

**Inhalation and Nasal Drugs: The Regulatory Landscape
November 6-8, 2006**

**Control of Suppliers, Component
Quality, and Quality by Design**

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Opening Remarks

- ∅ Drug master files (DMFs) complicate QMS, QbD, Component Quality, and Control of Supplier efforts.
- ∅ *IPAC-RS GMP Guideline for Suppliers of Components for Orally Inhaled and Nasal Drug Products* (based on ANSI/ISO/ASQ standard) can serve as a framework to address/document the above.
- ∅ OMB Circular A-119 and National Technology and Advancement Act (NTAA) provide the authority for government use and adoption of standards.
- ∅ QMS can serve as framework to document QbD, Component Quality, and Control of Supplier efforts.
- ∅ QMS framework and Auditing programs can modernize DMF process.

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Drug Master Files (DMF)

- Ø 21 CFR 314.420
 - Maintain confidentiality of proprietary information (e.g., manufacturing procedure)
 - Permit review of information referenced by a number of applicants (e.g., API for multiple ANDA sponsors)
 - No legal or regulatory requirement for filing
 - CMC information must be available for review (application or DMF).
 - Driven by business strategy
 - No AUTHORITY to approve DMF

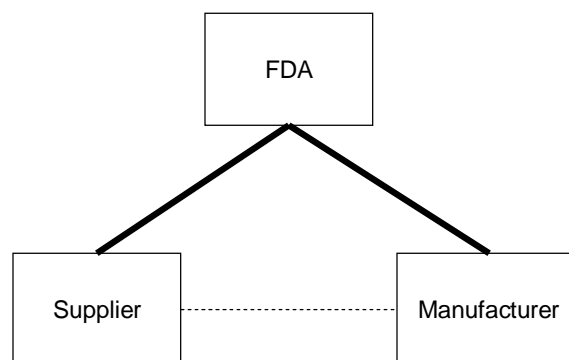
Drug Master Files (DMF)

øLetter of Authorization (LOA)

- Inclusion in submission permits review
- No LOA – No review
- References specific contents of DMF (especially Type III) – Code name, page number, *date of submission*, volume number
- Reviewed *only* when referenced by application

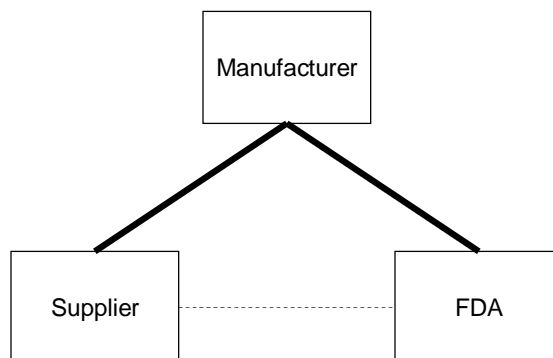
øSame standards as application review
(demonstration of knowledge and understanding)

Current Activity Diagram



HOW DOES THIS APPROACH ENSURE CONTROL OF SUPPLIERS, COMPONENT QUALITY, AND QUALITY BY DESIGN?

Desired Activity Diagram



HOW CAN WE USE QMS APPROACH INCLUDING ENHANCED AUDITING PROGRAMS TO MODERNIZE DMF PROCESS AND CUSTOMER-SUPPLIER RELATIONSHIPS?

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IPAC-RS Good Manufacturing Practices Guideline for Suppliers of Components for Orally Inhaled and Nasal Drug Products

∅ Based on ANSI/ISO/ASQ 9001-2000 Quality Management System (QMS) – Requirements

- Quality Management System – Management system to direct and control an organization with regard to quality
- “Specifies requirements for a QMS where an organization needs to demonstrate ability to provide products that fulfill customer and applicable regulatory requirements and aims to enhance customer satisfaction.”

∅ Opportunity to apply (Standard) process approach to OINDP drug development efforts

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ANSI/ISO/ASQ 9001-2000 Quality Management System (QMS) – Requirements

- ∅ 1.0 Scope – Meet customer needs/applicable regulatory requirements
- ∅ 2.0 Normative reference
 - ┆ ANSI/ISO/ASQ 9001-2005 Quality Management System – Fundamentals and vocabulary
- ∅ 3.0 Terms and definitions
- ∅ 4.0 Quality management system
 - ┆ General requirements - Document, implement, and maintain QMS
- ∅ 5.0 Management responsibility
 - ┆ Commitment to developing, implementing, and continual improvement of QMS
- ∅ 6.0 Resource management – Training, Infrastructure, and Work environment

- ∅ **7.0 Product realization (e.g., OINDP, FDA regulatory decision)**
- ∅ **8.0 Measurement, analysis, and improvement**

Product Realization

- ∅ Planning of product realization (e.g., processes)
- ∅ Customer related processes
 - ┆ Determination of requirements to the product
 - ┆ Review of requirements related to the product
 - ┆ Customer communication (e.g., enquiries, complaints)
- ∅ Design and development
 - ┆ Design and development planning, inputs, outputs, review, verification, validation, changes

Product Realization

- ∅ Purchasing
 - | Purchasing process
 - | **Purchasing information – requirements product and QMS**
 - | **Verification of purchased product - requirements**
- ∅ Product and service provision
 - | Control of product and services provision
 - | Validation of processes for production and service production
 - | Identification and traceability
 - | **Customer property (information sharing)**
 - | Preservation of property
- ∅ Control of monitoring and measuring devices - conformity

Measurement, Analysis, and Improvement

- ∅ General
- ∅ Monitoring and measurement
 - | Customer satisfaction
 - | **Internal audit (e.g., implementation and maintenance)**
 - | **Monitoring and measurement of processes and product**
- ∅ Control of nonconforming product
- ∅ Analysis of data (e.g., customer satisfaction, product requirements, suppliers)
- ∅ Improvement
 - | **Continual improvement**
 - | Corrective action
 - | Preventive action

Standards

- ∅ The National Technology and Advancement Act (NTTAA – PL104-113)
 - | Passed by Congress in 1996, signed by President Clinton
 - | Statute codified an existing OMB Directive
- ∅ OMB Circular A-119 - Federal participation in the development and use of Voluntary Consensus Standards and in Conformity Assessment Activities
 - | Issued several times previously dating back to the late 1970's

Standards

- ∅ The NTTAA and OMB A119 establish federal government policies to improve the internal management of the Executive Branch by directing agencies to use voluntary consensus standards in lieu of government-unique standards, except where inconsistent with law or otherwise impractical.
- ∅ NTTAA and OMB A119 serve as the basis for FDA involvement/adoption of appropriate standards.

Quality by Design

∅ Quality

- ∅ “Good pharmaceutical quality represents an acceptably low risk of failing to achieve the desired clinical attributes.”

∅ Quality by Design (QbD)

- ∅ “Means that product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches.”

Janet Woodcock (2004)

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Quality by Design – OPS Style

- ∅ Achieve patient needs and performance requirements through product design
- ∅ Meet product CQAs consistently through process design (customer expectations = safety and efficacy)
- ∅ Understand impact of process inputs, material attributes, and process parameters on quality
- ∅ Identify and control critical sources of process variability (i.e., those linked to quality)
- ∅ Monitor, evaluate, and update process continually
- ∅ Develop appropriate control strategies

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Quality by Design – OPS Style

- ∅ Establish link between CQAs and safety/efficacy and manufacturing process
- ∅ Understanding structure/function relationships
- ∅ Select desired product attributes (e.g., biotech products)
- ∅ Identify properties or physicochemical characteristics of the drug substance that effect drug product development, manufacture, or performance
- ∅ Document evidence to support compatibility between excipients and DS

Guideline/QMS offer a framework for addressing/documenting QbD efforts for OINDPs.

Supplier Control

- ∅ Follow a quality management system
- ∅ Communicate product quality requirements (performance and regulatory)
- ∅ Understand/document supplier process capability
- ∅ Perform scheduled audits
- ∅ Identify appropriate in-process controls
- ∅ Collaborate to develop a control/change control strategy based on compliance and performance requirements
- ∅ Emphasize cooperation, collaboration, joint problem-solving, and process for continual improvement/corrective action
- ∅ Define responsibilities of customer and supplier
- ∅ Maintain knowledge base of applicable standards

Component Quality

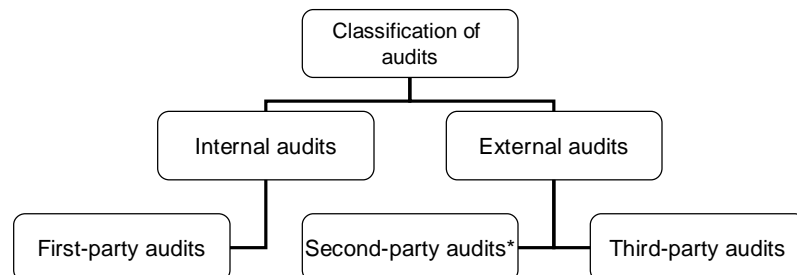
- ∅ Share information regarding product and process requirements
- ∅ Requires a cross-functional approach to define quality requirements
- ∅ Control product within allowable variables
- ∅ Assess supplier performance and process capability (e.g., auditing)
- ∅ Allows distribution of risk (i.e., cost) between customer and supplier
- ∅ Requires definition of performance metrics (product/capability)
- ∅ Effects continual manufacturing/supply
- ∅ Impacts product and process design and development
- ∅ Impacts fitness for use (performance) and regulatory compliance of product
- ∅ Establish mutual goals (customer/supplier)

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Auditing

- ∅ Definition - a systematic, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which the audit criteria are fulfilled



*Effectiveness depends on successful partnerships and alliances.

The ASQ Auditing Handbook, ASQ Quality Audit Division, J.P. Russell, Editor.

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Six Audit Categories

	Compliance Audit	Performance
System Audit	Consistent implementation of a defined system. Promotes stability	Ability to achieve organizational goals. Promotes change.
Process Audit	Performance of the ability in accordance with defined processes.	Ability of the processes to achieve desired characteristics.
Product Audit	Production of goods or services to defined requirements.	Suitability of the goods or services for intended use.

Quality Audits for Improved Performance, Dennis Arter.

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QMS, Quality by Design, Component Quality, Supplier Control, Auditing vs. Drug Master Files (DMF)

- ∅ How do we modernize the DMF process to be consistent with QMS, QbD, component quality, and supplier control efforts?
- ∅ Can the pharmaceutical industry benefit from enhancing auditing programs (including stronger partnerships and alliances) to meet customer needs?
- ∅ Should all CMC information pertaining to critical quality attributes (e.g., drug substance) be submitted in the application?
- ∅ Can the pharmaceutical industry benefit from 3rd party audits/certification (e.g., ASQ or ISO) and reduce the need for regulatory oversight?

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Proposal

Quality Management System (QMS) can serve as a framework to support Control of Supplier, Component Quality, and Quality by Design (QbD) efforts – regulatory and industrial application.

CDER QMS Efforts

- ∅ FDA developed SMG 2020 SMG 2020 - *FDA Quality System Framework for Internal Activities* (<http://www.fda.gov/smg/vol3/2000/2020.html>)
- ∅ OPS established a Standards and Technology Team (Leader: Chris Watts)
- ∅ FDA established a contract with Neptune & Company, Inc. to develop a QMS for the CMC review processes within CDER and CBER
 - | Develop a comprehensive quality system that will facilitate **systematic** positive changes to existing CMC review procedures – continual improvement
 - | Analyses of CMC review process have identified issues and opportunities for improved efficiency, transparency, consistency in the CMC decision making process
 - Build on what is being done right

Thank You

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