GMPs for the 21st Century

Steven Ostrove, Ph.D.
Ostrove Associates, Inc
www.ostroveassociates.com

Agenda

- Brief History of the FDA
- FDA Goals for 21 Century
- FDAs Current Approach to GMPs
  - Part 11
  - Modernization Act
  - PAT
  - QSIT
- Summary

The FDA Yesterday

History of the FDA and GMPs

- 1820 – US Pharmacopoeia formed
- 1848 – Drug Importation Act
- 1902 – Biologics Control Act
- 1906 – **FD&C Act**
- 1914 – Harrison Narcotic Act
- 1937 – Sulfanilamide Disaster
- 1938 – **FD&C Revised**

History Continued

- 1941 – Insulin Amendment
- 1944 – Public Health Service Act
- 1945 – Penicillin Amendment
- 1953 – **Factory Inspections**
- 1958 – Food Additives
- 1960 – Color Additives

History Continued

- 1962 – Thalidomide
  - Kefauver-Harris Amendment
- 1968 – Drug Efficacy Study **Implementation**
- 1970 – Patient Package Insert
- 1978 – Revised CGMP Regulations
- 1982 – **Tamper Resistant Packaging**

What Happened Next

- May 3, 1996
  - Revised GMPs published in Federal Register
- 21 CFR Part 11
  - August 20, 1997
- FDA Modernization Act – 1997
  - QSIT for CDRH Introduced
- 2000+ PAT, QSIT, and RISK Management

FDA Goals for the 21st Century

FDA Guiding Principles

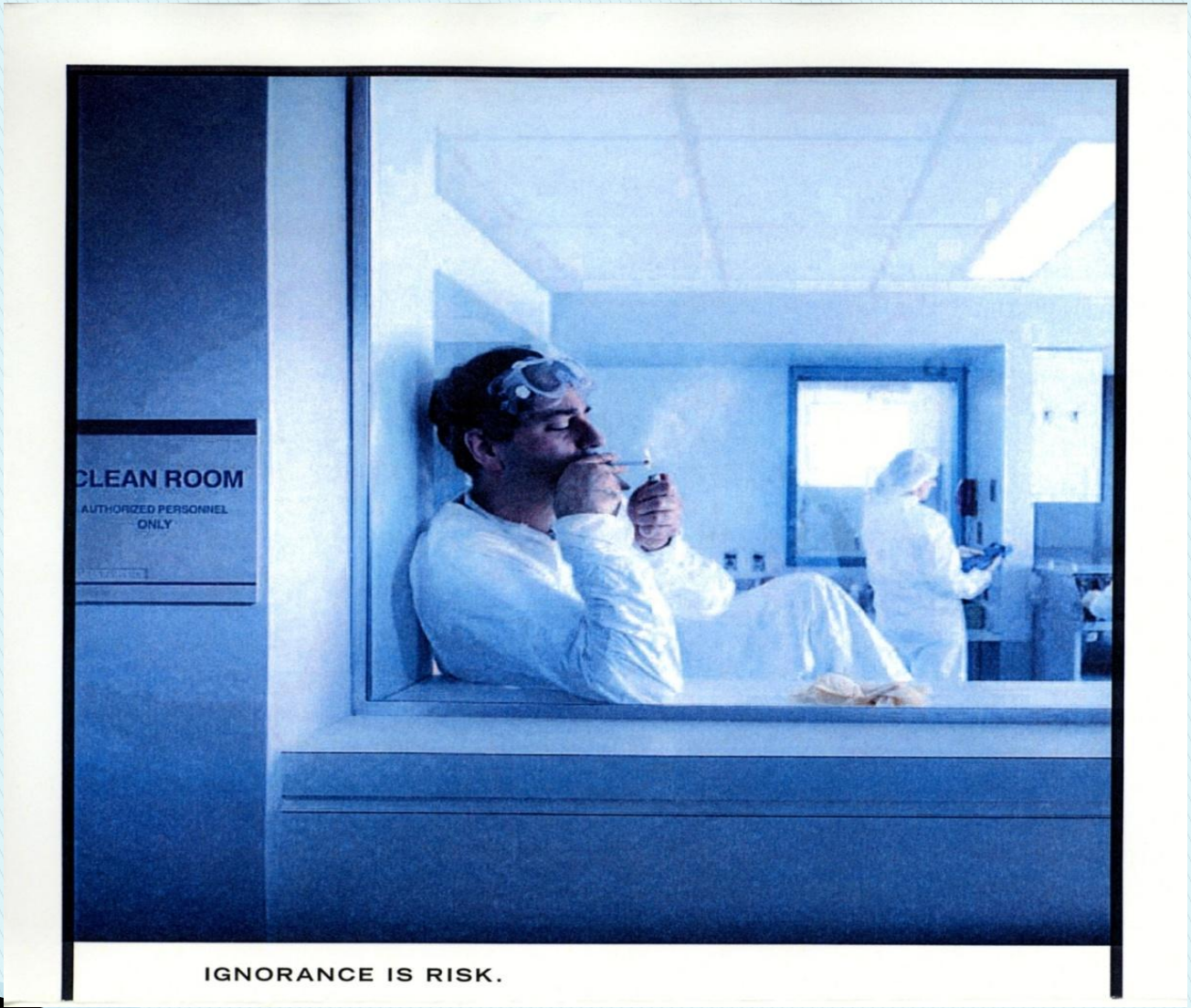
- Risk-Based Orientation
- Science-Based policies and standards
- Integrated quality systems orientation
- International Cooperation
- Strong Public Health Protection

Vision for the Next Century

- Critical Path Initiative
  - Transform medical product development
  - Keep pace with expected medical advances

RISK

Risk



Types of Risk

- Equipment
  - Machine Failure
  - Cleaning
- Ingredients
  - API
  - Excipients
- People
  - Operator skills
  - Maintenance
  - Cleaning
- Understanding
  - Training

RISK

- **IS**
  - How **severe** is it?
    - Production – Environment – Personnel
  - How **often** CAN it occur?
  - How will it be **detected**?
  - How will the **PATIENT** be affected?

- **IS NOT**
  - The possibility of getting caught

FDA APPROACH TO RISK

- PAT – Process Analytical Technology
- ICH Q9 – Risk Management

- QSIT – Quality Systems Inspections Technique

- **The Quality System Approach**

Science –Based

- Aseptic Process Guideline
- PAT Guidance
- Comparability Protocols Protein Drug Products …

Improved Integration

- Quality Management System (QSIT)
- ICH Harmonization
- Process Validation Guideline

PAT

PAT

PAT = Process Analytical Technology

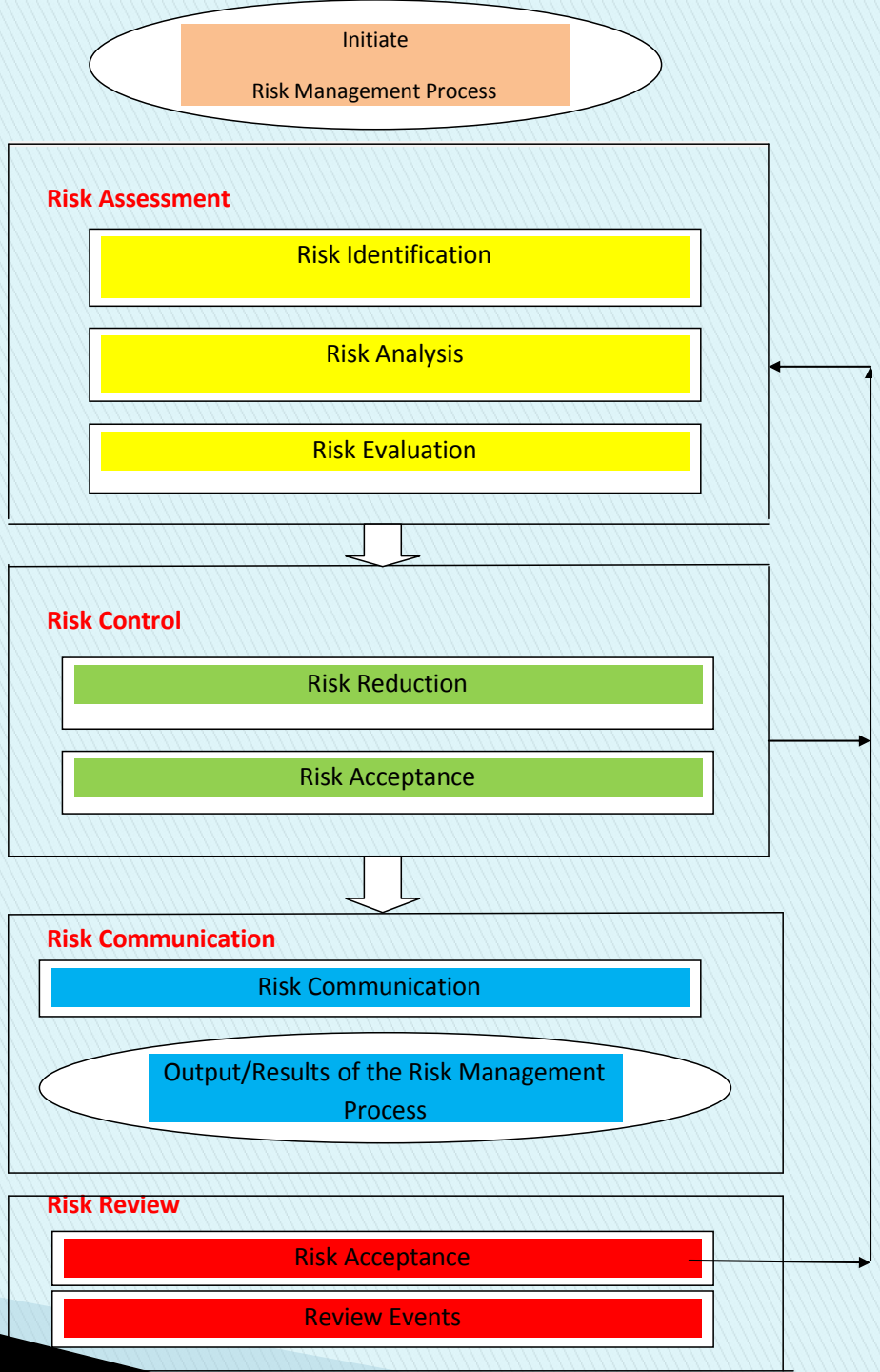
- Used in the Chemical industry for years
- Intended to make the process more accurate
- Need to FULLY understand the process before implementing

- Presents an automated control of a process

ICH Q9

ICH Q 9

- Prepared by the International Conference on Harmonization (ICH)
- Accepted by FDA


Initiate
Risk Management Process
Risk Assessment
Risk Identification
Risk Analysis
Risk Evaluation
Risk Control
Risk Reduction
Risk Acceptance
Risk Communication
Risk Communication
Output/Results of the Risk Management Process
Risk Review
Risk Acceptance
Review Events

QSIT

Quality System Investigation Technology (QSIT)

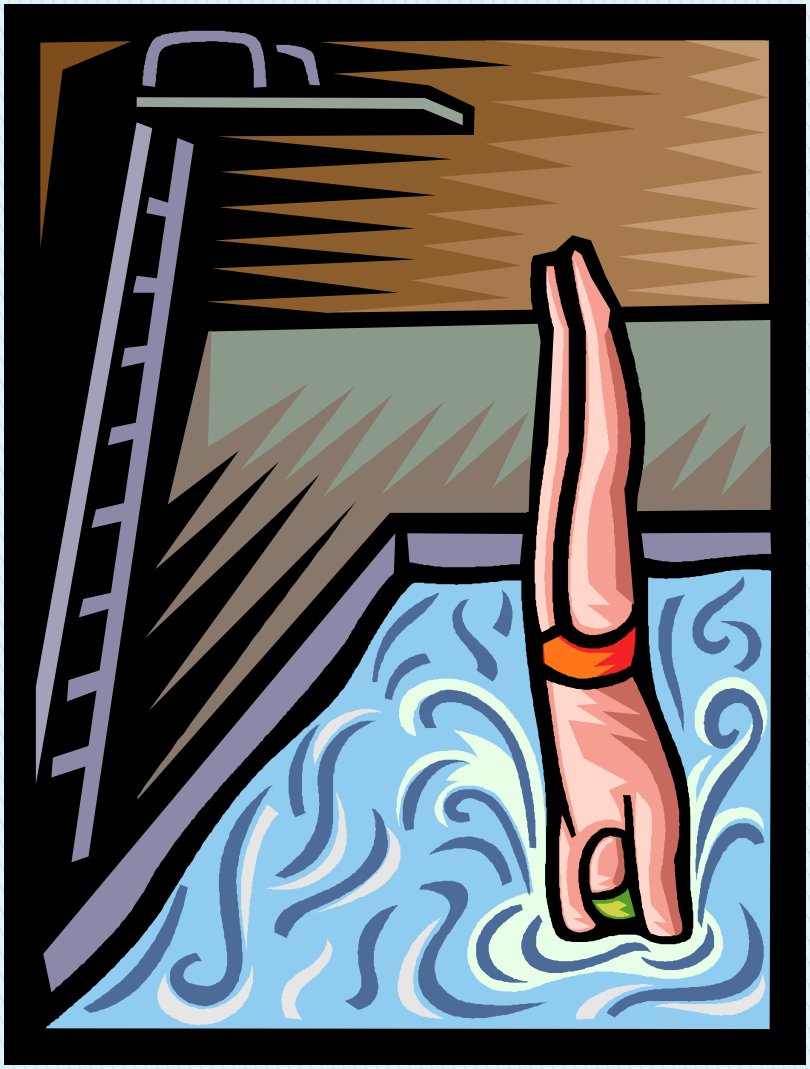
- Started in the Device Industry
- Holds Management responsible
- Moved to Pharmaceuticals in 2006

INSPECTIONS – Old Way

- Bottom Up

INSPECTIONS – New Way

- QSIT
  - Top Down



Order of Systems

- Management
- Design
- CAPA
- Production & Process Controls
- Conclude with Management

Quality System's Sub-systems

The Inspection Approach

- Top-down (versus Bottom-up)
- Sampling records (use tables)
- Pre-inspection activities (ask for and review documents)
- Start and end with Management

Definition of Quality in the Context of Mfg & Control of Products

- Fitness for intended use
  - Safe
  - Effective
  - Available
- Consistency
  - Process
  - Product
- Increased process and product knowledge leads to increased assurance of quality
- Must include customer (patient) expectations

Benefits of a Risk Based System

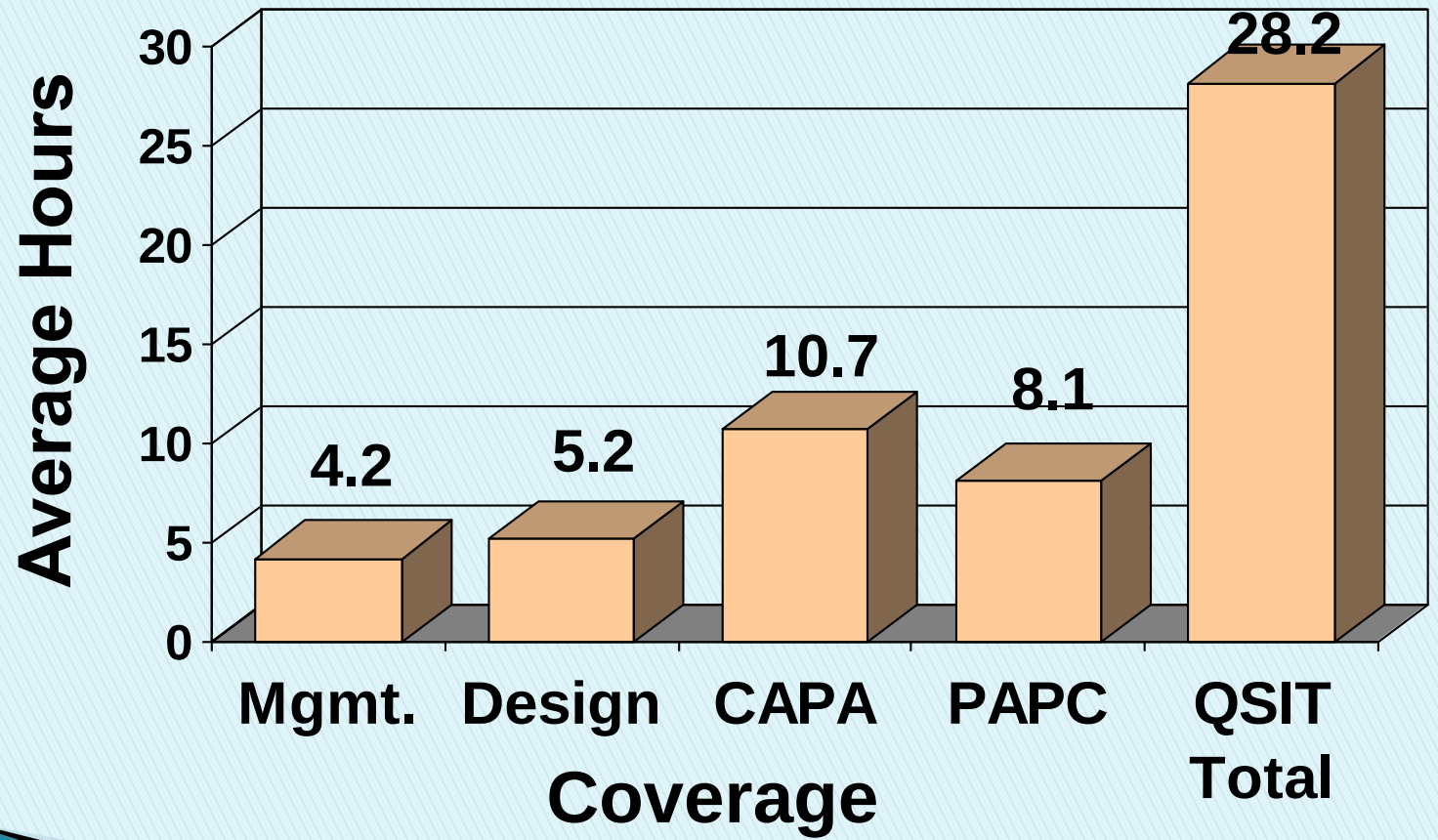
- Patients
  - Increased availability
  - Faster approval of new products
  - Continue to receive quality products

- FDA
  - More product and process knowledge shared by industry
  - More efficient resource allocation for review and inspection
  - Increased trust and understanding of industry decision making

Benefits of a Risk Based System

- Industry
  - Fewer, more efficient, science based inspections resulting in increased consistency
  - Faster, more consistent reviews
  - Potential for reduced regulatory burden
  - Less FDA oversight
  - Focuses resources on critical issues
  - Flexibility to focus on what should be done, not what can be done

QSIT Findings
In-Plant Time



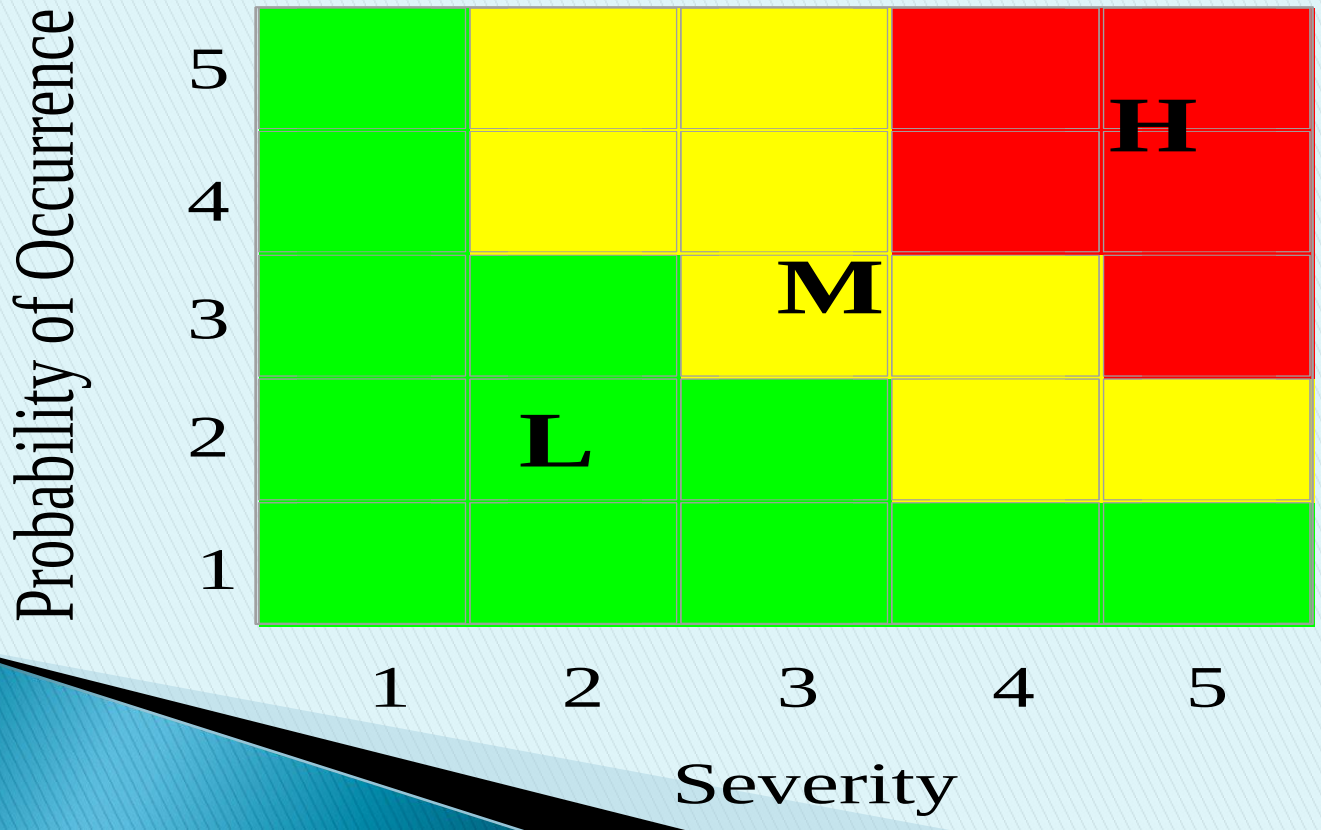
What Does this Really Mean

How to Conduct Analysis

1. Identify potential failure i.e. ways in which the system might fail.
2. Identify potential causes.
3. Rate severity, occurrence, and detectability.
5. Multiply the numbers together to determine the risk of each failure mode.
6. Identify ways to reduce or eliminate risk.

Project Risk Planning

Identify areas of potential risk based on probability of occurrence and severity.



Qualification of Equipment

- Low probability of failure, severity if it fails
  - Minimal Qualification
  - Preventive Maintenance needs to be maintained (PMs)
- Medium probability of failure, medium severity
  - More extensive Qualification
  - More monitoring between PMs
- High probability of failure, high severity
  - Extensive Qualification
  - Continuous monitoring

Process Validaiton

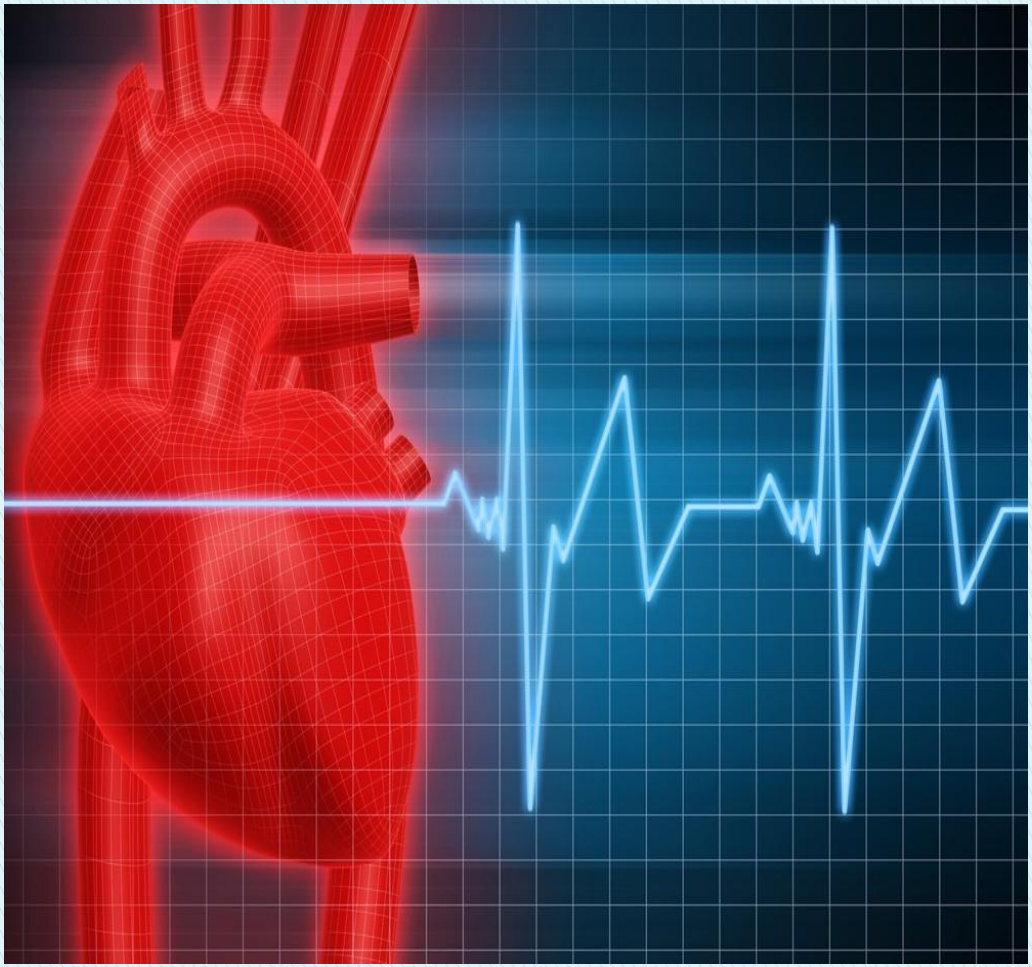
- Low risk to patient
  - Minimal testing – NOT ELIMINATED
- Medium risk to patient
  - More complete testing
- High risk to patient
  - Extensive testing

Common Risk Management Tools

- FTA (Fault Tree Analysis)
- FMEA (Failure Mode Effect Analysis)
- FMECA (Failure Mode, Effect and Criticality Analysis)
- HACCP (Hazard Analysis Critical Control Points)
- Risk Ranking and Filtering

Role of Science

USE IT



Role of Management

- Management is responsible for Implementing Quality System
- Start & Finish with Management
- All product, process, design & CAPA problems can be tied to management

SUMMARY

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THANK YOU

QUESTIONS?