

A Risk-based Approach to Part 11 and Predicate Rules

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Presented for: DIA 40th Annual Meeting
15-June-2004





Who We Are....

- The Leader in Information Technology Support and Services for the Clinical Research Environment
- Headquartered in Pottstown, PA
- Solutions include Services and Software Products
- Three Business Lines:
 - *Clinical Systems Services (CSS)*
 - *Clinical Reporting Services (CRS)*
 - *Compliance Services (CS)*



Who We Are....

- **Expert Consultants**
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 - *Project Management*
 - *System Selection, Development, Implementation & Support*
 - *Systems Validation*
 - *Migrations*
 - *Programming*
 - *Database Administration*
 - *Training*
 - *Regulations, e.g. GxPs, 21 CFR Part 11*
 - *Standards, e.g. IEEE, CDISC*
 - *e-Submissions*



Overview

- This presentation will discuss a risk-based approach to meeting Part 11 requirements for predicate rules.
- Let's break that down a little...



Risk-based Approach

- Risk-based Approach – Within an established quality system and for a particular manufacturing process, one would expect an inverse relationship between the **level of process understanding and the risk of producing a poor quality product.** (FDA's *Process Analytical Technology*)

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- August 2003 FDA P11 Guidance recommends a risk-based approach
- FDA PAT recommends a risk-based approach
- Risk-based approaches are the hot-topic in pharma but they've been a part of our every-day lives for years: medical procedure risk, credit risk, should I go to the RPS party the night before my presentation risk, etc.



Risk-based Approach

- For processes that are well understood, opportunities exist to develop **less restrictive regulatory approaches** to manage change. Thus, a focus on **process understanding can facilitate risk-based regulatory decisions** and innovation. (FDA's *Process Analytical Technology*)

Continue risk definition...



Risk-based Approach

- What is risk? Probability that the desired outcome will not be achieved.
- How is it applied to a computerized system? Risk that system will not meet requirements.
- How does this relate to predicate rule? Not meeting requirements of predicate rule
- Not meeting requirements of Part 11.

Define risk...



21 CFR Part 11

- Part 11, the FDA has narrowed the scope...but ***Note that Part 11 remains in effect.*** (August 2003 Guidance)

Discuss Part 11...



21 CFR Part 11

- Part 11 does not apply to a process with no electronic records.
- Part 11 does not apply to all electronic records, only those related to a predicate rule. It is important to document this decision.



Predicate Rules

- As noted in the Part 11 guidance, the underlying requirements set forth in the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and FDA regulations (other than part 11) are referred to as “predicate rules.”

From the P11 guidance...



Predicate Rules

- Identify your process
- Identify records required to be maintained under predicate rules or required to be submitted to the FDA
- Part 11 applies when electronic records are used in place of paper records for a predicate rule

Thought process for arriving at an electronic record that falls under Part 11.

Predicate rules more commonly known as GLP, GCP, GMP, etc.

Also includes records that are open to FDA audit

Consider records that are used to directly support predicate rule records



The process

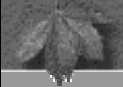
- The process of applying Part 11 to a particular computerized system in a particular predicate rule environment can seem daunting to say the least.
- A risk-based approach provides a framework for focusing on the major events that could affect patient health, drug efficacy and record integrity.

Risk-based framework...



Events

- In a computerized system these events are manifest in scenarios where Part 11 requirements are not achieved.



Focus

- Without due focus on risk, trivial areas of the system may gobble-up time and resources
- While the truly important areas of the system receive less than appropriate attention.
- This is where a risk assessment provides focus.



Scope

- Define the scope of the effort, which is based upon the business process.
- The people involved in the process,
- The drug(s) involved in the process,
- The portion(s) of the drug lifecycle involved in the process,
- Which leads to the predicate rule(s) involved in the process.

Emphasize combined requirements: user req, predicate req, part 11 req.



E-records

- With the rules identified, the pertinent electronic records can be determined.
- Applying Part 11 to the electronic records and the business process in which they are used, the overall requirements for the system may be determined.



Application

- The typewriter rules lives!
- For instance, validation would not be important for a word processor used only to generate SOPs. (FDA Final Part 11 Guidance)

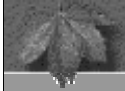
...but only if the ER is not subsequently used



Prioritize

- Potential events where these requirements are not achieved; prioritized by:
 - the impact of an event if it occurs,
 - the probability of the event occurring,
 - the chances of detecting the event once it has occurred.

Example: Manufacturing electronic records are generally high-risk, while supporting data-analysis electronic records could be of relatively low-risk.



Impact

- Patient safety,
- Drug efficacy, and
- Record integrity.

Don't forget the business impact—managerial buy-in



Probability of Occurrence

- System complexity,
- Novel use or technology,
- System history and reliability,
- Level of operators (significant experience and education, making independent assessments or just pushing buttons?)



Detection

- Manned system or automated system?
- Black box system?
- Are records verified or inspected?

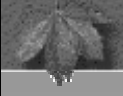
Do you trust the system? Why?



RiskMAP

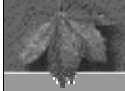
- Together, risk assessment and risk minimization form what FDA calls risk management; which may be summarized in a Risk Management Action Plan – RiskMAP.
- Risk management is the translation of what was learned in the risk assessment into actions that minimize the risk associated with an event to an acceptable level.

One of the risk management tools



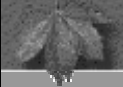
Risk Minimization

- This process may include:
 - Steps taken to avoid the occurrence of an event,
 - Steps taken to mitigate the impact of an event, or
 - Simply accepting the risk that an event might occur and planning contingencies for when the event occurs.



Risk insight

- Concerning drugs, but giving insight into the FDA's thoughts on risk management:



FDA insight

- Specifically, risk management is an iterative process of:
 - 1) **Assessing** a product's benefit-risk balance,
 - 2) Developing and implementing tools to **minimize** its risks while preserving its benefits,
 - 3) Evaluating tool effectiveness and **reassessing** the benefit-risk balance, and
 - 4) Making adjustments, as appropriate, to the risk minimization tools to further improve the **benefit-risk balance**.

Tools: RiskMap, process metrics, decision trees, templates or checklists for conducting assessments



FDA insight continued

- This four-part process should be **continuous** throughout a product's lifecycle, with the results of risk assessment informing the sponsor's decisions regarding risk minimization. (FDA Development and Use of Risk Minimization Action Plans, DRAFT 2004)

...much like you cannot ignore a lawn, a risk-based approach to compliance is an on-going process.



More FDA insight

- A **software requirements traceability** analysis should be conducted to trace software requirements to (and from) system requirements and to **risk analysis results**. (FDA General principles of software validation, 2002)

High-risk requirements should trace to more rigorous testing
Low-risk may trace to implicit testing



Still more FDA insight

- For lower risk devices, only baseline validation activities may be conducted.
- As the risk increases additional validation activities should be added...
- The resultant software validation process should be commensurate with the safety risk associated with the system, device, or process. (FDA General principles of software validation, 2002)

Emphasize balance of benefit/risk



References

- FDA General Principles of Software Validation (2002)
- IEEE Computer Society Press, *Handbook of Software Reliability Engineering* (1996)
- FDA Development and Use of Risk Minimization Action Plans, DRAFT (2004)
- PAT - A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance, DRAFT (2003)
- Good Automated Manufacturing Practices, GAMP 4 Guide
- Part 11, Electronic Records; Electronic Signatures — Scope and Application (2003)
- Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach (2002)



Conclusions

- A risk-based approach to Part 11 and the predicate rules can provide focus:
 - Improved patient safety, drug efficacy, and record integrity through greater focus.
 - Less restrictive regulatory focus to manage change.
 - Improved value by focusing on high-risk issues and spending less effort on low-risk issues.