New EU GMP Annex 1 and its Impact on Pharmaceutical Manufacturers

"If you fail to prepare, you prepare to fail"

8 Jun 2023

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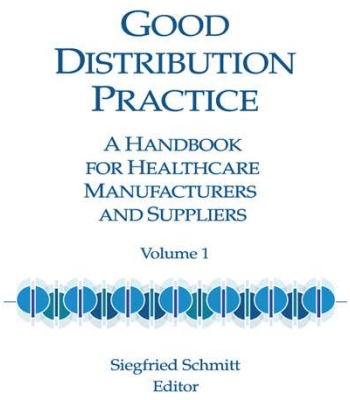
Disclaimer

The material and perspectives offered in this presentation are solely those of the presenter, and do not reflect the views or opinions of Management Forum.

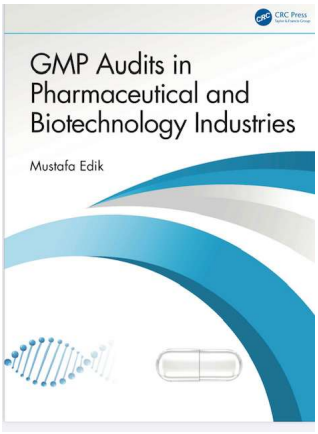
About Me

- Trainer, Consultant, Auditor
- More than 25 years of experience in the Pharmaceutical, Medical Device, and Cosmetics Industry
- IRCA Certificated GMP Lead Auditor
- LSS Black Belt
- Chemist + Biopharmaceutical Science & Engineering
- Worked for Bayer Türkiye as Laboratory Supervisor, Deputy QA Manager, Global Lead Auditor
- Worked for Turkish Atomic Energy Agency as Principal GMP Auditor and Consultant
- Trained more than 8000 delegates in various topics such as QA, QC, Validation, QRM, Human Error, Auditing
- Performed GXP Audits for more than 4000 hours
- Led several projects on behalf of approximately 150 Local and Global Companies

Publications



Author of Chapter 6
Published in 2019



Author
To be published in 2023

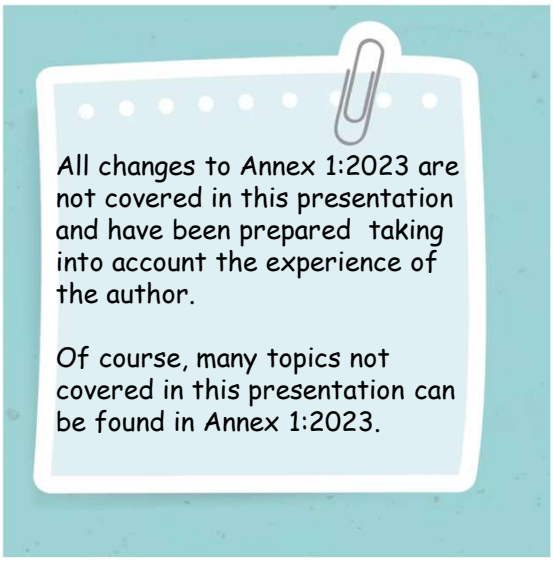
Agenda

- Brief history of Annex 1
- Why was revision needed to Annex 1?
- What are the expectations?
- Which path should you follow for preparing the Contamination Control Strategy main document?
- How should you adapt to the principles of Quality Risk Management?
- Q&A - Discussion

Have you finished aligning your site with the new Annex 1?

1. Yes
2. No
3. Unsure

A reminder to participants



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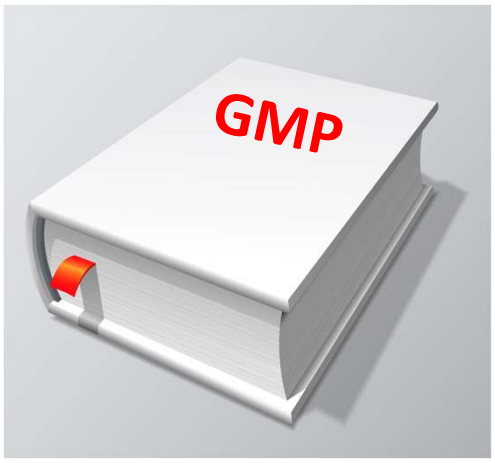
Brief history of GMPs & Annex 1



1960s-1970s → **PRESENT**

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Why was revision needed to Annex 1?

Communication with other GMP Annexes?

- ❑*Annex 2*
- ❑*Annex 11*
- ❑*Annex 12*
- ❑*Annex 15*
- ❑*Annex 17*
- ❑*…*

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Why was revision needed to Annex 1?

Communication with other GMP related documents and Standards

- ❑*FDA*
- ❑*ICH Q8*
- ❑*ISO 14644*
- ❑*ISO 14698 (1,2)*
- ❑*ISO 13408*
- ❑*ISO 17665*
- ❑*BS EN 17141???*
- ❑*PDA*
- ❑*ISPE*

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Why was revision needed to Annex 1?

What Else The Author Expects?

CCS or Similar and Audits/Inspections

CCS or Similar

CCS and Sterile Drug Products Produced by Aseptic Processing Revision

Aide Memoire on CCS and Changes to Annex 1

Do you remember this document?

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Why was revision needed to Annex 1?

What We Have So Far?

N E X T

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Why was revision needed to Annex 1?

16 Pages → 59 Pages

- EU Annex 1 was last revised in 2008. The new version was published August 22, 2022.
- Deadline for coming into operation is August 22, 2023.

Main changes;

- A Quality Risk Management
- Pharmaceutical Quality Systems (PQS)
- Contamination Control Strategy (CCS)

- All decisions and rationales must be scientifically justified.
- LOTS of increased expectations around facilities and equipment

Why was revision needed to Annex 1?

Innovative technologies

- The use of RABS, Isolators, Robotic systems
- Single-Use systems
- Rapid/alternative methods

Why was revision needed to Annex 1?

❑ **Barrier Technologies, e.g. RABS, Isolators, robotic systems**

– The use of different technologies should be based on process and product risks

– The use of robotic systems to reduce/eliminate human interventions
  - Robotic environmental monitoring
  - Robotic filling operations
  - Comply with regulatory requirements?

❑ **Single-Use Systems**

– Supplier/material qualification

– Complexity of the assembly and manual operations

– Leachables and Extractables

– Leaks

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Why was revision needed to Annex 1?

Rapid/Alternative Methods

• Rapid detection of potential contamination in the product and the environment

– Rapid microbial methods

– Continuous monitoring systems

• Full validation of non-compendial methods

– Demonstrate their equivalency or superiority to the compendial methods for the product and process.

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Why was revision needed to Annex 1?

Regulatory Issues

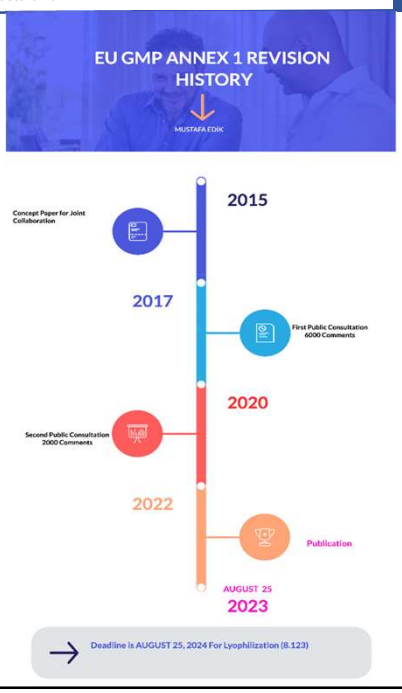
Inadequate root cause analysis

Ineffective use or application of CAPAs

Poor implementation of ICH Q9

International Collaboration

- ANSM/France
- TGA/Australia
- Health Canada/Canada
- TFDA/Chinese Taipei
- BMG & ZLG/Germany
- PMDA/Japan
- CPI/Poland
- HSA/Singapore
- Swissmedic/Switzerland
- MHRA/U.K.
- US FDA/U.S.A
- EMA
- WHO



International Collaboration - Stakeholders

- A3P Association
- AESGP (Association of the European Self-Medication Industry)
- Animal Health Europe
- APIC (Active Pharmaceutical Ingredient Committee)
- EEPC (European Association of Euro-Pharmaceutical Companies)
- ECA (European Compliance Academy)
- EFPIA (European Federation of Pharmaceutical Industries and Associations)
- EGGVP (European Group for Generic Veterinary Products)
- EIPG (European Industrial Pharmacists Group)
- GIRP (European Healthcare Distribution Association)
- ISPE (International Society for Pharmaceutical Engineering)
- Medicines for Europe
- PDA (Parenteral Drug Association)
- PHSS (Pharmaceutical & Healthcare Sciences Society)
- EQPA (European Qualified Person Association)
- Vaccines Europe

It is the first document published by EMA/WHO/PIC/S

Annex 1 - 2008 Content

- Principle
- General
- Clean room and clean air device classification
- Clean room and clean air device monitoring
- Isolator technology
- Blow/fill/seal technology
- Terminally sterilised products
- Aseptic preparation
- Personnel
- Premises
- Equipment
- Sanitation
- Processing
- Sterilisation
- Sterilisation by heat
- Moist heat
- Dry heat
- Sterilisation by radiation
- Sterilisation with ethylene oxide
- Filtration of medicinal products which cannot be sterilised in their final container
- Finishing of sterile products
- Quality control

Annex 1 - 2022 Content

1. Scope
2. Principle
3. Pharmaceutical Quality System (PQS)
4. Premises
5. Equipment
6. Utilities
7. Personnel
8. Production and specific technology
9. Environmental and process monitoring
10. Quality Control
11. Glossary

What is the most MENTIONED word in the new Annex 1?

A. Data
B. Risk
C. Contamination
D. Air

Let's have a look at some "KEY" words

Do you think that RA expectations have increased?

Air is the champion:>180 times

	Annex 1 2008	Annex 1 2022	
Risk/s	20 times	124 times	ICH Q9
Qualification/s, Validation	18 time	111 times	EU GMP Annex 11, 15
Appropriate ????	24 times	123 times	EU GMP Annex ???
Environmental	2 times	43 times	ISO 14644, ISO 14698, PDA TR:13
Monitoring	26 times	127 times	
Pyrogen/Endotoxin	4 times	51 times	Pharmacopoeia, PDA TR:13
Contamination	33 times	137 times	
Data	1 time	31 times	PHSS, ECA, PDA CCS
Data Integrity	NONE	NONE	Big Data, IoT, Digital twin,Blockchain,ML ChatGPT,AI, Pharma 4.0/5.0

Let's have a look at some "KEY" words

Annex-2008: None

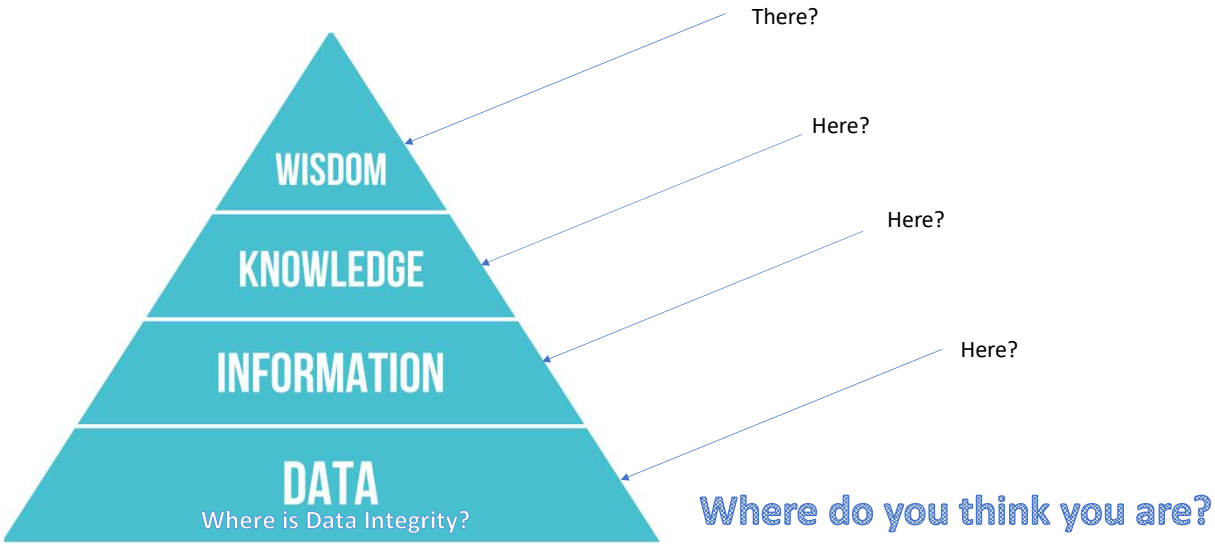
Annex-2022: 16 times

Surprizing Word?

KNOWLEDGE

How do you ensure that your staff has the **knowledge** necessary to perform his/her duty on a daily basis?

What does the Pyramid Tell Us?



What does the FDA Think about the Annex 1:2022?

- FDA's existing guidance for sterile drug manufacturing is largely aligned with Annex 1
- FDA has no plans **(???)** to enforce EU's GMPs Annex 1 in the US
  - Has their own national laws and guidances
  - Are not obligated to comply with Annex 1
- For similar reasons, FDA will not be enforcing PUPSIT
  - PUPSIT continues to be a challenge topic
  - FDA's guidance provides risk-based approaches to filter integrity testing

Let us have a look at the main changes

Annex 1 is a dense document to read and interpret; and some changes will require expert interpretation.

Let us have a look at the main changes

The objective of the Annex 1:2022 is still to define the requirements to

«minimize the risk of microbiological, particulate and pyrogen contamination in sterile products»

Be Careful!

Cambridge Dictionary
Make your words meaningful

Should ***modal verb*** **(ADVISE)**

Shall ***modal verb*** **(CERTAINLY WILL)**

I must confess that there is much confusion about the intent in the word «Should» in Annex 1:2022

Sorry to say that but Annex 1:2022 fails to make this classic differentiation.

We must therefore decide ourselves is a clause is really a «Shall» or «Should» clause.

2008: Isokinetic sample heads shall be used in unidirectional airflow systems.

2022:Isokinetic sampling heads should be used in unidirectional airflow systems.

Introduction of the Quality Risk Management (QRM) and Pharmaceutical Quality System (PQS) principles

The new Annex has moved from an almost residual mention of the concept of risk to the application of a more emphatic and reinforced Quality Risk Management (QRM) approach in all activities. QRM has become an essential methodology to use at the level of procedures, equipment, facilities, services, personnel, and processes. The incorporation of the two concepts was necessary to align the guideline with other current guidelines, such as ICHQ9 and ICHQ10.

The implementation of the Contamination Control Strategy (CCS)

The new Annex places a stronger emphasis on thorough oversight and examination of sterile product areas through a Contamination Control Strategy (CCS).

CCS is presented as a mandatory document, which should define all critical control points, measures, and assessment of effectiveness to control all risks associated with product contamination.

The Annex not only considers the current state of control but also underlines the need for innovative technology or techniques to fill any gaps.

Premises- Cleanrooms, areas, and barrier technologies

A strong emphasis on using new barrier technologies to prevent contamination from materials or personnel shredding in Grade A areas.

Now, Grade A is considered a critical zone for high-risk operations, whereas Grades B, C, and D are considered cleanrooms

Old version of Annex 1, Grade A was met by using a laminar airflow. Now, laminar airflow has been replaced by unidirectional airflow.

The access of personnel into the Grade A area should also be limited through the design of facilities, equipment, processes, and procedures.

Air pressure differentials must now be continuously monitored; and there must be an alarm system in case of out-of-limit values. In contrast, the legacy version only required this to be recorded periodically

Premises- Airlocks

The new Annex recommends separating personnel airlocks for entry and exit from those used for the movement of materials between different areas or cleanrooms.

The Annex also recommends having an interlock mechanism in place for Grade A and B areas, although it would seem logical to apply this principle to all cleanroom grades.

The entry and exit doors of airlocks leading to Grade A and B areas should not be opened simultaneously. This can be achieved by using an interlocking system.

However, in the case of airlocks leading to Grade C and D areas, a visual and/or audible warning system is sufficient.

If the CCS indicates a high risk of cross-contamination, the annex states that separate changing rooms for the entry and exit of personnel should be considered.

Premises- Airflow visualization

Airflow patterns and complex gas flows within cleanrooms and zones should be visualized to demonstrate that air does not ingress from lower grade (i.e., more contaminated) to higher grade (i.e., less contaminated) areas.

Premises- Pressure Difference

2008- Adjacent rooms of different grades should have a pressure differential of 10 – 15 pascals (guidance values).

2022 -Adjacent rooms of different grades should have an air pressure difference of a minimum of 10 Pascals guidance value).

Premises- «Clean up» period

2008- ‘‘clean up” period of 15-20 minutes (guidance value) in an unmanned state after completion of operations.

2022 -The "clean up" period (guidance value of less than 20 minutes) should be determined during the qualification of the rooms, documented and adhered to in procedures to reinstate a qualified state of cleanliness if disrupted during operation.

Premises- Entry of personnel & materials

Personnel that enters the space should flow from lower to higher grade areas of increasing cleanliness (for example, from Grade D to C, from C to B, and then from B to A). However, the new annex does not state the flow of personnel who leave the space, which potentially allows for skipping grades on the way out.

The movement of materials from lower-grade cleanrooms to higher-grade areas should be subject to cleaning and disinfection, depending on the risk and the CCS.

Premises- Entry of personnel & materials

4.17 Facilities should be designed to permit observation of production activities from outside the grade A and B areas (e.g. through the provision of windows or **remote cameras** with a full view of the area and processes to allow observation and supervision without entry).

GDPR - General Data Protection Regulation

Who's watching us?

Premises- Cleanroom monitoring

The new annex strongly focuses on environmental monitoring since continuous cleanroom monitoring and environmental monitoring is the most effective way of reducing contamination risk.

However, this should not be a substitute for poor environmental control. It means that Quality by design and risk assessment principles need to be introduced in the process design beforehand. Cleanroom monitoring should be part of the overall CCS.

The controls and monitoring practices are to be based on sound scientific reasoning and should be able to effectively assess the cleanroom environment, airlocks, and pass-through hatches. Ensure that these conditions are properly monitored and evaluated.

Premises- Cleanroom and air equipment qualification

It is obvious that cleanrooms and clean air equipment must be classified and qualified for the manufacture of sterile products. However, the legacy document did not define what tests would need to be executed for this.

For the first time, the new annex includes a list of tests to perform for the qualification of cleanrooms. Qualification should include testing for: filter system, airflow, air pressure, microbial contamination, temperature, humidity, recovery, and containment leak. (Agree with EN ISO 14644-1,2,3)

The classification of cleanrooms is based on the total particle concentration limits (at 0.5 microns and 5 microns),and is part of the cleanroom qualification process.

The initial classification should be performed during simulated operations in both “at rest” and “in operational” states.

In addition, the qualification of cleanrooms is completed by the determination of microbial contamination level. The number of samples taken and their sampling locations should depend on the risk assessment.

Premises- Cleanroom and air equipment qualification

The speed of air criterion for unidirectional airflows (homogeneous values within 0.36-0.54 m/s) is maintained at the working position unless scientifically justified in the CCS.

The legacy Annex included microbial contamination limits for the monitoring of clean areas or areas in operation. The new Annex specifies that the microbial concentration level must be determined during qualification both “at rest” and “in operation” and must be verified by three methods indicated in Table 2 (Chapter 4.31) Otherwise, adequate justification must be given for not carrying out any of the methods.

Premises- Cleanroom and air equipment qualification

There are two changes in the maximum permitted microbial contamination levels appearing in the new annex:

The average calculation of results is not considered in the table; and

No growth of microbial contamination should be seen for Grade A cleanrooms

The annex specifies **for the first time** the frequency or maximum time interval for qualification:

6 months for Grade A and B areas; and 12 months for Grade C and D areas.

Premises- Cleanroom and air equipment qualification

The document also requires the maximum number of people present in the clean area during operation.

Requalification is also needed whenever there is a change to equipment, facility, or process, and based on the change management process.

Moreover, it is not enough to qualify or validate facilities, equipment, and processes. Continuous verification and regular reviews must be conducted.

Premises- Disinfection

Cleaning needs to take place before disinfection. However, cleaning must not leave residues, as these may interfere with disinfectants.

Different types of disinfectants can be used, as they have different modes of efficacy in order to increase the spectrum of disinfection. A sporicidal agent must be included in the disinfection plan across all grades of cleanrooms.

The disinfection process must be supported by the use of validated disinfectants and be assessed through the environmental monitoring program, including different types of organisms that are potentially resistant.

Premises- Disinfection

The annex requires any disinfectant that is diluted to be assessed for its microbial content, including hold times and expiry times.

The text requires that disinfectants and detergents used in Grades C and D may

also require sterilization when determined

by the CSS. When they are prepared by the manufacturer, microbial contamination should be monitored by the supplier; when supplied “pre-diluted”, the supplier’s certificates of analysis can be accepted as long as the supplier is qualified.

The cleaning validations should respect the expiry dates of the prepared solutions.

Equipment

A detailed description of equipment and services (process and instrumentation diagrams) should be available at the initial qualification and kept up to date as part of the continuous review of the CCS.

Process and equipment alarms should be evaluated for trends.

Direct and indirect product contact parts (parts in contact with sterilized critical components) should also be sterilized.

Particle counters, including their sampling tubing, should be qualified. The new annex specifies that the length of the tubing must not exceed 1 meter and should have a minimum number of bends.

Utilities

The criticality of each utility system needs to be assessed as part of the CCS and covered by a risk assessment. Higher-risk utilities in descending order of criticality include:

Major risk: Utilities that directly contact product, such as water for washing and rinsing, gases, and steam for sterilization.

Utilities that contact materials that will ultimately become part of the product.

Utilities that contact surfaces that come into contact with the product.

Other utilities that may directly impact the product.

Utilities

Results of critical parameters and Critical Quality Attributes (CQA) of high-risk utilities need to be trended regularly to ensure the system's suitability. For example, trends of pressure differentials, steam Quality, and water Quality.

Pipes and ducts are to be avoided in cleanrooms. Our interpretation of this requirement is to minimize their impact on the cleanliness and contamination control of the environment. Cleanrooms need to be designed with minimal airborne and surface contamination, so the presence of pipes, ducts, and other utilities that penetrate the walls or ceiling can introduce contaminants from other areas into the cleanroom.

Utilities- Water Systems

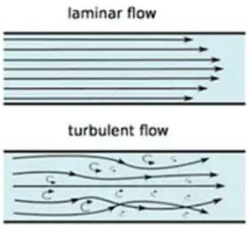
The requirements for water systems focus on actions that prevent microbiological contamination, particulate matter, and endotoxins/pyrogens.

Water for injections (WFI) that is free from microorganisms, particulates, and endotoxins should comply with the current monograph of the European Pharmacopeia. Water should be in constant circulation at a temperature above 70ºC to maintain Quality and minimize the risk of microbiological growth. Special care should be taken for microbial contamination from vent filters installed in storage tanks. Dead legs in pipelines should be avoided wherever possible.

Biofilm formation is another challenge. The risk of microbial adhesion and biofilm formation in the pipes can be minimized if the water flow is turbulent, and sterilization, disinfection, or regeneration of water systems is planned.

6.9 Water flow should remain turbulent through the pipes in water distribution systems to minimize the risk of microbial adhesion, and subsequent biofilm formation. The flow rate should be established during qualification and be routinely monitored.

- Laminar flow when R < 2300
- Transient flow when 2300 < R < 4000
- Turbulent flow when R > 4000



Utilities- Water Systems

Special care should be taken due to seasonal variation. After disinfection is done, testing must be carried out before using the water system.

Continuous TOC and conductivity monitoring must be in place in WFI systems. These values can indicate the performance of the water system and alert probable excursions before they happen.

Values exceeding the alert levels should be documented and include a trend analysis to determine if this is an isolated event or if it is indicative of loss of control or deterioration of the system. The root cause and impact on the Quality of products or processes in which it is involved should be determined.

Utilities- Steam used as a direct sterilizing agent

Pure steam generators must be designed, qualified, and operated in such a way as to comply with the defined specifications of chemical substances and endotoxins.

When steam is used as a direct sterilization agent of materials or surfaces in contact with the product, the condensates must comply with the current EP monograph for WFI. A regular sampling plan must be in place to ensure representative samples of pure steam are tested for analysis in which additionally non-condensable gases, dryness value and superheat must be analyzed.

Utilities- Gases and vacuum systems

Gases that come into direct product contact must be of the appropriate chemical, particulate, and microbial Quality, including oil and water content.

The design of the gas and vacuum system should prevent backflow to avoid potential risks of contamination.

In the case of gases used in aseptic processes, an additional filtration step is needed to remove basic bacteria. A sterilizing grade filter with a pore size of a maximum of 0.22 microns needs to be used at the point of use.

Utilities- Heating and cooling and hydraulic systems

There is a risk of spillage and cross-contamination with heating, cooling, and hydraulic systems. To avoid this risk, it is recommended that they are placed outside the filling room. In the event of leakage, a warning alarm should be in place.

Personnel

The basic requirement of having trained, qualified, and experienced personnel with a focus on sterile product protection is maintained in the annex. It is the manufacturer's responsibility to ensure that sufficient appropriate personnel is available.

Particular importance is given to training, specifying the areas in which relevant staff must be trained: hygiene, microbiology, cleanroom practices, contamination control, aseptic techniques, behaviors, gowning, and protection measures.

The training should be comprehensive, being in accordance with the criticality of the activities and areas of work to be carried out by each person.

Behaviour???

How shall a cleanroom person bahave according to Annex 1:2022

- Operator behaviour
- Aseptic behaviour

Personnel

The entry of non-qualified personnel to Grade A and B cleanrooms in operation is restricted. For exceptional cases where access is necessary, written procedures outline the situations in which access is allowed and what steps are to be taken, including direct supervision by a qualified and authorized person.

Clothing with low particle shedding is required. Appropriate garments for sterile areas must be worn prior to entry to Grade B areas and visually inspected for their integrity.

Reusable clothing must be cleaned using a qualified procedure that ensures clothing is not damaged and contaminated.

The annex mentions that personnel qualification procedures and a disqualification system must be in place. To reinstate a disqualified employee for aseptic practices, retraining and requalification is required.

Personnel-Gowning Qualification

(Pavičić & Wagner, 2019)

Personnel-Mobile Phones / Electronic Devices

7.9 . Wristwatches, make-up, jewellery, other personal items such as mobile phones and any other non-essential items should not be allowed in clean areas. Electronic devices used in cleanrooms, e.g. mobile phones and tablets, that are supplied by the manufacturer
solely for use in the cleanrooms, may be acceptable if suitably designed to permit cleaning and disinfection commensurate with the grade in which they are used. The use and disinfection of such equipment should be included in the CCS.

Production and Specific Technologies

Not much has changed regarding production technologies for terminal sterilization. The CCS should identify the risks of contamination in different areas and cleanrooms. If a high risk of contamination has been identified in the processing of bulk solutions, a filtration step should be used to reduce the bioburden levels prior to the filling process. The cleaning of primary packaging containers and components should also be validated. The new annex encourages the use of RABS, isolators, and robotics to reduce the risk of contamination and the need for human interventions.

4.3:Their use should be considered in the CCS. Any alternative approaches to the use of RABS or isolators should be justified.

Do we have any alternative? Robotics?

What would be the justification for NOT considering Barrier Technology or deciding they were inappropriate.

Production and Specific Technologies

First Air:

Refers to filtered air that has not been interrupted prior to contacting exposed product and product contact surfaces with the potential to add contamination to the air prior to reaching the critical zone.

❑Isolators "Open"

- Requires Grade A +UDAF and "First Air"
- Background minimum Grade C What about legacy isolator installations in Grade D?
- Test interfaces –mouse holes

❑Isolators "Closed"

- Requires Grade A + UDAF and "First Air" for processing lines
- Can have Grade A+ non-UDAF for simple operations What are simple operations?
- Background minimum Grade D
- Negative pressure isolators only if essential for hazard, must protect product

Gloves and Decontamination

The weakest link

❑More guidance, mush more specific

❑Gloves

- Testing frequency defined
- Includes both application Sterilization &Disinfection

❑Bio-decontamination

- Objective is surfaces free from viable microorganisms
- Automated process advised
- Gloves should be extended
- Focus is H_2O_2. (Ignores ClO_2, NO_2, Are these agents excluded?)

Production and Specific Technologies- Human Interventions

Human interventions during aseptic processing are serious issues. They can increase the risk of introducing contamination into the aseptic filling area. The new annex requires that human interventions are carefully designed, evaluated via risk assessment, and qualified.

Interventions can disrupt first air. So, we can say that the best practice is to avoid any kind of intervention whatsoever. If this is not possible, we should limit the number and complexity of human interventions as much as possible.

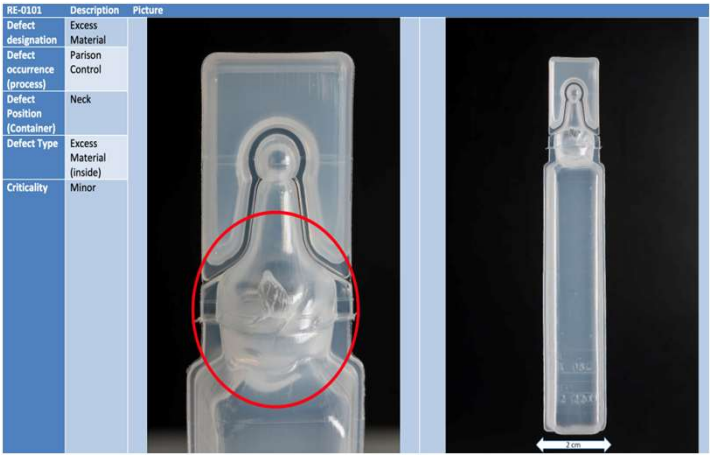
Non-qualified interventions should be performed exceptionally with the authorization of the Quality unit, which should perform a risk assessment, an investigation, and an evaluation prior to batch disposition.

Due to the potential for microbial growth, manufacturers should typically conduct studies to define acceptable hold times for process intermediates. There should be a maximum permissible time for each specific product and preparation.

Production and Specific Technologies- Defect Library

A defect library should be generated and maintained which captures all known classes of defects. The defect library should be used for the training of production and quality assurance personnel.

The qualification should be undertaken using appropriate samples from the manufacturer's defect library sets and taking into consideration worst case scenarios (e.g. inspection time, line speed where the product is transferred to the operator by a conveyor system, container size or fatigue) and should include consideration of eyesight checks.



Production and Specific Technologies- Sterilization

The new annex includes a large section on sterilization technologies:

- ❑Sterilization by heat
- ❑Moist heat sterilization
- ❑Dry heat sterilization
- ❑Sterilization by radiation
- ❑Sterilization with ethylene oxide
- ❑Filter sterilization

Production and Specific Technologies- Sterilization

Use scientific principles in the selection of the sterilization procedure.

Validate the sterilization process - repeatability and reliability - by physical measurements and biological indicators.

Use heat sterilization, which is the preferred system; otherwise use another method described in the current European Pharmacopeia.

There are some concerns with the use of ethylene oxide. It should only be used when no other method is practicable, because of the difficulty to ensure that no residues or reaction products are controlled at acceptable limits.

Review and verify the sterilization process at scheduled intervals according to the risk assessment and CCS.

Deviations must be investigated.

Sterilization records should be reviewed and approved for batch release purposes by a knowledgeable person.

Production and Specific Technologies- Single Use Systems, Closed System

SUS

•Recognize specific risks of using SUS versus rigid systems in CCS
•☐Sterility assurance and qualification of suppliers and sterilizers
•☐Evaluation of compatibility and Extractables & Leachables
•☐Maintaining SUS integrity throughout processing
•☐Assembly and connections per APS

CS

•Advantages of minimizing risks of contamination (particles, microbial)
•Design and selection to ensure sterility of all contact surfaces
•System pressure integrity testing
•Use of intrinsic sterile connection devices
•If risk to integrity, background Grade
A. If not, lower grade

Production and Specific Technologies- Lyophilization

2008

- No specific paragraph dedicated to lyophilization

-2 requirements related to freze-drying process and describing grade environment for pre-stoppered vials until full stoppering
- 1 requirement for sealed vials under vacuum

-Lyophilization/lyophilized/lyophilizer: 0 times
- Freeze-drying/ freze-dryer: 2 times

2017

• Introduction pf specific paragraph for lyophilization where specific requirements applied
• Requirements also described in other sections and paragraphs

2022

- Dedicated paragraph for lyophilization where specific requirements applied with a focus on:
o CCS
o sterilization
o integrity of vent filter
o leak rate of the freeze-drier
o loading of the vials
•Paragraph included in section 8
•Pages: ~1 page
•Lyophilization is also detailed and considered in other sections and paragraphs:
o aseptic preparation and processing for barrier technology
o moist heat sterilization
o environmental monitoring
o aseptic process simulation (APS)
o finishing of sterile products for vials sealed under vacuum
•Lyophilization/lyophilized/lyophilizer: 37 times
•Freeze drying/freeze dryer: 1 times

Environmental and Process Monitoring

As an important verification tool in the CCS, the environmental program will ensure the air cleanliness of cleanrooms and equipment and will detect deviations from established acceptance criteria. All controls are effective when they are considered holistically and not individually. The guidance applies to ongoing routine monitoring.

Environmental and Process Monitoring

Environmental monitoring comprises the following:

- ❑Particle monitoring (the particle monitoring program should be risk-based to establish samples locations, types of samples and methods selected, samples sizes and volumes, sampling time, frequency, and strategy for personnel monitoring)
- ❑Viable particle monitoring
- ❑Temperature monitoring
- ❑Relative humidity monitoring
- ❑Aseptic process simulation (APS) or media fill

Environmental and Process Monitoring

These parameters are good indicators of the areas' cleanliness and their good aseptic processing conditions.

Temperature and humidity are important environmental parameters that can affect the stability and shelf life of the product. It can also impact the growth and survival of microorganisms, which can pose a risk of contamination to the product.

It is important to note that the Annex considers positively the use of rapid monitoring methods, appropriately validated, which speed the early detection of microbial contamination.

Environmental and Process Monitoring - APS

When	How many
New filling lines	Three media fills minimum
Modification to the HVAC system Change to equipment Changes to process Changes to the number of shifts and numbers of personnel Major facility shutdown	Three media fills minimum
Each aseptic process, each filling line and each shift	Twice per year
Last event before shutdown	One media fill per line
Each operator	Once per year
Prior to line decommissioning	One media fill
Prior to line relocation	One media fill
Upon line relocation	Three media fills minimum
Following a media fill failure	Three media fills minimum

Media fills, rebranded as 'aseptic processing simulations' (APS), is a key qualification exercise and probably deserving of a standalone section. For media fills, the acceptance criteria is now firmly set at zero. In other words, the growth of a single unit requires the suspension of the line and an investigation.

Environmental and Process Monitoring

Alert levels and action limits need to be established based on qualification tests. Trending data should be reviewed periodically. In the case of having out-of-alert/action limits, they should be investigated to find the root cause and apply appropriate CAPAs.

The annex describes that APS or media fill is periodic verification effectiveness that should be done based on Risk Assessment of the aseptic process (e.g., qualification, validation, or after changes). APS should cover aseptic manipulations and interventions, as well as worst-case scenarios.

Environmental and Process Monitoring

All routine monitoring data obtained in production should be trended and used as part of the routine batch release and periodic assessments. Trends should include different types of excursions, such as increasing numbers of excursions, consecutive excursions, isolated excursions, or changes in microbial patterns.

9.4 Risk assessments should be performed in order to establish this comprehensive environmental monitoring programme, i.e. sampling locations, frequency of monitoring, monitoring methods and incubation conditions (e.g. time, temperature(s), aerobic and/or anaerobic conditions).

These risk assessments should be conducted based on detailed knowledge of; the process inputs and final product, the facility, equipment, the criticality of specific processes and steps, the operations involved, routine monitoring data, monitoring data obtained during qualification and knowledge of typical microbial flora isolated from the environment

How do you achieve understanding of the typical microbial flora?

9.11 Trends should include, but are not limited to:

i. Increasing numbers of excursions from action limits or alert levels.

ii. Consecutive excursions from alert levels.

iii. Regular but isolated excursion from action limits that may have a common cause, (e.g. single excursions that always follow planned preventative maintenance).

iv. Changes in microbial flora type and numbers and predominance of specific organisms

FDA : Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice

«Significant changes in microbial flora should be considered in the review of the ongoing environmental monitoring data»

How do you know if you have an atypical microorganism without an accurate identification?

Quality Control

The QC part of the annex includes requirements on:

- QC/QA personnel training and experience Specifications
- Types of microbiological tests (e.g., bioburden or sterility)
- Sampling
- Method verification/validation
- Parametric release
- Data review

Glossary

Provides guidance on specific terminology, avoiding ambiguity and inconsistencies.

Do you believe that the CSS document will be a document like SMF?

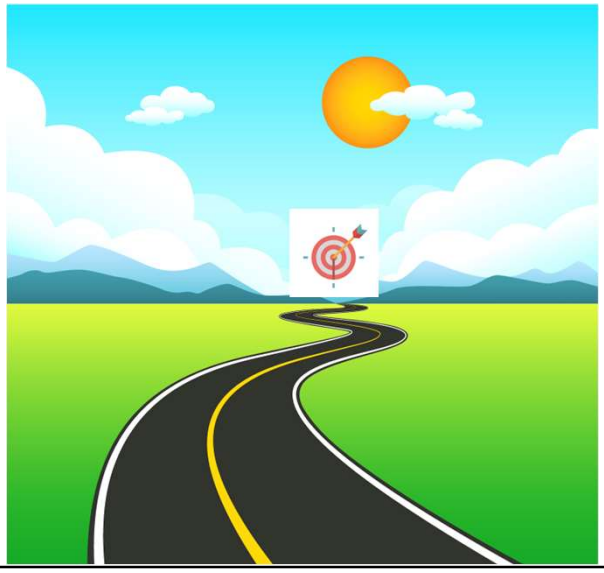
A. Yes
B. No
C. Unsure

Contamination

Control

Strategy

AS IS ----------TO BE



What is CCS?

Definition

Glossary (Annex 1:2022)

A planned set of controls for microorganisms, endotoxin/pyrogen and particles, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

Why they added CSS into Annex 1?

Criticality

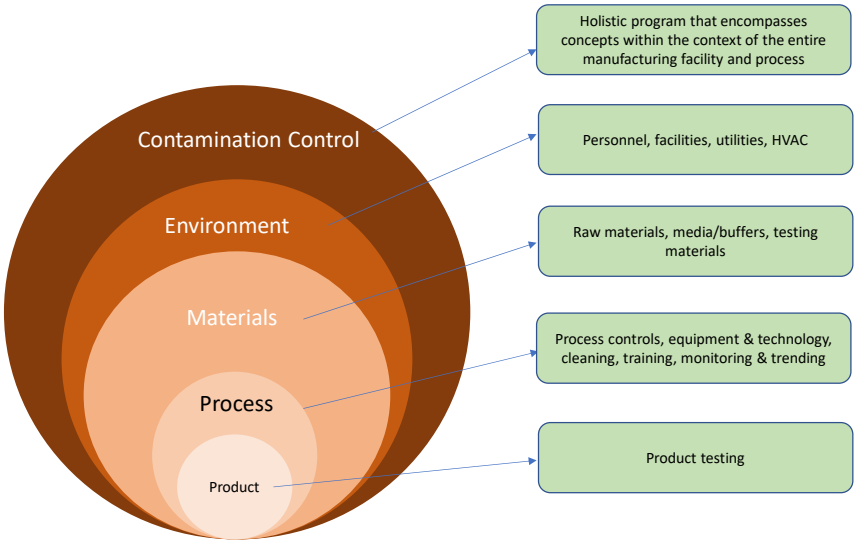
- Recent recalls/citations show the contamination of products is a real and current problem
- Humans arguably learn best from trial and error. Unfortunately, this way of learning, when working with pharmaceutical products is far from safe

"Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established..." FDA citation

"The control systems necessary to prevent contamination or mix-ups are deficient..." FDA citation

"Non-microbial contamination was observed in your production area. Specifically, thick white powder residues were observed on the ceiling intake vent and on top of the hood..." FDA citation

What's involved



Elements to be considered within a CCS should include (but are not limited to):

i. Design of both the plant and processes including the associated documentation.

ii. Premises and equipment.

iii. Personnel.

iv. Utilities.

v. Raw material controls – including in-process controls.

vi. Product containers and closures.

vii. Vendor approval – such as key component suppliers, sterilisation of components and single use systems (SUS), and critical service providers.

viii. Management of outsourced activities and availability/transfer of critical information between parties, e.g. contract sterilisation services.

ix. Process risk management.

x. Process validation.

xi. Validation of sterilisation processes

xii. Preventative maintenance – maintaining equipment, utilities and premises (planned and unplanned maintenance) to a standard that will ensure there is no additional risk of contamination.

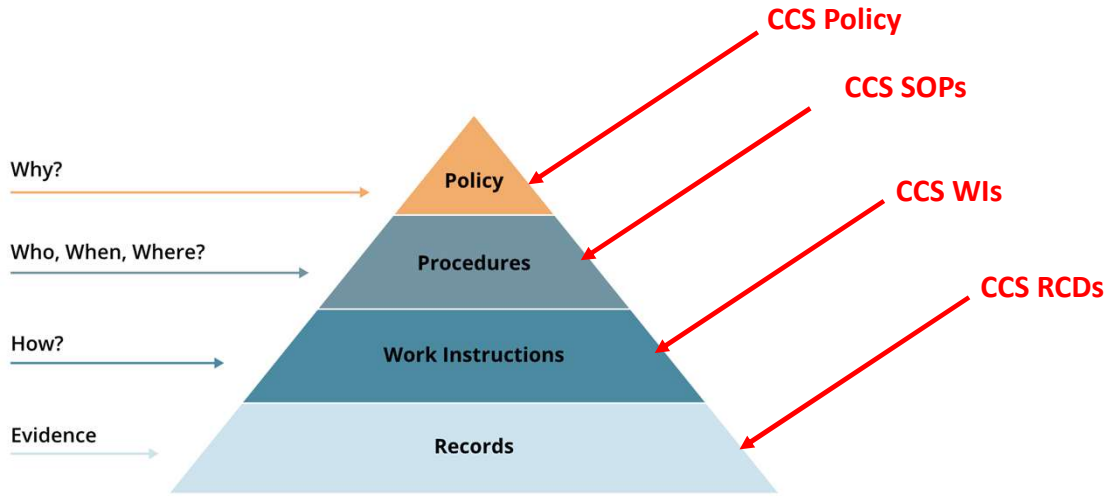
xiii. Cleaning and disinfection.

xiv. Monitoring systems - including an assessment of the feasibility of the introduction of scientifically sound, alternative methods that optimize the detection of environmental contamination.

xv. Prevention mechanisms – trend analysis, detailed investigation, root cause determination, corrective and preventive actions (CAPA) and the need for comprehensive investigational tools.

xvi. Continuous improvement based on information derived from the above.

Do you have a policy?



CSS Policy

Scope

Control of microbial (bacteria &viruses), pyrogen & particle contamination during the end-to-end manufacturing process of a sterile product(including bioburden control steps)

Sites may develop one or more CCS depending on complexity: products, manufacturing steps, facilities.

Objective

A single document which provides a holistic overview of contamination risks, control& monitoring.

Visible to Senior Management (Site and Global) for management and governance purposes driving corrective actions and continuous improvement

Policy Elements:
Describes the key elements from Annex 1 and provides high level instruction, referencing a standard template

CCS Policy ensures:

- The current and future strategy is reviewed in a single document.
- Structured approach to review potential contamination sources

- Hierarchy of controls:

➢ Design
➢ Procedural
➢ Monitoring

- Incorporates a performance review

How to Start?

Title 1	Introduction
Title 2	Scope
Title 3	Design Strategy and Validation
Title 4	Procedural Controls
Title 5	Monitoring Systems
Title 6	Overview Control Improvements
Title 7	Performance Data
Title 8	Conclusion

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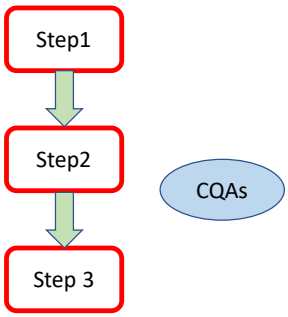
How to Start?

Title 1	Introduction	Context & Structure of CCS
Title 2	Scope	Process description and flow diagrams



- Provides the reader with an overview of the assessment approach
- Describes process at a high level, including critical quality attributes

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How to Start?

Title 3	Design Strategy and Validation	Overview of documentation related to design and validation
Title 4	Procedural Controls	Documents describing how controls are implemented (e.g., SOPs for gowning, disinfection)

- Summary of the Design and Procedural controls
- Conclusion regarding assurance of product/process as a consequence of design and procedural controls
- Appendices provide full list of documentation reviewed, including validation documentation, risk assessments and procedures
- Appendices follow structure provided in Annex 1 section 2.5

2.5 The development of the CCS requires detailed technical and process knowledge.
Potential sources of contamination are attributable to microbial and cellular debris
(e.g. pyrogen, endotoxin)
as well as particulate (e.g. glass and other visible and sub-visible particles).
Elements to be considered within a
CCS should include (but are not limited to):
i. Design of both the plant and processes including the associated documentation.
ii. Premises and equipment.
iii. Personnel.
iv. Utilities.
v. Raw material controls –including in-process controls.
vi. Product containers and closures.
vii. Vendor approval……

How to Start?

Title 5	Monitoring Systems	Overview of documents for Monitoring Systems (EM, utilities monitoring, alarms, VI, Quality Systems etc.)

- Summary of the monitoring processes in place
- Conclusion regarding assurance of product/process resulting from monitoring systems
- Appendices provide full list of documentation reviewed
- Appendices follow structure provided in Annex 1 section 2.5

2.5 The development of the CCS requires detailed technical and process knowledge. Potential sources of contamination are attributable to microbial and cellular debris (e.g. pyrogen, endotoxin) as well as particulate (e.g. glass and other visible and sub-visible particles). Elements to be considered within a CCS should include (but are not limited to):
xiv. Monitoring systems -including an assessment of the feasibility of the introduction of scientifically sound, alternative methods that optimize the detection of environmental contamination.
xv. Prevention mechanisms –trend analysis, detailed investigation, root cause determination, corrective and preventive actions (CAPA) and the need for comprehensive investigational tools.

How to Start?

Title 6	OverviewControl Improvements	Summary of ongoing CCS improvement initiatives(projects, change controls etc)
Title 7	Performance Data	Summary of KPI of previous year (EM / product / Utilities etc.)
Title 8	Conclusion	Conclusion on effectiveness of controls and actions for improvement

- Titles 6-8 subject to annual update (other sections reviewed)
- Improvement initiatives may be identified from a number of sources to remediate gaps or continuously reduce risk.
- Improvements follow the hierarchy of design-procedural-monitoring
- The review of performance aims to provide confirmation that processes remain under control
- The review includes an assessment of monitoring trends and unplanned events
- Conclusions provide an overall assessment of effectiveness of controls

Quality Risk Management (ICH Q9)


ICH
harmonisation for better health

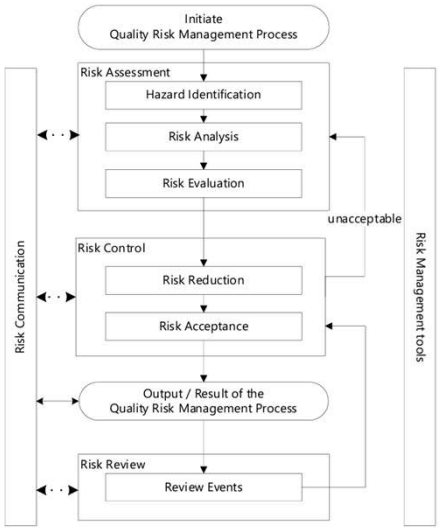
INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

QUALITY RISK MANAGEMENT
Q9(R1)

Final version
Adopted on 18 January 2023

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 ICH regions.



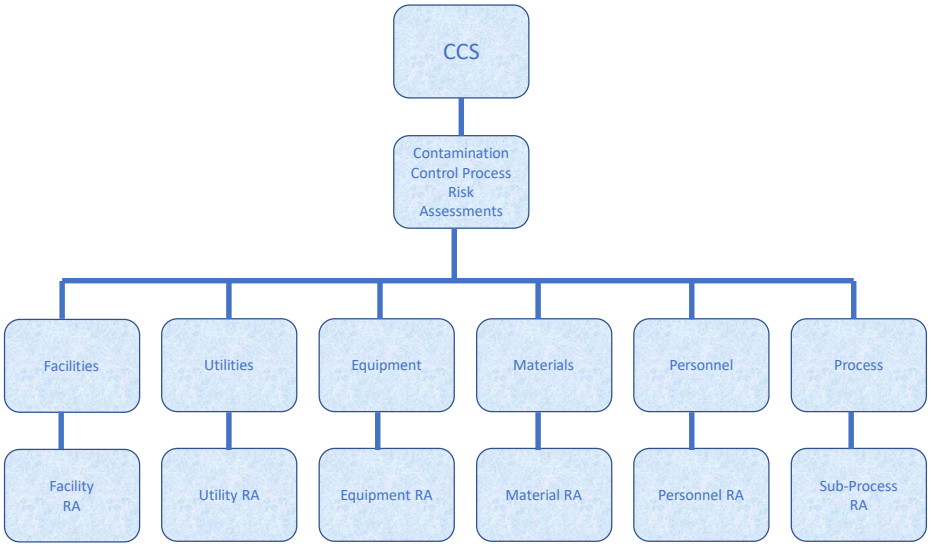
Principles

The evaluation of risk to quality should be based on scientific knowledge and ultimately link to the **protection of the patient**. *Note: Risk to quality includes situations where product availability may be impacted, leading to potential patient harm.*

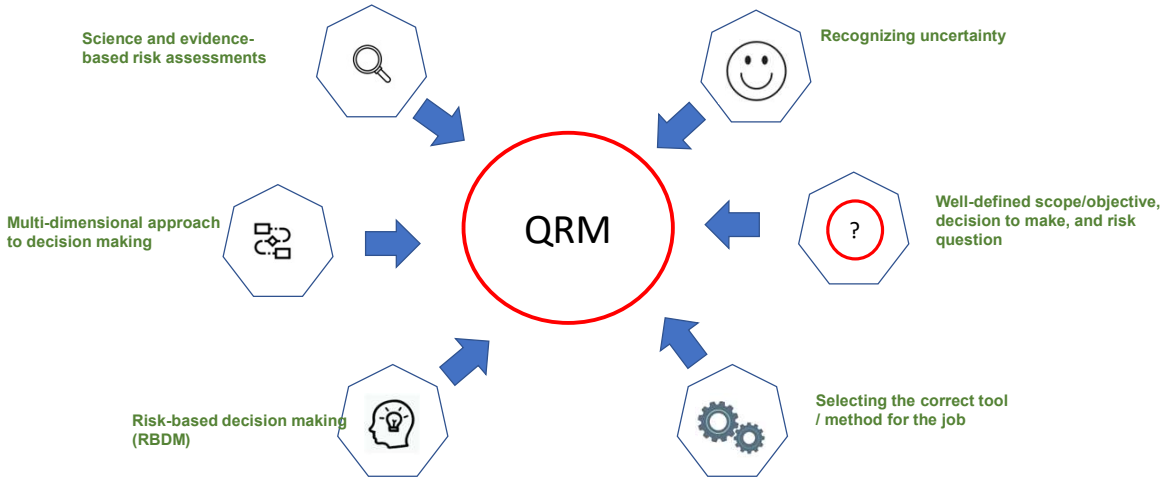
The level of effort, formality and documentation of the QRM process should be **commensurate with the level of risk**.

Use of knowledge management and quality risk management enable the PQS. These enablers provide the means for **science-and risk- based decisions related to product quality**.

CCS Strategy Map



How to Apply Principles



Ask These Questions?

1. What can go wrong?
2. What is the likelihood that it could happen?
3. What are the consequences if it does happen?
4. What are the “priority risks” to address?
5. What can be done and what are the options available?
6. What can be done to communicate what has been done?
7. What can be done to document what has been done?
8. How will we know if any conditions or assumptions have changed?

How To Choose The Best RM Approach?

Uncertainty

• How much do you **know** about the system you are assessing?

Complexity

• How complex is the system?

Importance

• What is the criticality of the system?

Risk Parameters

• How will risk be measured?

How to measure overall Risk?

Occurrence × Severity × Detection = Risk

Right Tool vs Wrong Tool?

RISK TOOL

ENABLES

APPLICATION

Checklists and Decision Trees

Rule-based decision making

When you need to do the same assessment multiple times
> Classification of raw material
> Excursion response

?

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Examples –PHA*

RISK TOOL

ENABLES

APPLICATION

Preliminary hazard analysis

Hazard identification and analysis and evaluation of hazardous situations

Process changes
New equipment
Facility Updates
New Facility Assessment

* PHA: Preliminary Hazard Analysis

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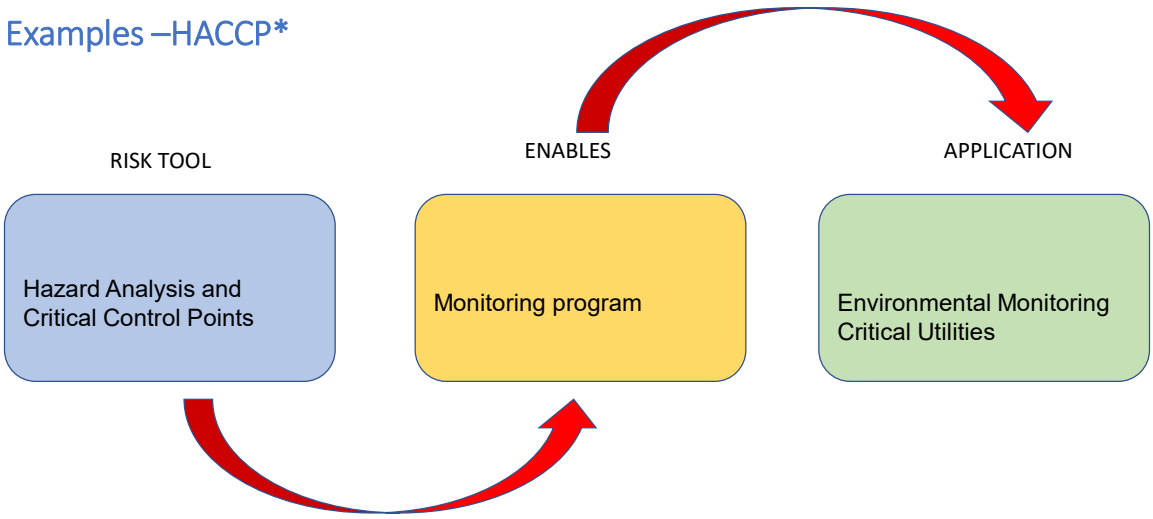
Examples –HACCP*



* HACCP: Hazard Analysis & Critical Control Points

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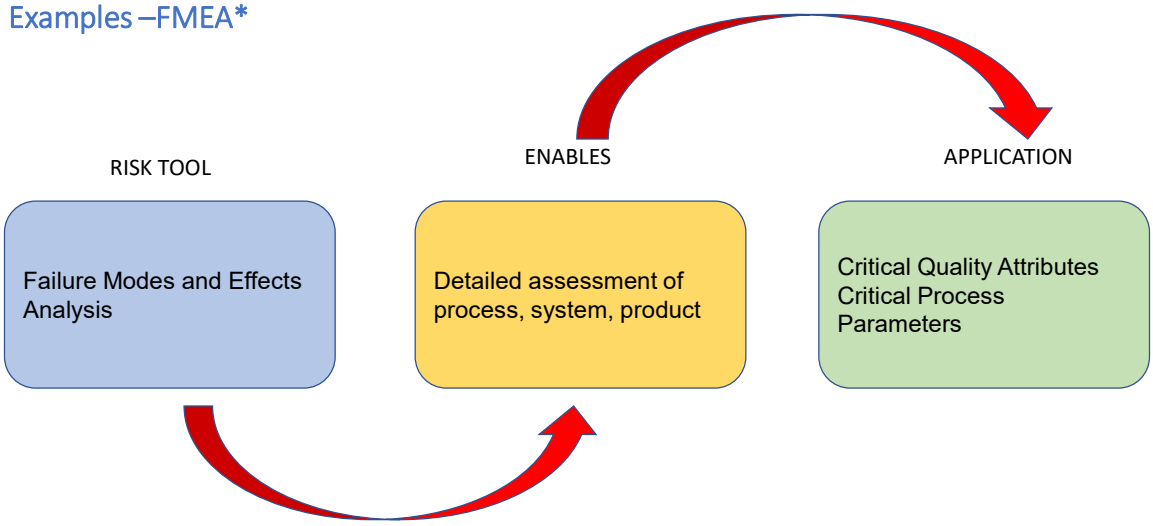
Examples –FMEA*



* FMEA: Failure Modes and Effects Analysis (FMEA)

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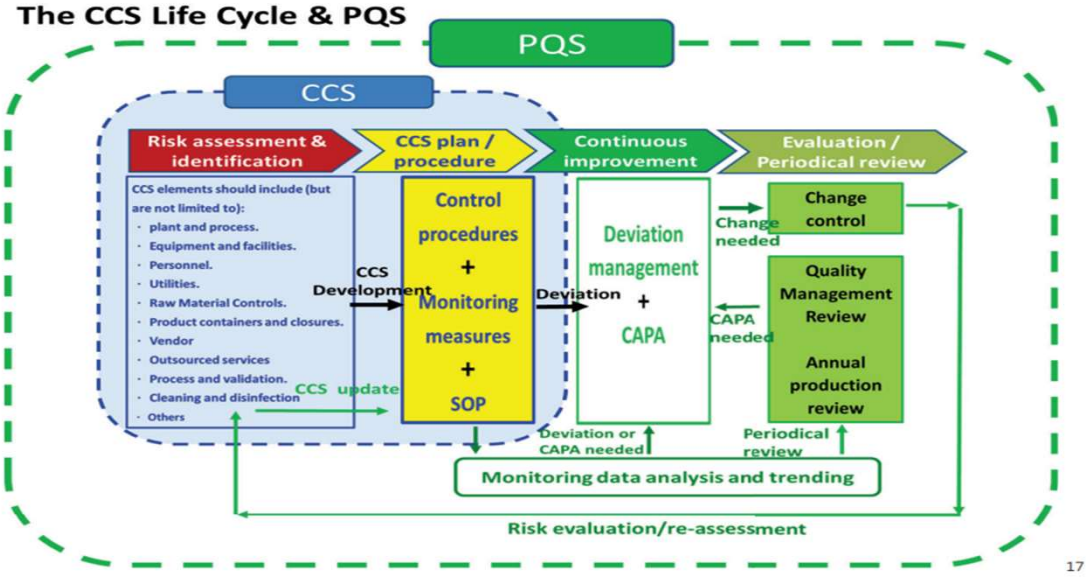
In Brief

If you're working on…	Try…
A *new* project and are *very early* in the development process with *limited data* available	PHA
A *new* project but are *later* in the development process with a *fair amount of experience*	FMEA
A *mature* process, but you are interested in developing a *very thorough understanding* of the risks to recommend improvements	FMEA
Development of a *monitoring program* for in-process operations, critical utilities or environmental monitoring	HACCP
Understanding how a piece of *equipment impacts* manufacturing operations	FMEA
A relatively insignificant or moderately significant *change* which is well understood	REM*
A project where you need to make *decisions about next steps* using the risk	REM

*REM: Risk Estimation Matrix

An Example Approach



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