Issues in Complying with the Prescription Drug Marketing Act (PDMA)

Background

In July of 1985, a congressional subcommittee reported to Congress that in many situations, American consumers were not able to purchase prescription drugs with the assurance that the products were safe and effective.

Subsequent to this report, federal and state authorities reported numerous problems regarding the safety, efficacy, storage, and handling of pharmaceutical samples with alarming frequency.

The reported problems included drug products that were mislabeled, sub-potent, adulterated, expired, and even counterfeited. Additionally, legislators identified a secondary diversion market as the primary source of the substandard drugs introduced into the U.S. distribution system.

Three channels fed the diversion market:

- Previously exported drugs re-imported as American goods returned
- Diverted pharmaceutical samples
- Below wholesale-priced prescription drugs resold by healthcare organizations

To correct the situation, Congress voted to amend the Federal Food, Drug and Cosmetic Act of 1932, enacting the Prescription Drug Marketing Act of 1987 (Public Law 100-293).

The Prescription Drug Marketing Act (PDMA) signed into law by then President Ronald Reagan on April 22, 1988, established specific requirements in several vital areas:

- Distribution
- Storage
- Disposal
- Prescriber Validation
- Re-importation
- Inventory Management and Reconciliation
- State Licensing of Wholesale Prescription Drug Distributors (21 CFR Part 205)
- Record-keeping
- Security
- Violations and Penalties
- Strict enforcement of civil and criminal penalties to both individuals and corporations

PDMA Implementation and Guidance

The Prescription Drug Marketing Act implemented with 21 CFR Part 203 and the amendment of 21 CFR Part 205, dealing with drug distribution management and inspection, became effective December 4, 2000.

In response to industry requests, the FDA has delayed the effective date of 21 CFR Parts 203.3(u) and 203.50, and the applicability of Part 203.3(q) for wholesale distribution of blood derivatives by health care entities until April 1, 2004.

The enactment of 21 CFR Part 203 brought with it additional regulatory requirements.

Specifically, an entity using electronic records and/or electronic signatures inherited the compliance issues associated with *21 CFR Part 11 Electronic Records; Electronic Signatures.*

Between 1997 and 2002, which saw the enactment of 21 CFR Part 11, numerous industry experts and the FDA gradually increased the scope of Part 11's applicability for implementation of electronic records and electronic signature systems and the compliance requirements to 21 CFR Part 11.

During this same period, the FDA and GAMP (Good Automated Manufacturing Practices) published draft guidance documents to assist the pharmaceutical industry in implementing 21 CFR Part 11.

In January 2002, the FDA published *General Principles of Software Validation; Final Guidance for Industry and FDA Staff,* which supplanted the June of 1997 draft document.

The General Principles of Software Validation document published by the Centers for Devices and Radiological Health (CDRH) is applicable and considered by the FDA to represent current thinking on the topic of validation and compliance as specified in section *'2.4 Regulatory Requirements for Software Validation' of that document.*

It says, *"In addition, computer systems used to create, modify, and maintain electronic records and to manage electronic signatures are also subject to the validation requirements. (See 21 CFR § 11.10(a).) Such computer systems must be validated to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records."*

The General Principles of Software Validation document addresses many aspects of good software engineering such as planning, verification, testing, traceability, and configuration management.

It also blends Quality System Management attributes supporting the conclusion that software is validated. The focus of the document is an integration of software life cycle management and risk assessment focusing on the software's intended use, relevant safety factors, and integrity of the data.

To simplify compliance issues regarding 21 CFR Part 11 and to synchronize the FDA's approach to validation, thereby providing industry assistance in achieving and maintaining a system's validation, the

FDA published a draft guidance document *Guidance for Industry Part 11, Electronic Records; Electronic Signatures – Scope and Application* in February 2003.

The publication of this document, along with the recall of other FDA Draft Guidance documents associated with compliance to Part 11, provided notification to the Industry that 21 CFR Part 11 would be re-examined in light of the FDA's shift in regulatory compliance focus to a risk based approach.

(For detailed information on 21 CFR Part 11, see CimQuest, Inc., white paper *'21 CFR Part 11; Where Are We Now?').*

Dealing with the realities of PDMA Implementation

Risk assessment and containment is normally associated with software engineering at the development level.

However, the FDA's focus and use of risk assessment as the precursor in determining both the degree of validation necessary for a software application used to support regulated activities, and the degree and depth of control requirements identified for these same systems in 21 CFR Part 11, requires both Information Systems and Business Area organizations to rethink their approach to Part 11 and validation compliance.

The Business Areas must now be included in discussions with Information System Areas at each phase of the software life cycle and include additional criteria examining the system's use, regulatory impact, containment, and mitigation.

Additionally, the Business Area and sponsor of the software development project must accept more ownership in the management of the Validation effort in determining the strategy and extent of validation necessary for any given project.

Decisions concerning project execution, compliance issues relative to 21 CFR Part 11, and decisions specific to the validation effort should be fully justified or stated within project documentation.

Consider two related purposes for this action. (1) It is rare that the FDA would perform an inspection at the time of implementation when all project and Business Area management participants' memories are capable of recreating the thought processes involved in project implementation. (2) The justifications or reasons for specific actions and decisions plus other project documentation allow personnel currently responsible for that Business Area management to trace and recreate the rationale involved in project execution and implementation.

Industry's implementation of the PDMA typically includes a blended solution of paper-based processes with electronic systems comprised of electronic records and / or electronic signatures. Because this combination

creates a blended solution, it becomes more important to validate the entire system (people, machines, and software) to identify potential issues requiring remediation, mitigation, or control.

Validating systems used in support of compliance to the PDMA necessitates formalized policies, plans, and procedures consistent with current Industry standards and good practices. The collection, more commonly identified as a Quality Management System, incorporates an organization's business processes of which software development is a component, into a solution satisfying the organization's business objectives. Establishing a consistent monitoring (auditing) program assists Business Area Management in ensuring compliance to the stated quality requirements.

Recommendations

Organizations striving to maintain compliance to the PDMA must adopt a holistic approach to Validation using cross-functional teams capable of addressing among other disciplines:

- Risk Assessment
- Validation Planning
- Quality Assurance Planning
- Software Engineering
- Corrective and Preventative Action Management
- Configuration Management
- Change Control
- Testing
- Problem Reporting and Resolution
- Document Management
- Training
- Regulatory Compliance (predicate rule requirements)
- Project Management

Using Risk Assessment to determine how much validation is enough for a given software application implies a formal written evaluation of the risk, the justification for the course of action taken, and the mitigation, remediation, or control associated with that risk. Risk Assessment permits, under considered circumstances, an organization to

provide specific justification in determining the appropriate level of both system validation and the controls required by 21 CFR Part 11 based on the intended use of the product, relevant safety factors, and integrity of the data.

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