QRM and it's Application in GMP for Sterile Products

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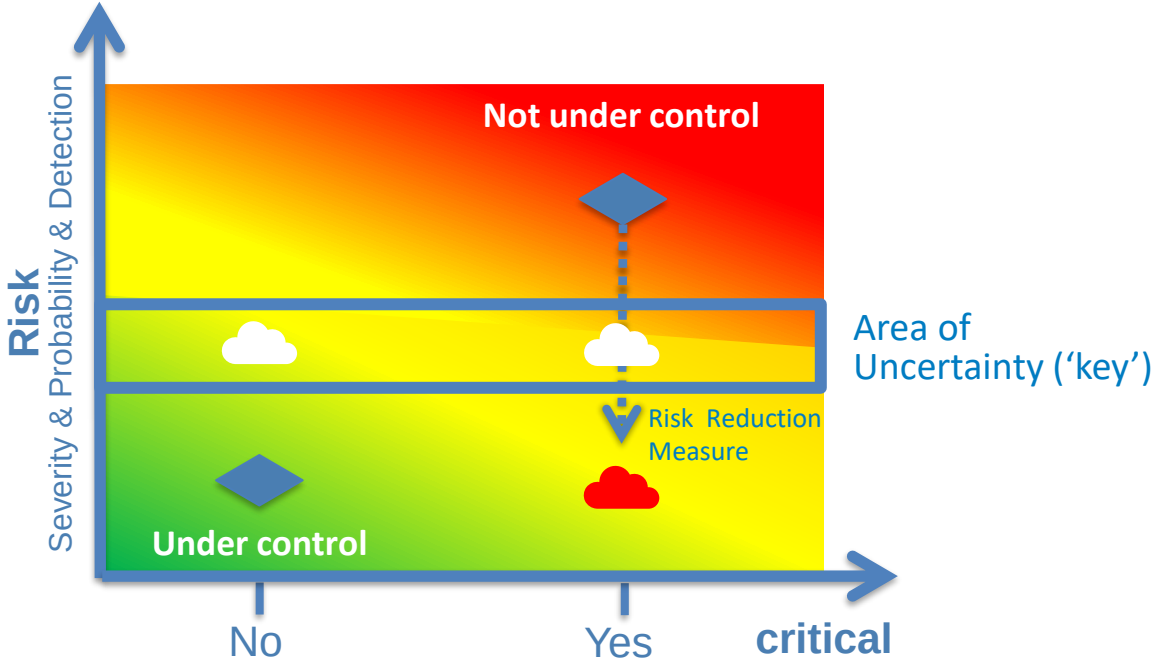
Managing Risk Means Awareness of Uncertainties

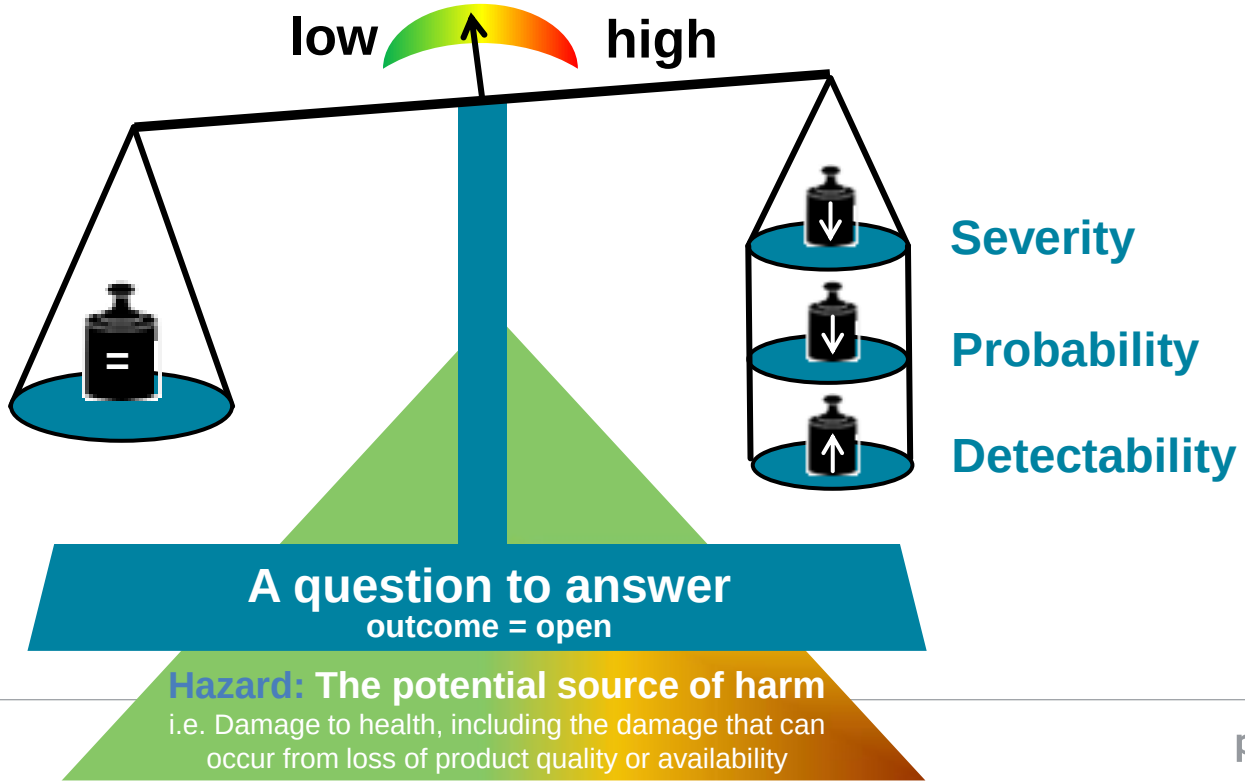
Critical

A high risk of **significant impact** to quality, safety or efficacy which requires a **degree of control**

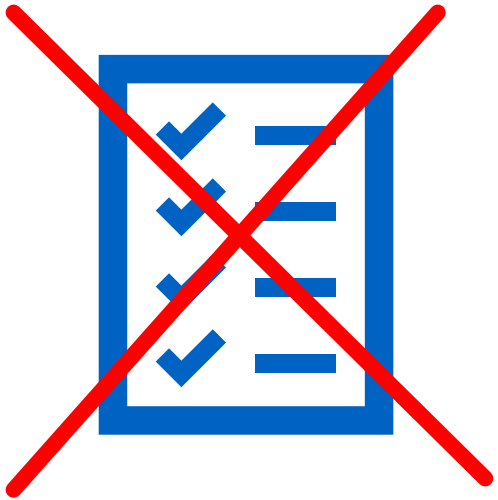


Risk is Not the Same as Hazard

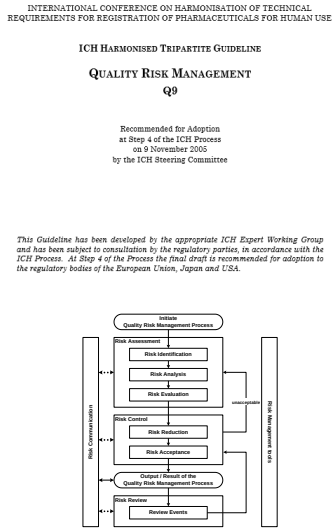
Risk



A QRM Process is Linking to Behavior



Yes
No



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

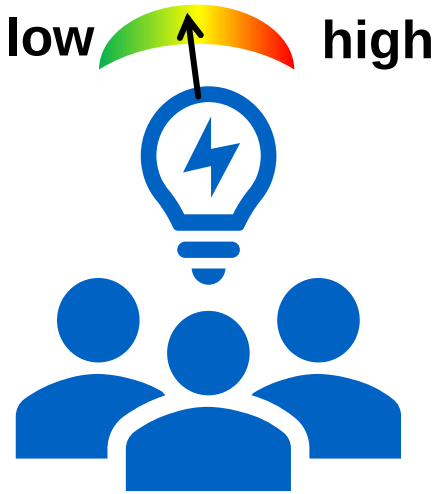
ICH HARMONISED TRIPARTITE GUIDELINE

QUALITY RISK MANAGEMENT
Q9

Recommended for Adoption
at Step 4 of the ICH Process
on 9 November 2005
by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

The way in which something operates



Collaborate towards an informed decision

QRM Struggles with Implementation

low high

Decision Making

Enabler

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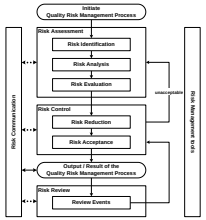


The way in which something operates

Formality

Subjectivity

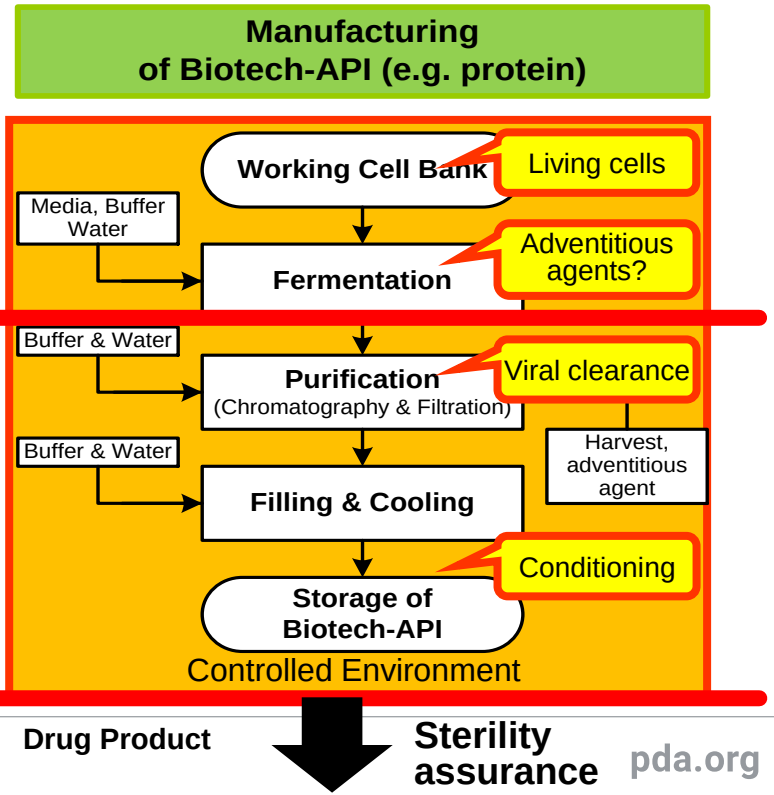
Confirm a Hypotheses

Different Hazards Drive Different Risk Control Measures

- **The Hazard**
  Potential growing of adventitious agent
  which may can be neither detected nor removed
- **The Problem**
  Optimal growth conditions
  Working with cell banks, media and buffer
- **The Control**
  Requirements for a low bioburden

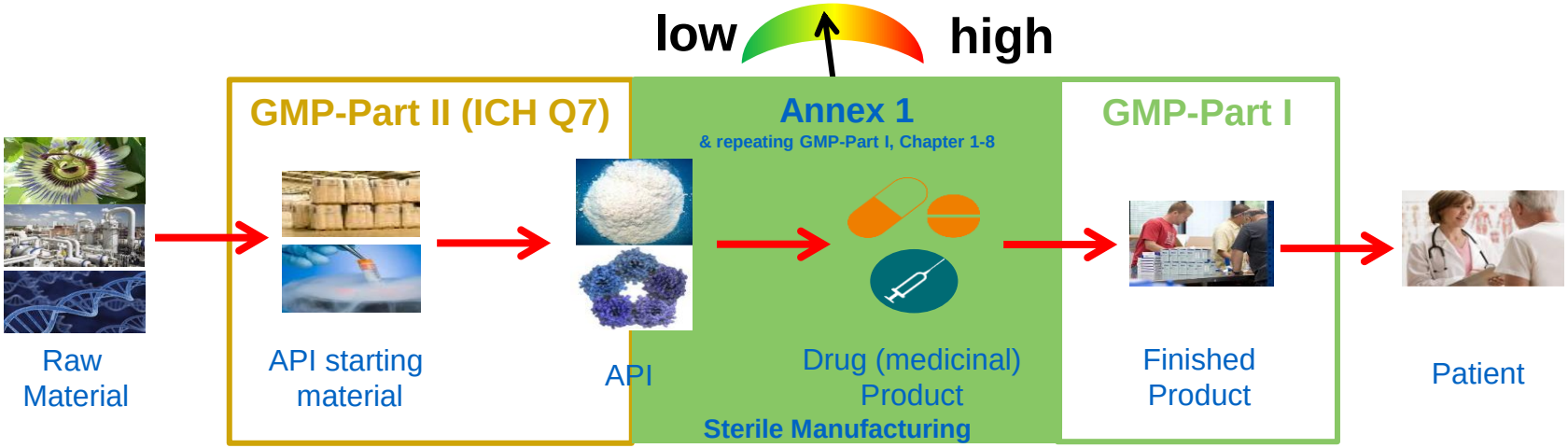
Protect

1. Manufacturing Process (ICH Q7)
2. Employees (EHS)
3. Patients (Annex I)



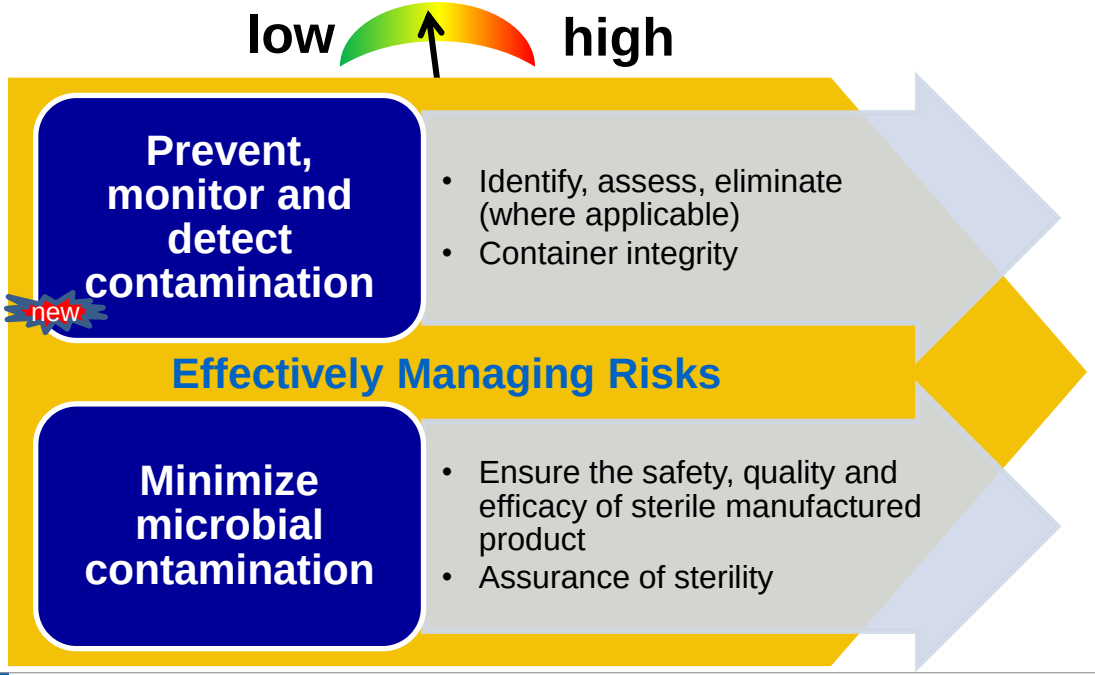
low high

GMP According to Annex 1 Applies for Manufacture of Drug (medicinal) Products



In general, changes in GMP for sterile products (annex 1) encourage the use of risk based approaches

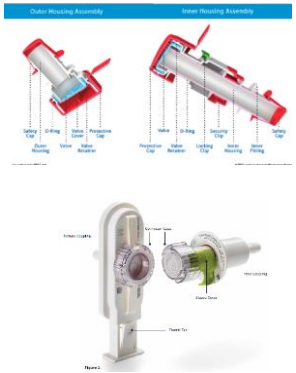
Annex 1 Asks to Prevent Contamination by Establishing Additional Controls and Measures to Ensure Quality



Steps to success

1. Sufficient knowledge and expertise
2. Root Cause Analysis and CAPA
3. Quality release

Practical Examples of an Integrated Risk-based Control of Microbial Contamination From Raw Material Until the Final Product Release



Raw Materials

- Supplier Qualification Program
- Raw Material Controls

Facility

- Pest Control
- Facility Cleaning and sanitization
- Gowning
- Clean Utilities
- Material Flow and Cleaning

Process Controls

- Media Hold Validation
- Engineering controls tested per lot
- Environmental Monitoring Program
- Media Fill and Airflow Visualization Study

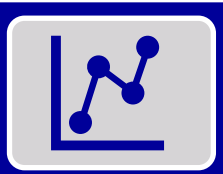
DP Testing

- Endotoxin
- Sterility
- Annual Stability Program
- Campaign post process Environmental Monitoring

The Contamination Control Strategy is based on Minimizing the Risk of Microbiological, Particulate and Pyrogen Contamination

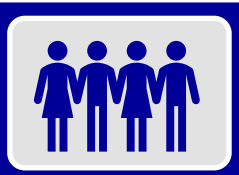
Facility, Equipment and Process design

- Must be optimized qualified and validated



Processes and Monitoring Systems

- Designed, commissioned, qualified & monitored, e.g. qualify particle counters including sampling tubing



Personnel: Protect the sterile product

- Must have appropriate skills, training and attitudes (hygiene)

GMP

&

new

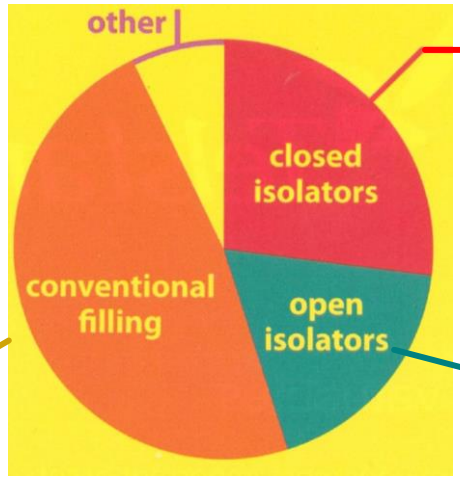
Regulatory filing
Manufacturing Process and IPC testing is approved

Dossier

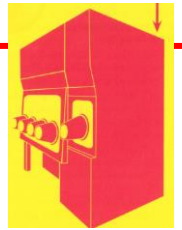
Barrier Technology shall be used in the Design and Qualification of Premises, Equipment and Utilities (water, air and vacuum)

- **Different Equipment Exists and Can be Operated in Compliance**

conventional line

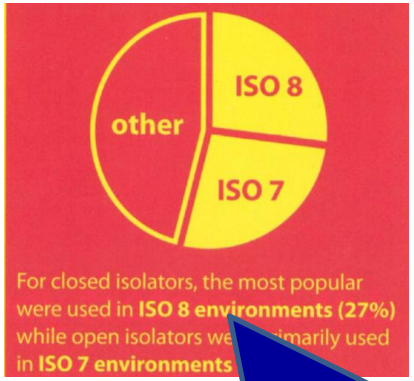


PDA letter, June 2019, p.34; based on the PDA research Survey 2017.



Glove-Box

RABS-Unit



Clean room classifications (ISO 14644) and their qualification

- Measure particles equal to or greater than 0.5 µm
- Maintained in recommended limits for the monitoring of non-living particles

Annex 1 May Prevent Innovation as it Lists ‘How to Do’ Requirements for Production and Specific Technologies

Approaches to sterilization

- Aseptic and terminal sterilization processes
- For Products, equipment and packaging components

new

Different technologies

- Lyophilization
- Form-Fill-Seal (FFS), Blow Fill Seal (BFS), Single Use Systems (SUS)

new

Viable and non-viable environmental and process monitoring

- Setting of alert limits and reviewing trend data
- Aseptic Process Simulation (APS) [= media fill]

new

Quality Control

- Testing is only the last step in a series of control measures
- Representative samples Bioburden assay on each batch
- Environmental monitoring data part of batch record
- Rapid microbial methods

GMP for Sterile Products, Annex 1 draft v2, EMA, Ares(2020)1024161 - 18/02/2020, Chapter 8, 9, 10

Protecting Patients can Follow a Holistic View Taking into Account Elements Described in Different Documents

Guidance documents are intended to be read in its entirety regardless of the nature of the activities being conducted to fully understand the linkages between certain sections and successfully implement appropriate GMPs at all stages of the supply chain.

According to the ICH Q7 Q&A

Aknowledgement: Greg Claycamp, FDA; Hal Basement, Valsource, Myrta Atiles and Kris Evens, Enid Marin-Vallejo Amgen & Gabriele Gori, GSK – *thanks for the discussions*