
Biokinetics
Optimum Solutions -Concept to Product

Risk Based Validation

Why, How and with what tools?

Tech Talk Agenda

- History of FDA GMP initiative for the 21st Century.
- Industry response to FDA initiative.
- Harmonisation through ICH.
- ASTM Standard on Risk Based Qualification.
- Old Validation approach Vs New Risk Based approach.
- ISPE Baseline Guide on C&Q and GAMP
- Sample Risk Assessment process.
- Summary.

History

- FDA announces it's 2 year "Pharmaceutical cGMPs for the 21st Century – A Risk Based Approach" (2002).
  - To encourage the early adoption of new technological advances by the pharmaceutical industry.
  - To facilitate industry application of **modern quality management techniques**, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance.
  - To **encourage** implementation of **risk-based approaches** that focus both industry and Agency attention on critical areas.
  - To ensure that regulatory review and inspection policies are based on state-of-the-art **pharmaceutical science**.
  - To enhance the consistency and coordination of FDA's drug quality regulatory programs.

History

- ICH begins activities on the following documents (2003):
  - Q7 ICH technical Requirements
  - Q8 Pharmaceutical Development
  - Q9 Quality Risk Management (2005).

  These recommend "harmonised" ways of complying with regulatory requirements.
- ASTM begins work on their "Standard guide for a Science and Risk Based Approach to qualification of Biopharmaceutical and Pharmaceutical Manufacturing Systems".

  This recommends **how** to comply with regulatory requirements.

Why Change?

- Make all we do Science and Risk based which is easier to rationalise and defend.
- Based on the science of the product and process.
- To ensure a common understanding of regulatory requirements.
- To facilitate companies moving to the new “Desired State”
- To move away from “Reactive” to “Proactive” management.
- Transparency in all we do.
- Improved communications (through RM process) at sites and with regulatory authorities.

Industry Impact

- FDA seeks to "**integrate quality systems and risk management** approaches into the existing programs"
- **ICH** who were setup to harmonise standards between Europe, Japan & the US have developed the **Q9 Quality Risk Management Guide** to address this issue.(Nov 2005)
- **ASTM** in response to FDA initiative, generate a standard for a science and risk based approach to qualification **but without describing the risk management process.** It does reference Q9.
- As a result of the ASTM standard, **ISPE** will change their Baseline Guide on "**Commissioning and Qualification"**.

Industry Impact – ICH

- **Q9 Quality Risk Management Guide**
  - Is a guideline proposed for Japan, Europe and the US.
  - Provides an iterative process for determination of risk, it's severity and impact throughout a process (engineering, manufacturing, materials, logistics etc).
  - A systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle.
  - Provides an Annex of different tools which can be used depending on the requirements.
  - Allows use of different information – qualitative, quantitative and expert judgement.

Industry Impact - ICH

- **Q9 Quality Risk Management Guide Tools Mentioned**
  - Failure Modes Effects Analysis (FMEA) – IEC60812.
  - Failure Modes Effects & Criticality Analysis (FMECA)
  - Fault Tree Analysis (FTA) – IEC61025
  - Hazard Analysis and Critical Control Points (HACCP)
  - Hazard Operability Analysis (Hazop) – IEC61882
  - Statistical Tools such as control charts, DoE etc.
- Tools are well known to industry so decide on and use the one best suited to the particular task.
- Not a “One size fits all” approach.

Principles of QRM.

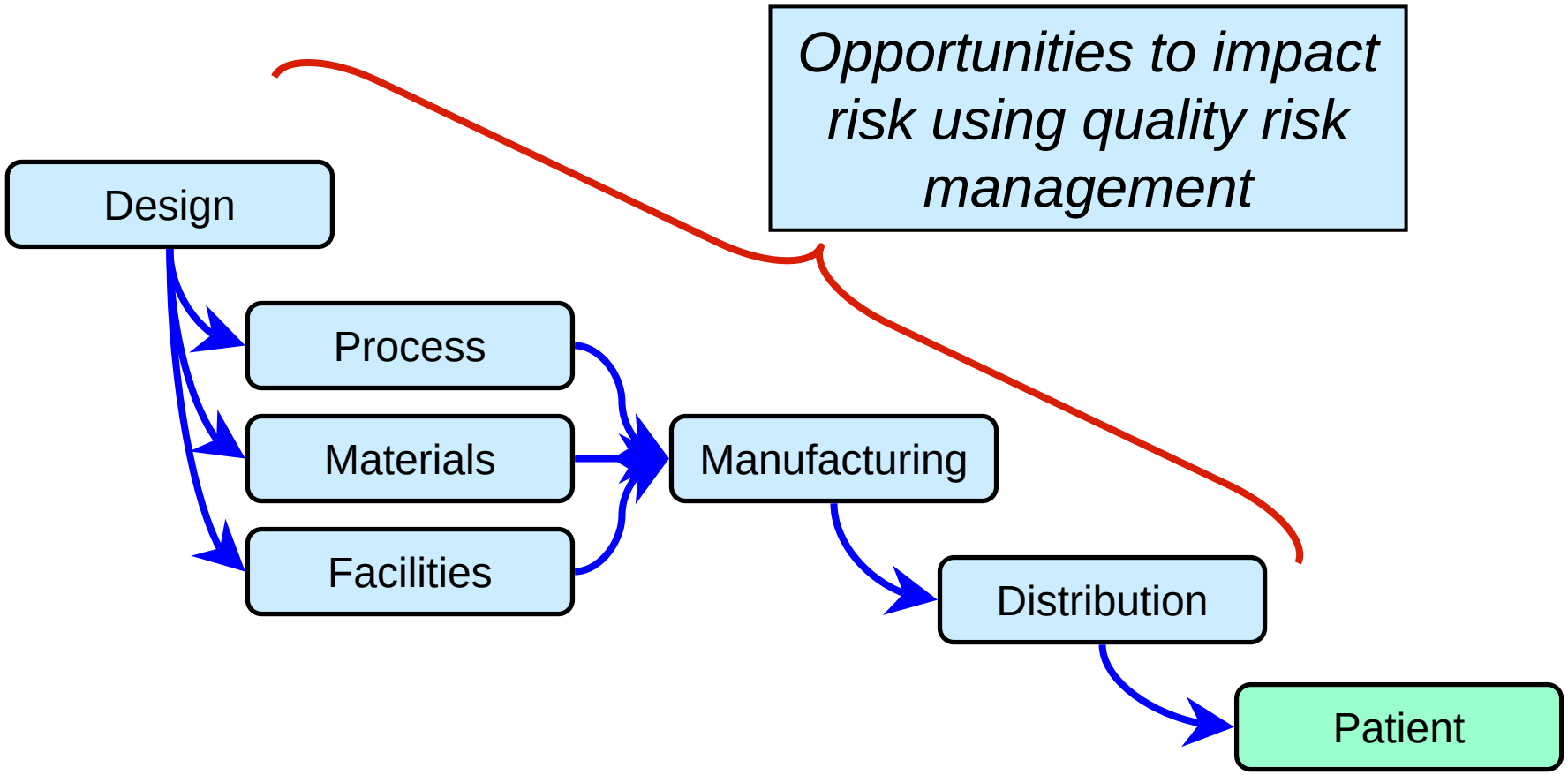
- "The evaluation of the risk to quality should be based on scientific knowledge and ultimately link back to the protection of the patient.

  and

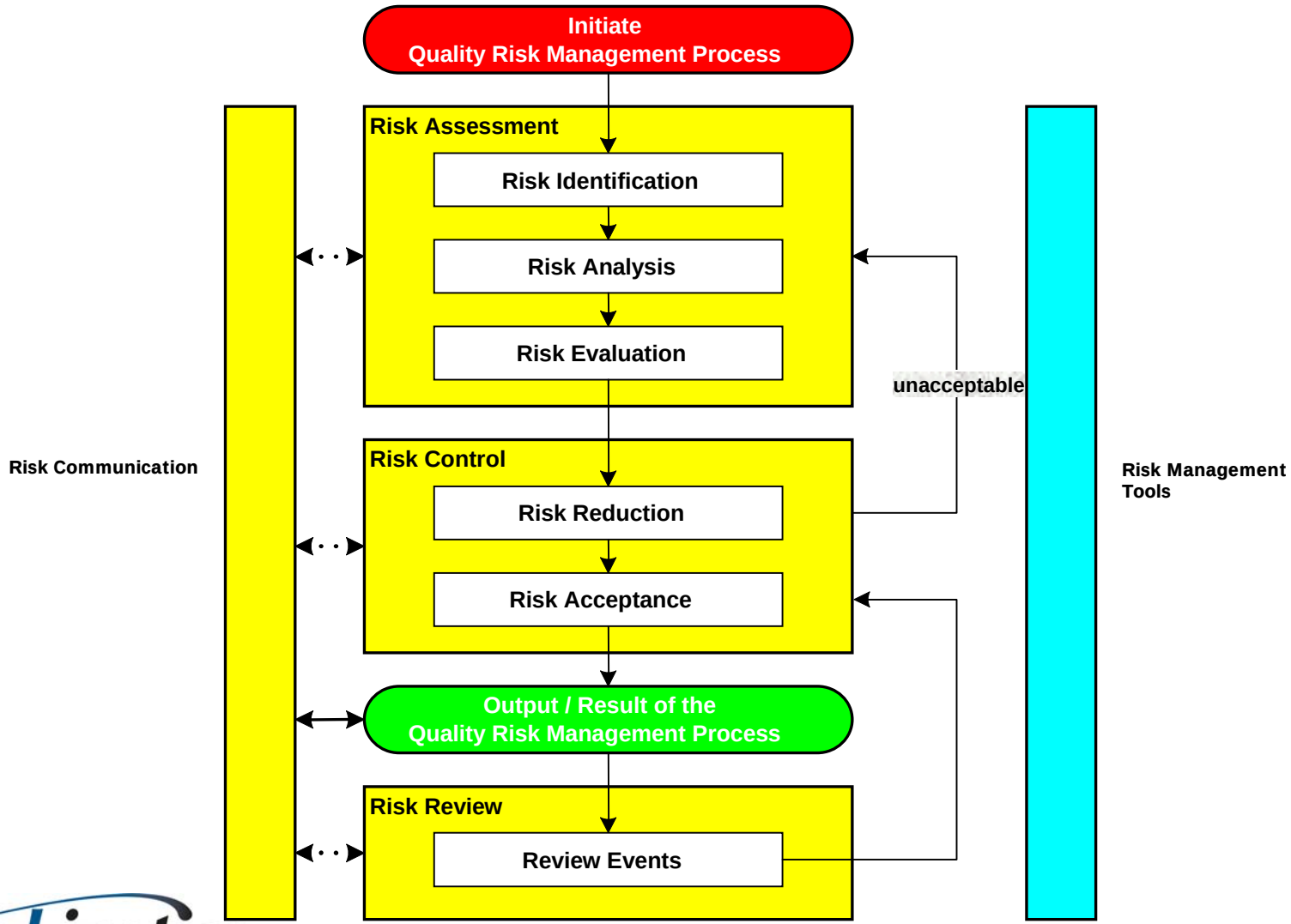
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk."

- Provides another level of risk management to an organisation so it is not new (Companies already use RM to look at financial, compliance, strategic and operational risks from Business perspective)

Linking back to Patient risk.



General RM Process in Q9



Pharma Industry response to RM

- Pharma industry has been slow to adopt formal RM processes when initiating new projects.
- If they do, the use is patchy i.e. Hazop for design but nothing for other aspects of the project.
- Other industries are using RM on a continuous basis i.e. Food (HACCP) and Medical Devices (ISO 14971).
- Usually not integrated with the quality management system.
- Used primarily as an engineering tool in projects.

Summary – Good RM allows companies to focus time, effort, personnel and money on the important aspects of a project (determined through risk categorisation) which provides quality assurance to patients.

What does Q9 give us?

- A common approach to Quality Risk Management for industry and Regulators.
- Common terminology.
- Principles for implementation.
- Risk Management Tools and Techniques.

What Q9 does not give us.

- The total and specific requirements for your Risk Management system.
- Too much Risk Management theory (Quantitative Techniques).
- A prescriptive list of tools or techniques that can be used by your organisation.

Summary of Q9

- Guideline for Japan, Europe and the US for pharmaceutical and Biopharmaceutical Quality Risk Management.
- All regulatory authorities see risk management as the “Tool of choice” when deciding and rationalising the impact of new projects and changes.
- Will become “Best Practice” over time.
- All regulatory authorities want industry to focus their efforts on the important aspects of their processes and facilities.
- Risk is determined by concensus so is seen as the ideal when deciding on a way forward, as the decisions are made by many subject matter experts and so is seen as more accurate.
- Companies can choose whether to use formal QRM, leading to regulators being more flexible in their audit approach.

Implementation of Q9

- One implementation of Q9 is the new ASTM E55.03 standard "Science and Risk Based **Approach to Qualification**".
- Standard has legal relevance.
- FDA sit and vote on the ASTM committee and support it's activities.
- FDA discuss ASTM activities at conferences so are seen to be promoting their work.
- ISPE have taken the ASTM standard and put a working group together to implement it's requirements into:
  - Commissioning & Qualification Baseline Guide
  - GAMP 5.0

Why change Current Situation?

- Commissioning and Qualification costs vary but for new facility/equipment projects can be as high as 25% of total installed cost (TIC).
- Because C&Q is at the end of the project lifecycle if it takes too long, it can cause delays in product approvals. Also, poor quality or lack of requirements lead to rework.
- Poor commissioning, or unnecessary duplication of activities between commissioning and qualification.
- C&Q efforts focused on documentation deliverables.
- Need for greater focus on process performance and impact on product quality.

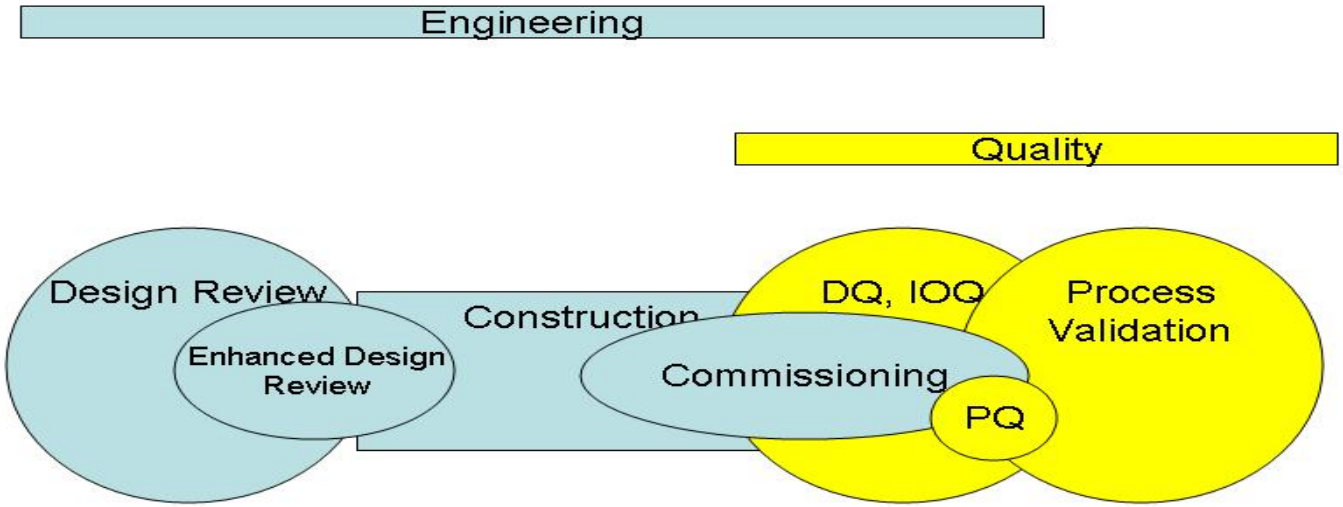
David Petko, ISPE Conference, June 2007

Why change Current Situation?

- Late involvement of QA leading to changes in requirements.
- Product and process failures encountered after apparently "successful" qualification.
- Lack of Operations input leading to design changes when the "Real" operational requirements of the equipment are "figured" out.

David Petko, ISPE Conference, June 2007

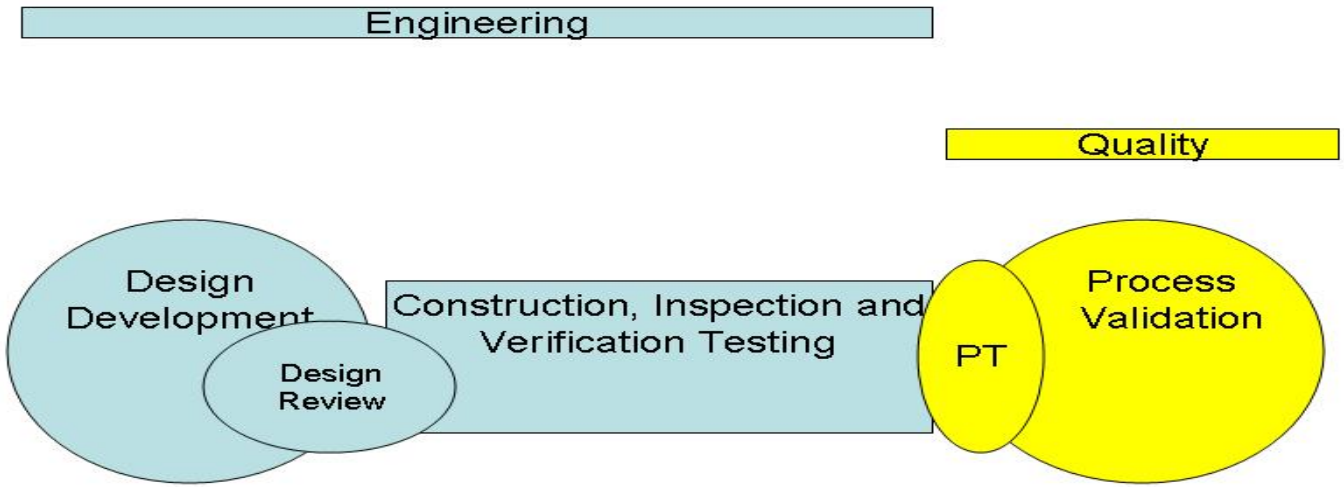
The EXISTING C&Q Approach



The EXISTING C&Q Approach

- From ISPE Baseline Guide on C&G:
  - Assessment of Critical and Non-Critical systems.
  - Required System and Component level impact assessments.
  - Proposes use of Design Qualification.
  - Required Commissioning with overlaps between Commissioning & Qualification.
  - Used structured IQ's, OQ's and PQ's with associated Acceptance Criteria.
  - Overlaps between Engineering & Quality ownership.
  - Large focus on the documentation required.
  - Not "Change" friendly.

The PROPOSED "Verification" Approach



Verification Approach

- Removes Commissioning & Qualification activities.
- Requires science based approach to determining requirements.
- Makes use of quality vendors and documentation to aid Verification. Not new to some companies.
- **Design Reviews** replace Design Qualification.
- Impact Assessments replaced with formal **Risk Assessment**.
- **Verification** is used for activities up to PT & PV.
- **Performance Testing** is the fundamental proof of that equipment/systems/automation are fit for purpose.
- IQ's, OQ's and PQ's replaced with Verification Testing using **Critical Control Parameters** to define Acceptance Criteria.

Other Major Changes in 55.03

- Critical Elements and associated Acceptance Requirements are defined through Risk Assessment.These are the basis for testing.
- Qualification protocols (IQ and OQ) to be replaced with Commissioning Documents.
- Quality Control of commissioning (IV/OV) is delegated to Technical Experts who lead the verification activities.
- Verification documents managed by Engineering incl deviations.
- Commissioning Report indicates verification complete and handover
- Clear boundaries between GEP and Quality ownership.
- Focus is on the product (from development), process (from Engineering) and patient safety.
- Project Change Management used throughout project to ensure critical elements and acceptance criteria changes are managed.
- Continuous Improvement built in after completion (RCA/CAPA/Periodic Review).

Misconceptions with ASTM 55.03

- Engineering are taking over the validation.
- Engineering don't have to involve Quality in any design review processes.
- The standard was written by Engineers for Engineers to allow facility design and construction without objective oversight.
- Quality have no input into project phases before qualification.
- Validation are heaviliy involved in verification.

Sample RM Process - FMEA

- Procedure for carrying out an FMEA.
  - Select a product or process to be analysed.
  - Select/arrange a multi disciplinary team for the FMEA.
  - Start by describing a function.
    - Describe possible failure modes.
    - Describe effect of failure.
    - Describe cause of failure.
    - Estimate the frequency of occurrence and severity.
    - Estimate detection possibilities.
    - Calculate the RPN
    - Follow up.

FMEA - Occurrence

PROBABILITY of Failure	Failure Probability	Ranking
Very High: Failure is almost inevitable	**>1 in 2**	**10**
	1 in 3	**9**
High: Repeated failures	**1 in 8**	**8**
	1 in 20	**7**
Moderate: Occasional failures	**1 in 80**	**6**
	1 in 400	**5**
	1 in 2,000	**4**
Low: Relatively few failures	**1 in 15,000**	**3**
	1 in 150,000	**2**
Remote: Failure is unlikely	**<1 in 1,500,000**	**1**

FMEA – Detection

Detection	Likelihood of DETECTION by Design Control	Ranking
Absolute Uncertainty	Design control cannot detect potential cause/mechanism and subsequent failure mode	10
Very Remote	Very remote chance the design control will detect potential cause/mechanism and subsequent failure mode	9
Remote	Remote chance the design control will detect potential cause/mechanism and subsequent failure mode	8
Very Low	Very low chance the design control will detect potential cause/mechanism and subsequent failure mode	7
Low	Low chance the design control will detect potential cause/mechanism and subsequent failure mode	6
Moderate	Moderate chance the design control will detect potential cause/mechanism and subsequent failure mode	5
Moderately High	Moderately High chance the design control will detect potential cause/mechanism and subsequent failure mode	4
High	High chance the design control will detect potential cause/mechanism and subsequent failure mode	3
Very High	Very high chance the design control will detect potential cause/mechanism and subsequent failure mode	2
Almost Certain	Design control will detect potential cause/mechanism and subsequent failure mode	1

FMEA – Severity

Hazardous without warning	Very high severity ranking when a potential failure mode effects safe system operation without warning	10
Hazardous with warning	Very high severity ranking when a potential failure mode affects safe system operation with warning	9
Very High	System inoperable with destructive failure without compromising safety	8
High	System inoperable with equipment damage	7
Moderate	System inoperable with minor damage	6
Low	System inoperable without damage	5
Very Low	System operable with significant degradation of performance	4
Minor	System operable with some degradation of performance	3
Very Minor	System operable with minimal interference	2
None	No effect	1

FMEA Resulting Worksheet

System	LTN2001 GPS SSU	**Potential Failure Mode and Effects Analysis (Design FMEA)**								**Revision**	B					
Subsystem	Receiver Card									**Prepared By**	Robert Crow					
Part Number	468230-100									**FMEA Date**	8/18/1992					
Design Lead	J. Davies									**Revision Date**						
												Action Results				
Item / Function	**Potential Failure Mode(s)**	**Potential Effect(s) of Failure**	**Sev**	**Potential Cause(s)/ Mechanism(s) of Failure**	**Prob**	**Current Design Controls**	**Det**	**RPN**	**Recommended Action(s)**	**Responsibility & Target Completion Date**	**Actions Taken**	**New Sev**	**New Occ**	**New Det**	**New RPN**
Circuit Block 4.1.1	Output loss from pre-amp	Receiver & output data loss; track loss; GPS shut-down	5	C1 short	1	PR-20 & HW-5	2	10	QA Proc 20-6	R. Jones, 11/30/92	Added to control plan	2	1	1	2
			5	C88 short	2		2	20	QA Proc 20-6	R. Jones, 11/30/92	Added to control plan	2	1	1	2
			5	L1 open/short	3		2	30	QA Proc 20-3	R. Jones, 11/30/92	Added to control plan	2	2	1	4
			5	U21 function	4		2	40	Test 147	R. Jones, 11/30/92	Added to control plan	2	3	1	6
								0							0
Circuit Block 4.1.2	Undetected & insignificant component failure mode	No noticeable system effect	1	C1open/chg val.	2	None	8	16	None						0
			1	C88open/chg val	2		8	16	None						0
								0							0
Circuit Block 4.2.1	Loss of signal from 2nd RF amplifier & 1st down converter	Loss of position, velocity & time output data; track loss; GPS shut-down	4	C2 short	1	PR-20 & HW-5	2	8	QA Proc 20-6	B. Howell 10/15/92	Added to control plan				0
			4	C3 short	1	PR-20 & HW-5	2	8	QA Proc 20-6	B. Howell 10/15/92	Added to control plan	2	1	1	2
			4	C4 open/short	2	PR-20 & HW-5	2	16	QA Proc 20-6	B. Howell 10/15/92	Added to control plan	2	1	1	2
			4	C5 short	2	PR-20 & HW-5	2	16	QA Proc 20-6	B. Howell 10/15/92	Added to control plan	2	1	1	2
			4	C66 open/short	2	PR-20 & HW-5	2	16	QA Proc 20-6	B. Howell 10/15/92	Added to control plan	2	1	1	2
			4	C99 short	3	PR-20 & HW-5	2	24	QA Proc 20-6	B. Howell 10/15/92	Added to control plan	2	2	1	4
			4	FL1 short/open	5	None	2	40	100% Insp.	B. Howell 10/15/92	Added to control plan	2	2	2	8
			4	FL2 short/open	5	None	2	40	100% Insp.	B. Howell 10/15/92	Added to control plan	2	2	2	8
			4	R2open/chg val	2		2	16	None						0
			4	R18 open/chg val	2		2	16	None						0

Summary

- FDA wants companies to move to science

  and risk based system of compliance.
- ICH has taken FDA requirments on board to develop Q7, Q8 and Q9. Q9 relates to Quality Risk Management.
- Q9 provides tools for use but it is dependant on your application and expertise.
- ASTM have developed a standard for risk based qualification which has contentious issues built in.
- ASTM allows Engineering to focus on engineering and Quality to focus on process and product quality.
- ISPE are updating their baseline guides and GAMP to incorporate risk and verification.
- Compliance with risk based approaches is not mandatory at this time

ANY QUESTIONS?

For further Information on this presentation, contact:

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