

Workshop on Extractables and GMP for Components of
Inhalation and Nasal Drug Products
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Control of Suppliers, Component Quality,
and Quality by Design

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Opening Remarks

- Ø Drug master files (DMFs) complicate control of supplier and component quality, and quality by design (QbD) efforts.
- Ø The current DMF process does not allow a holistic approach to the above (Big Q approach).
- Ø QMS can serve as framework to systematically document and manage control of supplier, component quality, and quality by design (QbD) efforts.
 - *Example: IPAC-RS GMP Guideline for Suppliers of Components for Orally Inhaled and Nasal Drug Products is based on ANSI/ISO/ASQ standard and can serve as a framework to address/document the above.*
- Ø OMB Circular A-119 and National Technology Transfer and Advancement Act (NTTAA) provide the authority for government use and adoption of standards.
- Ø Standards-based approaches are complementary to regulatory processes.
- Ø QMS framework and other standards based approaches (i.e., auditing programs) can modernize DMF process.

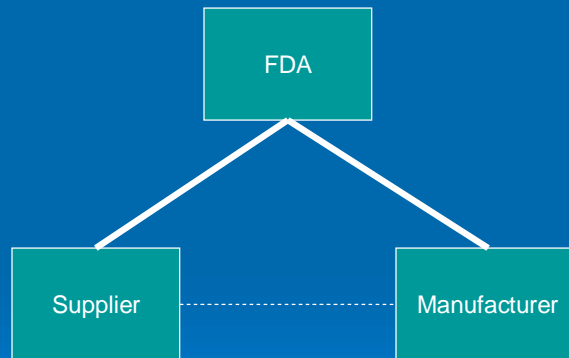
Acknowledgements

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Drug Master File (DMF) – Current State

- Ø 21 CFR 314 – Applications for FDA Approval to Market a New Drug (NDA/ANDA)
 - ┆ CMC information must be available for review (application or DMF).
- Ø 21 CFR 314.420 – Drug Master Files
 - ┆ Maintains confidentiality of **proprietary information** (e.g., manufacturing procedure, drug substance)
 - ┆ Permits review of information referenced by a number of applicants
 - ┆ No legal or regulatory requirement for filing/reviewing.
 - ┆ Unable to approve DMF
 - ┆ Driven by business strategy not regulatory science process (i.e., provision not requirement)

Current State for DMF Activities



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

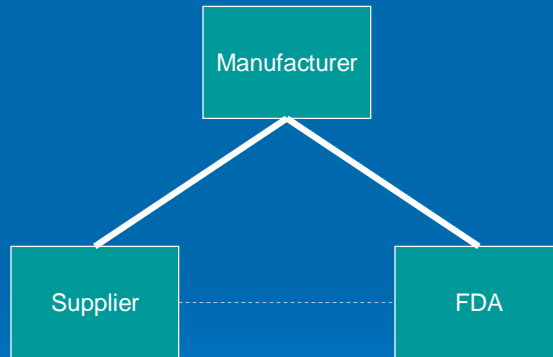
QMS Approach and Supplier Communications

- Ø The organization shall determine and implement effective arrangements for communicating with customers in relation to
 - ┆ Product information
 - ┆ Enquiries, contracts or order handling, including amendments, and
 - ┆ Customer feedback, including customer complaints

(ANSI/ISO/ASQ 9001-2000 Quality Management Systems – Requirements – section 7.2.3 – Customer communication)
- Ø Design and implement techniques for communicating with suppliers including scheduled meetings, routine and emergency reporting procedures, presenting explicit expectations, confirming awareness of criticality, etc.

The Certified Manager of Quality/Organizational Excellence Handbook, 3rd edition.

Desired State for DMF Activities



HOW CAN WE USE QMS APPROACH TO MODERNIZE DMF PROCESS?

“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight”. *Janet Woodcock*

Desired State for DMF Activities

- ∅ Depend more on manufacturer/supplier quality systems
- ∅ Learn to use quality agreement to support product quality efforts
- ∅ Better identification/management of confidential/proprietary information

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, including drug master file efforts.

Building a Bridge Between Current and Desired State for DMF Process

- Ø *Example: IPAC-RS Good Manufacturing Practices Guideline for Suppliers of Components for Orally Inhaled and Nasal Drug Products (Link: <http://www.ipacrs.com/supplier.html>)*
- Ø *Based on ANSI/ISO/ASQ 9001-2000 Quality Management System (QMS) – Requirements*
 - | *QMS - Defined as 'a structured and documented management system describing the policies, objectives, principles, organizational authority, responsibilities, accountability, and implementation plan of an organization for ensuring quality in its work processes, products (items), and services.' (ANSI/ASQ E4-2004)*
 - | *Say what you do and do what you say*
 - | *Aligns with Product Quality Initiative*
- Ø **Opportunity to apply Standard-based approach to drug development efforts**

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

- Ø 1.0 Scope – Meet customer needs/applicable regulatory requirements
- Ø 2.0 Normative reference
 - | ANSI/ISO/ASQ 9001-2005 Quality Management System – Fundamentals and vocabulary
- Ø 3.0 Terms and definitions
- Ø 4.0 Quality management system
 - | General requirements - Document, implement, and maintain QMS
- Ø 5.0 Management responsibility
 - | Commitment to developing, implementing, and continual improvement of QMS
- Ø 6.0 Resource management – Training, Infrastructure, and Work environment
- Ø 7.0 **Product realization (e.g., OINDP, information on DMFs)**
- Ø 8.0 **Measurement, analysis, and improvement**

Standards

- Ø Taxonomy of standards by developer
 - | Regulation (mandatory) – Developed and promulgated by government authority – no consensus
 - | Consensus (voluntary) – developed through the consensus process by American National Standards Institute (ANSI) accredited SDO – all interested parties participate
 - | Industry (corporate, consortium) – developed by a single entry or non-consensus consortium – limited consensus

Standards

∅ Why Involve FDA?

- | Address elements of the FDA Performance Plan
- | Optimize the utilization of FDA resources
- | Accomplish international trade commitments
- | Enables cooperation between governments
- | Encourages improvements in industrial productivity by basing requirements on accepted standards
- | National Technology Transfer and Advancement Act (PL104-113) & OMB Circular A119

Standards

∅ The National Technology Transfer and Advancement Act (NTTAA – PL104-113)

- | Passed by Congress in 1996, signed by President Clinton
- | Statute codified an existing OMB Directive

∅ OMB A119 – provides for 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

- ∅ Together 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 and adoption of standards.

Considerations for Supplier Control

- ∅ **Follow a quality management system approach**
- ∅ Communicate product quality requirements between supplier and manufacturer - performance and regulatory
- ∅ Understand/document supplier process capability
- ∅ Perform scheduled audits
- ∅ Identify appropriate in-process controls
- ∅ Collaborate to develop a 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

The current DMF process interferes with these efforts.

Considerations for Component Quality

- Ø **Follow a quality management system approach**
- Ø Share information regarding product and process requirements
- Ø Implement a cross-functional approach to define quality requirements
- Ø Control product within allowable tolerances
- Ø Assess supplier performance and process capability (e.g., auditing)
- Ø Define performance metrics (product/ capability)
- Ø Document product and process design and development
- Ø Identify/understand fitness for use (performance) and regulatory compliance requirements
- Ø Establish mutual goals (customer/supplier)

The current DMF process interferes with these efforts.

Quality by Design

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

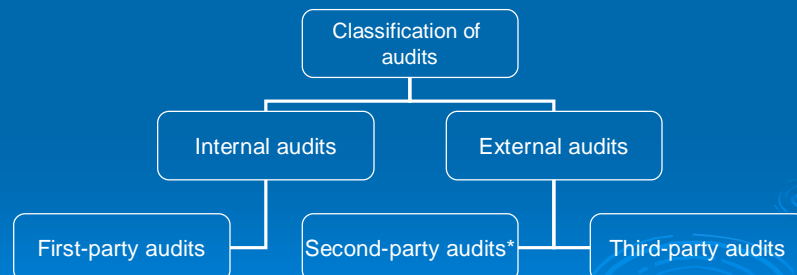
Janet Woodcock (2004)

Some Steps to Achieving Quality by Design

- Ø Follow a QMS approach for process and product development to document the scientific rationale.
- Ø Implement standards that meet your objectives.
- Ø Timely implementation based on product requirements and evolution of quality system – stepwise approach may be more appropriate.
- Ø Identify process and product controls - designed to meet patient expectations.
- Ø Audit suppliers to ensure efforts to meet component controls.

Auditing

- Ø 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.

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.

Auditing and Drug Master Files

- Ø Implementing an effective auditing program can minimize the need for DMFs.
- Ø Auditing benefits include stronger partnerships and alliances to meet QMS (customer-supplier focused) needs and quality by design efforts.
- Ø DMF content could be limited to letter of certification by accrediting organization (i.e., ASQ, etc.) and information on critical quality attributes.
- Ø Modernizing the DMF process requires collaboration by the pharmaceutical industry and FDA.

CDER QMS Efforts

- Ø FDA developed SMG 2020 SMG 2020 - *FDA Quality System Framework for Internal Activities*
(<http://www.fda.gov/smg/vol3/2000/2020.html>)
- Ø Guidance on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations
(<http://www.fda.gov/cder/guidance/7260fnl.pdf>)
- Ø OPS established a Standards and Technology Team (Leader: Chris Watts)
- Ø 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
 - | Analyze CMC review process to identify issues and opportunities for improved efficiency, transparency, consistency in the CMC decision making process
 - Incorporate internal auditing program

Closing

- Ø David's Big Q(uestion)
 - | Can the pharmaceutical industry modernize the DMF process and move further along the road of Big Q?
- Ø Definition:
 - | Big Q, Little Q: *A term used to contrast the difference between managing for quality in all business processes and products (big Q) and managing for quality in a limited capacity—traditionally only in factory products and processes (little q).*
American Society for Quality
- Ø "I think he really did hope that someone would come along, challenge him and try to define Quality for him. But no one ever did."
 - | *Zen and the Art of Motorcycle Maintenance – An Inquiry Into Values* – Robert M. Pirsig

Thank You

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