose: To evaluate the Quality System for its effectiveness; to identify areas where changes are needed; to revise the QMP to reflect Quality System changes.

As discussed in Section 7.3, the CMC review process can be routinely analyzed to identify issues that affect the quality and consistency of the CMC review product. In the same fashion, the Quality System itself should be subject to continual scrutiny and improvement.

Periodically this QMP and the QIPs tiered to this document need to be reviewed to determine if they contain an effective and up-to-date set of tools for ensuring the quality of the CMC review process. Whenever improvements are being made to the CMC review process, it is important to ensure that the QMP reflects these changes as appropriate. But even in the absence of significant changes to the CMC review process, the Quality System should be routinely revisited to determine which parts of it are working, and which should be improved, discarded, or replaced with a better tool. The following questions can be used to evaluate the effectiveness of QMP initiatives:

- What new approaches were implemented through the QMP?
- How were these approaches deployed?
- What effect did they have on performance metrics?
- How were lessons learned integrated?

At a minimum, this QMP should be formally revised and reissued every five years. It is likely that in the first few years of its implementation, the QMP may need to be revised more frequently, based on lessons learned, to remain relevant.

7.5 INCORPORATING QUALITY ISSUES INTO EMPLOYEE PERFORMANCE EVALUATIONS

Purpose: To evaluate employees' performance with respect to their roles in implementing the Quality System.

As the Quality System is implemented, it is important for CMC review staff to understand their quality roles and be motivated to fulfill them. The QMP and QIPs tiered to the QMP define roles and responsibilities for all staff involved in the Quality System. It is important to make sure that all employees understand their roles and responsibilities and how to fulfill them as part of the overall Quality System. By building these responsibilities into employee performance evaluations, managers will have an opportunity to discuss and document the contributions made to the Quality System by the employee being evaluated.

Performance evaluations are an opportunity to discuss the expectations of the employees in fulfilling the roles and responsibilities described in the QMP. The performance evaluations serve as a way to document the employees' contributions to the success of the Quality System implementation and encourage them to continue the good work. The evaluations also provide a way to discover what might motivate employees to better support the Quality System and document these actions in their files in order for management to follow up with the employees.

Supervisor feedback regarding a reviewer's performance is an important quality tool and should occur more often than once a year. Feedback should be given to reviewers for good work to keep up their morale. Feedback should also be provided so reviewers know areas where they can potentially improve their performance.

8.0 COMPONENT 5: INFRASTRUCTURE

8.1 PROJECT MANAGEMENT SYSTEM

Purpose: To provide in-depth understanding of the workload, beyond the number of submissions, by tracking factors such as review deadlines, complexity of submissions, and interactions with sponsors.

In order to efficiently manage staff workload for the conduct of the CMC reviews, a project management system should be used to track the status of the reviews, and ideally the issues that may be associated with each review. As submissions are received from sponsors and distributed for review, the project management system should be able to track the status of submissions at any given time to allow management to address issues related to workload, as well as to provide technical support and direction for reviewers as needed. Performing a complete review and meeting review deadlines are both important objectives. Such a tracking system would allow managers to recognize when to assist the reviewer through mentoring and when to supply additional expertise, and would facilitate following up to determine what would help the reviewer be more efficient and effective in conducting reviews.

A tracking system can also address the basic information associated with submissions including how many submissions were received, how many submissions have been approved, how long the approval process is taking, and whether the deadlines are being met (if applicable). Information that is specific to individual submissions and reviewers would also be part of the tracking system. This may include when the submission was received, which reviewer was assigned, the complexity of the submission, interactions with sponsors, participation in work-related roles (such as being a mentor or a committee member) and when the review is due. This information is helpful to the reviewers in organizing their workload, not only to meet deadlines but to alert management to issues where additional expertise may be needed that may cause potential review delays.

Because the submissions may be distributed throughout multiple Offices, a centralized project management system at the Center level may provide an overall picture of the progress made and potential problems that may influence the quality of the review effort.

8.2 DOCUMENT CONTROL SYSTEM

Purpose: To control Quality System and CMC review documents and records; to track guidance and other resource materials.

Document control is important for tracking documents related to this Quality System and to the CMC review process. Controlling documents by identifying dates of development and schedules for review helps ensure they stay current and accurately reflect the processes being conducted and/or applied during CMC reviews. Recording approvals of documents ensure the information contained within is supported by the appropriate quality and/or management staff.

Document control procedures will be developed and/or referenced for all documents key to the CMC review process. These include the following, although others may be identified:

- Quality System documents (plans, audit reports, etc.)
- CMC review documents
- Transmittals to sponsors
- Guidance
- Internal resource materials

8.3 INFORMATION MANAGEMENT SYSTEM

Purpose: To implement Quality System tools; to facilitate access to and sharing of data and information relevant to CMC reviewers.

FDA's Information Management System operations and issues are complex and diverse, and cannot be addressed directly by means of the CMC Review Quality System. However, many of the Quality System tools described in this QMP have a strong IMS component, examples include the following:

- QIPs
- External web site for guidance and policies affecting sponsors
- Intranet site for internal resource materials
- On-line training presentations
- Training tracking system
- Self-evaluation tool
- Data base of sponsor comments
- Searchable data bases for reviewers
- Monthly reports on performance metrics
- Project management system
- Document control system

Thus for the Quality System to be successful, both CBER and CDER will need to engage the participation of IMS support in developing and maintaining these tools.

More broadly, much of this QMP has focused on the vital need for CMC primary and secondary reviewers to have ready access to the information-based resources that they need for the successful accomplishment of their jobs. It has also emphasized the importance of robust and reliable communication links between CMC reviewers and numerous other parties. These are areas where a solid and high-performing Information Management System is instrumental to success. In this sense, the IMS itself is one of the most crucial Quality System tools.

REFERENCES

Quality System Framework for Internal Activities, version 2.0; (FDA Staff Manual Guide 2020)

ANSI/ISO/ASQ Q9001-2000: Quality management systems-Requirements (American Society for Quality, 2000)