21 CFR Part 11
Risk Analysis

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Risk and Part 11
What does FDA tell us?

21 CFR Part 11

- The regulation itself does not reference risk or define a risk based approach
- The preamble uses the word risk when discussing security and other risks but does not discuss a risk-based approach

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Part 11 Final Guidance

- Discusses risk in several sections
- Mentions use of justified and documented risk assessment
- Suggests two types of risk be considered. Potential effect on:
  - product quality and safety
  - and record integrity
- Mentions the CDER GMP modernization effort which focuses on a risk-based and quality systems approach

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Guidance Risk Excerpts - Validation

III.C.1 Validation

- **"We suggest that your decision to validate computerized systems, and the extent of the validation, take into account the impact the systems have on your ability to meet predicate rule requirements. You should also consider the impact those systems might have on the accuracy, reliability, integrity, availability, and authenticity of required records and signatures.**
- **Even if there is no predicate rule requirement to validate a system, in some instances it may still be important to validate the system.**
- **We recommend that you base your approach on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety, and record integrity. For instance, validation would not be important for a word processor used only to generate SOPs."**

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Guidance Risk Excerpts – Audit Trails

- **III.C.2 Audit Trails**
- **"Persons must still comply with all applicable predicate rule requirements related to documentation of, for example, date … time, or sequencing of events, as well as any requirements for ensuring that changes to records do not obscure previous entries."**
- **"Even if there are no predicate rule requirements to document, for example, date, time, or sequence of events in a particular instance, it may nonetheless be important to have audit trails or other physical, logical, or procedural security measures in place to ensure the trustworthiness and reliability of the records. We recommend that you base your decision on whether to apply audit trails, or other appropriate measures, on the need to comply with predicate rule requirements, a justified and documented risk assessment, and a determination of the potential effect on product quality and safety and record integrity."**
- **"We suggest that you apply appropriate controls based on such an assessment. Audit trails can be particularly appropriate when users are expected to create, modify, or delete regulated records during normal operation."**

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Guidance Risk Excerpts - Retention

III.C.5 Record Retention

- **"We suggest that your decision on how to maintain records be based on predicate rule requirements and that you base your decision on a justified and documented risk assessment and a determination of the value of the records over time."**

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Guidance Risk References

- *"Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach* (FDA 2002)
- ISO 14971:2002 Medical Devices- Application of risk management to medical devices (ISO, 2001)"
- **Value of these references to developing a specific Part 11 Risk-based approach – LOW.**

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Summary Risk Factors

- Impact on –
  - Integrity and security of regulated records and signatures
  - Completeness of regulated records
  - Retention of regulatory records
  - Product safety and effectiveness
  - Service/support
  - Quality System
  - Product Development

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Risk based flexibility

- Can reduce effort
- Can decrease consensus and increase uncertainty
- Provides enough rope to …
- The alternative of one size fits all is less attractive
- For devices this has been a way of life in many aspects of compliance

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21 CFR 820.70(i) Validation

Quality System Regulation 820.70(i)

"When computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities and results shall be documented."

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Regulatory Guidance GPSV

- **"Any software used to automate any part of the device production process or any part of the quality system must be validated for its intended use, as required by 21 CFR 820.70(i). This requirement applies to any software used to automate device design, testing, component acceptance, manufacturing, labeling, packaging, distribution, complaint handling, or to automate any other aspect of the quality system. "**

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GPSV Preamble

- **"… it appears that some parties may not have realized the full breadth of the quality system regulation. The software validation requirement in 21 CFR 820.70(i) of the quality system regulation also applies to automated tools used to design medical devices and tools used to develop software."**

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How much is enough? - FDA Guidance

- **The level of validation effort should be commensurate with the risk posed by the automated operation. In addition to risk, other factors such as the complexity of the process software and the degree to which the device manufacturer is dependent upon that automated process to produce a safe and effective device, determine the nature and extent of testing needed as part of the validation effort..**

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How much is enough? - FDA Guidance (cont.)

- **Documented requirements and risk analysis of the automated process help to define the scope of the evidence needed to show that the software is validated for its intended use. For example, an automated milling machine may require very little testing, if the manufacturer can show that the output of the operation is subsequently fully verified against the specification before release. On the other hand, extensive testing may be needed for a plant-wide electronic record and electronic signature system, for an automated controller for a sterilization cycle or for automated test equipment used for inspection and acceptance of finished circuit boards in a life-sustaining / life-supporting device.**

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How Much is Enough? - GPSV

- Software verification and validation are difficult because a developer cannot test forever, and it is hard to know how much evidence is enough.
- In large measure, software validation is a matter of developing a "level of confidence
- The level of confidence, and therefore the level of software validation, verification and testing effort needed, will vary depending upon the safety risk (hazard) posed by the automated functions of the device.

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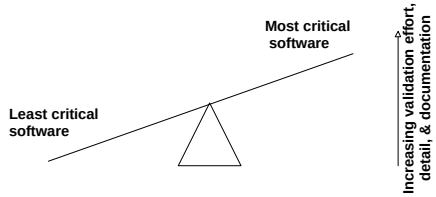
Focus on Critical Areas



The more likely that a mfg or QS application could result in shipment of unsafe or defective product or affect regulatory record integrity (due to a bug, unforeseen functional requirement, or operator error) the more rigorous the validation, and its associated documentation, should be.

FDA allows that validation effort, and documentation detail, can be scaled to criticality

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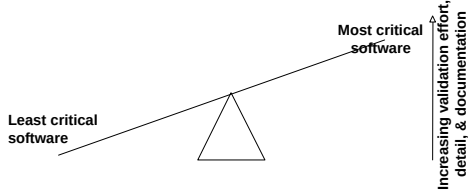
The Leveling Effect

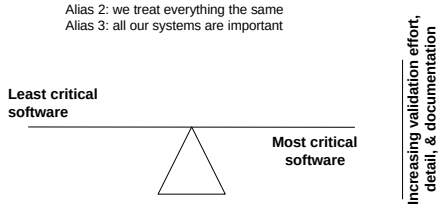
Inconsistent: the way it should be



Consistent: inefficient and/or ineffective

Alias 1: we treat everything as critical

Alias 2: we treat everything the same
Alias 3: all our systems are important



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Some Types of Production/QS Software

- Manufacturing
- Quality Control
- Service
- Complaint Handling
- Electronic records
- Documentation Control
- Laboratory Systems
- Labeling Systems
- Data Acquisition
- Statistical
- Clinical Trials

- COTS
- Custom In-house
- Custom Vendor
- Configurable
  - Spreadsheets
  - Databases
- Equipment
  - PLCs
  - Embedded automation
- Design Tools
- Product Variants

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Risk-Based Approaches

Scope

- Consider Scope of Part 11
  - If not within scope then Part 11 is not an issue
    - Legacy systems
    - Predicate rule does not require the records
    - Incidental to creating another form of the record
    - Procedures make it clear that that the electronic records are not relied on for regulated activities
    - Etc…
  - But, 820.70(i) validation may still be

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Risk Analysis Procedure

- Define your approach
  - Separate procedure
  - Or, integrate into existing validation or Part 11 procedures
- Risk Factors
- Risk ratings
- Risk rationale
- What will be different based on risk?
  - If you can't answer this then of what value is the analysis?

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Risk Factors and Ratings? Ex. 1

- 1. Directly results in :
  - A) release of unsafe or ineffective product
  - B) inability to do a proper or timely recall
  - C) release of product that does not meet spec.
  - D) loss or corruption of primary regulatory records
  - E)…etc.
- 2. In-process problem that could lead to A-E… above but would be likely to be caught later in the process.
- 3. Could result in loss or corruption of
  - A) secondary (less important) regulatory records
  - B) electronic records for which other full or partial copies are available
  - C)…etc.

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Risk Factors and Ratings? Ex. 2

- 1. Affects clinical trials records/analysis
- 2. Affects finished product QC Testing
- 3. Affects product manufacturing or Device History Record(DHR)
- 4. Affects other primary regulatory records (DHF, DMR, QSR)
- 5. Affects design V&V
- 6. Affects other quality system activities and records
- 7. Affects product development
- …there are many other possibilities

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But do the ratings matter?

- Not unless you do different things based on them
  - Do you approach validation activities differently?
  - Do you require different functionality for security/data integrity?
  - Do you require more detailed documentation?
  - Do you require more rigorous administrative procedures (e.g., access rights, backup, monitoring, …)?

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What can be different?

- Maybe some aspects of validation
  - Required reviews and approvals
  - Requirements at the intended use level vs. very detailed functional specifications (but still needs to be testable)
  - Degree of abnormal and stress testing
  - Specificity of test steps
  - Extent of test evidence
- Maybe system functionality
  - Security features
  - Data integrity checks
  - Audit trails

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What else can be different?

- If the system is used for primary regulatory records:
  - Requirements and Design Specs should include specification of data integrity and record keeping requirements
  - Test protocols and results should verify this functionality and show they work under a range of conditions – no back doors, integrity despite system failures, …
  - Security applies to system documentation as well as the system itself
  - Additional administrator and user training

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Issues

- FDA has not been specific on what would be "justified" based on risk analysis
- It can be difficult to create cookbook risk ratings and fixed requirements based on them (given technology factors, OTSS vs. custom, complexity, etc.)
  - Rather then using specific ratings could consider a textual analysis and justification for approach taken (will need this anyway to explain/defend approach and defend integrity of records)
  - Over time develop models for different types of systems and risks – based on internal experience and FDA enforcement over time
  - Its hard to standardize approach with no experience and no precedents/explicit guidance

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Available on Web Site

1. Part 11 Reference Manual
2. News Updates related to Part 11 and Software Validation and Regulation
3. Software related excerpts of Recalls, MDRs & Warning Letters
4. Bulletins, Newsletter, and Educational materials including sample documents and procedures (for subscribers)

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