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Case Study

ICH Q9 Risk Management Applied to Manufacturing Pharmaceutical Facilities Case Study: Cleanrooms Classified Space

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Abstract

Risks management represent a major tool and an essential step in the process validation implementation during all the life cycle of a given pharmaceutical plant from its conceptual design (URS) until its operation. Therefore, risks management and mitigation tools are very critical to reduce chemical and biological hazardous and explosive processes, mechanical and design risks and related capital costs as well. It will also assist in the choice of reasoned approaches for the proper management of the change controls (maintenance, metrology). In this article, few examples are given to show how is powerful this approach C&Q [1] (Commissioning and Qualification). Furthermore, through the examples presented, this risk management approach is quite justified in particular when it comes to deal with complex processes, multi-products plants, highly potent products (Cephalosporin, Betalactamin, Penicillin, Hormones, Cytotoxic, Oncological products) of grade HP1 to HP5 according to the standard Safe Bridge or equivalent) or by implementing flammable solvents (alcohol etc.) or explosive raw materials to character (sugar, starch, spiramycin, etc.) of grade ATEX1 to ATEX3 [6], NFPA 30) as well as Biosafety Levels: BSL1 to BSL4 of biological compounds containment (vaccines, hormonal products...). This new approach, thanks to the prior identification of critical parameters of pharmaceutical facilities, helps to orient and to optimize the steps of qualification (Design Qualification: DQ, Installation Qualification: IQ, Operation Qualification: OQ, Performance Qualification: PQ) that arise. It allows to struggle the effort in a rational manner during the commissioning, and no need to repeat these tests during the subsequent qualification stages IQ, OQ. In this perspective, only the tests are the most critical are then to be done during equipment qualification and process validation as well [1].

Keywords: *ICH Q9; Risk Management; Cleanrooms Classified Space*

Introduction

In the pharmaceutical sector and related fine chemistry, biotechnology, cosmetics, so on, the manufacturing operations must be carried out in facilities with qualified equipment and validated processes to ensure the reproducibility of the productions batches and the conformity of the products to the specifications established during the validation.

The GMP focuses mainly on the critical aspects in terms of compliance, quality/sterility of the finished products, quality controls, sanitisation and cleaning procedures, however, these GMP criteria cover less the aspects related to the safety issues of facilities and the protection of employees as well. Also, Additional standards and norms, such as: ICH (International conference on harmonisation), ISO (International Organization for Standardization), ASME-BPE (American Society of Mechanical Engineers, Bio-Process Equipment), WHO (World Health Organization), ISPE (International Society for Pharmaceutical Engineering), inspection guides, should be used to fill the mentioned gaps [1-15].

Therefore, as reported by Mr Steven S Kuwahara, who said that about 45% of the recalls of drugs and devices are due to design problems [16].

Like several multinationals, it is vital for the project managers, engineers, and validation specialists, quality assurance and production managers, good understanding of the basic elements of this approach of risk management applied to the validation according to ICH Q9, and this, in order to reduce the operating costs and investment (particularly by reducing the volume of validation [1,2,5]), ensure quality of products and facilities cGMP compliance, of critical systems, equipment and clean utilities to meet the USP or PhEu, and the regulatory requirements of cGMP as well, but also the related standards ICH Q9 [1,2], ISO-14644 [6], ASME BPE (2016) [7], ASTM (American Society for Testing and Materials) 2500 [17,18] and ISPE volume guides [9,10].

Risk management and risk analysis approach and regulation overview

The Risk Analysis as prescribed by ICH-Q9 is part of the project life cycle flow diagram. ICH Q8, Q9, Q10 and Q11 form together the process validation [1,2]. ICH is the organisation bringing together the different regulatory authorities. It has tried to harmonize the different methods of risk analysis that were implemented in 2004 by the US-FDA with the cGMP. GMP history is summarized below, with the general principles being approximately 40 years old (Figure 1).

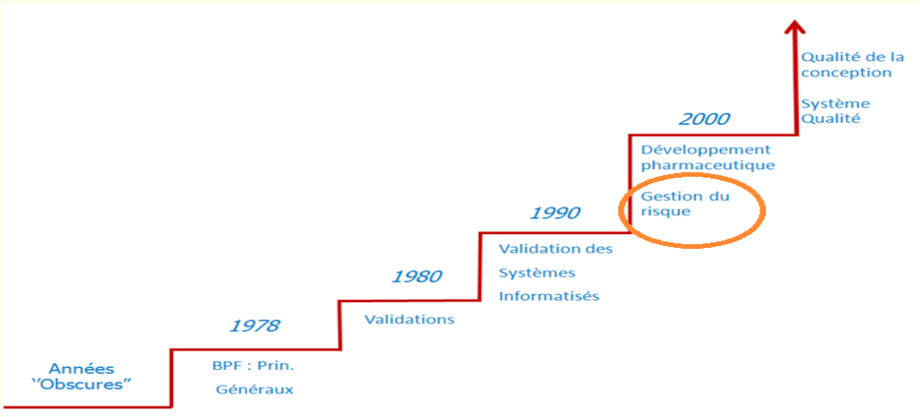

Figure 1: *History of the GMP [2].*

In the whole project life cycle (Figure 2), the risk management hysteresis is contained in the loop composed by the DS (Design specifications), RA (Risk Analysis), FRA (Functional Risk Analysis) and DR (Design Review).

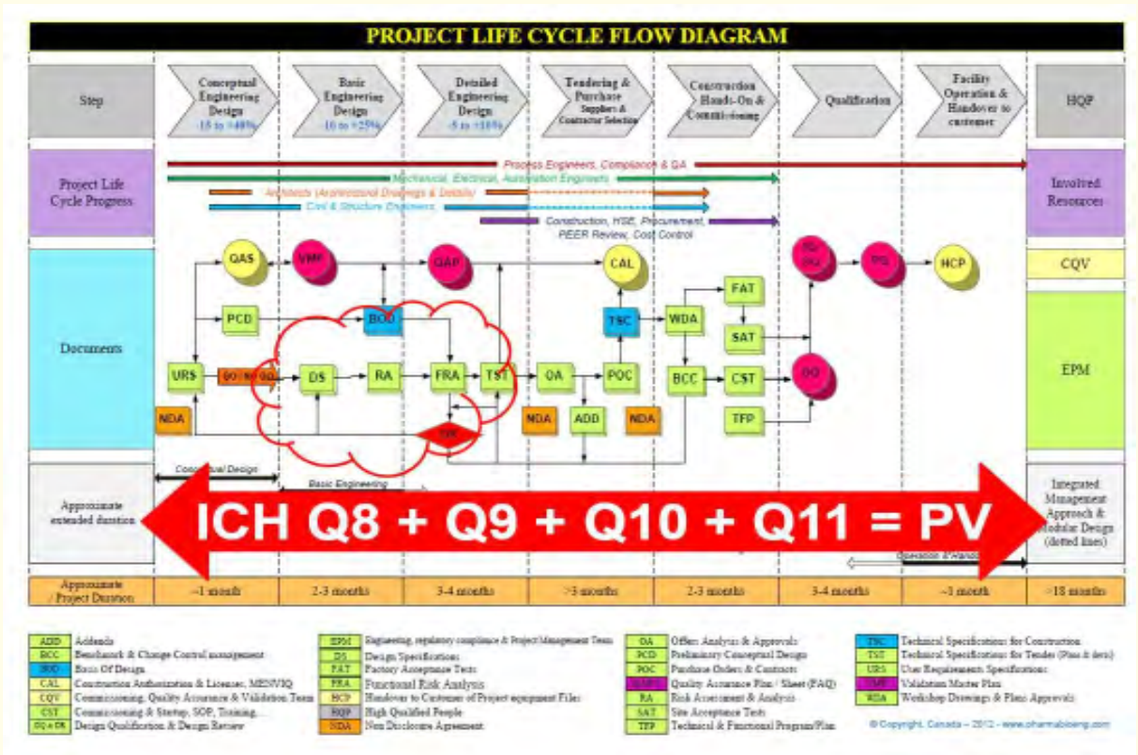

Figure 2: *ICH Q9 Quality Risk Management applied to pharmaceutical industries (Developed by author).*

This life cycle project management is part of the integrated V-model, which is the structure of the project phases the professionals will have to go back and forth between until the completion of the project. This V-Model diagram emphasises on the link between engineering design and related qualification steps. So, functional design specifications are submitted under risk analysis assessment to reduce cost and set up the operational requirements and controls. These steps are very critical because they impact directly operation qualification requirements and related tests to be performed (Figure 3).

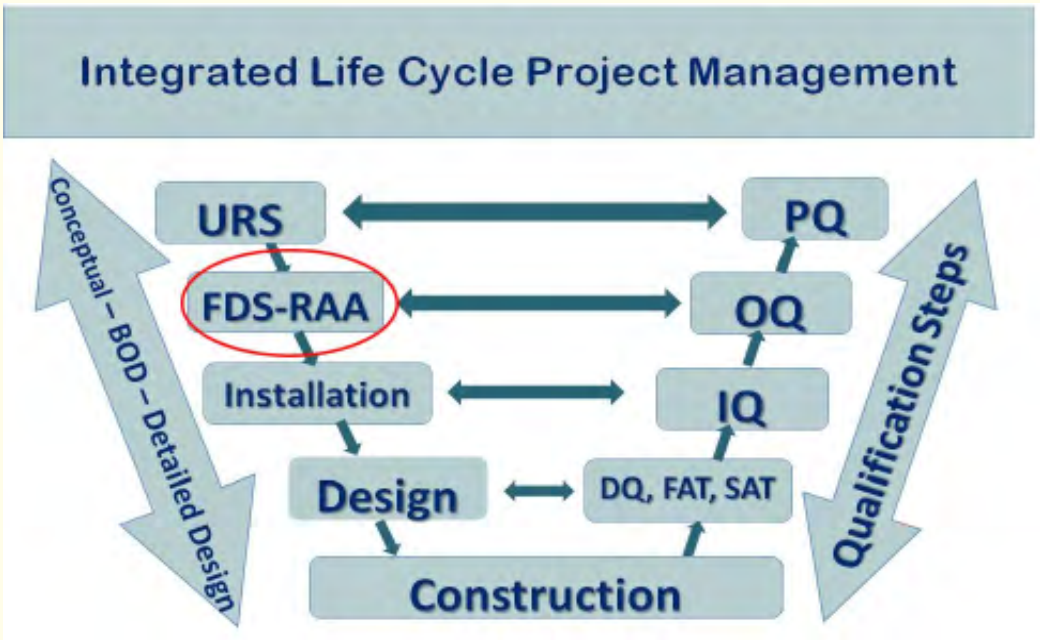

Figure 3: *V Model for Integrated Life Cycle Project Management [9].*

ICH also fills a gap in the cGMP guideline, the safety aspect which wasn't considered before. Now is part of the ICH requirements. Figure 4 illustrates these new requirements.

Figure 4: *ICH Q9 Quality Risk Management [1,2].*

The basis of the commissioning and validation are set up on the URS (User Requirement Specification) and the related critical process/ environmental parameters (CPP/CEP). It contains all the information upon which the validation is based. The operation range of process parameters is also validated. Acceptable ranges of operating conditions are given by the six-sigma rule which are challenged by risk analysis assessment of the related CPP and CEP, such as illustrated below (Figure 5).

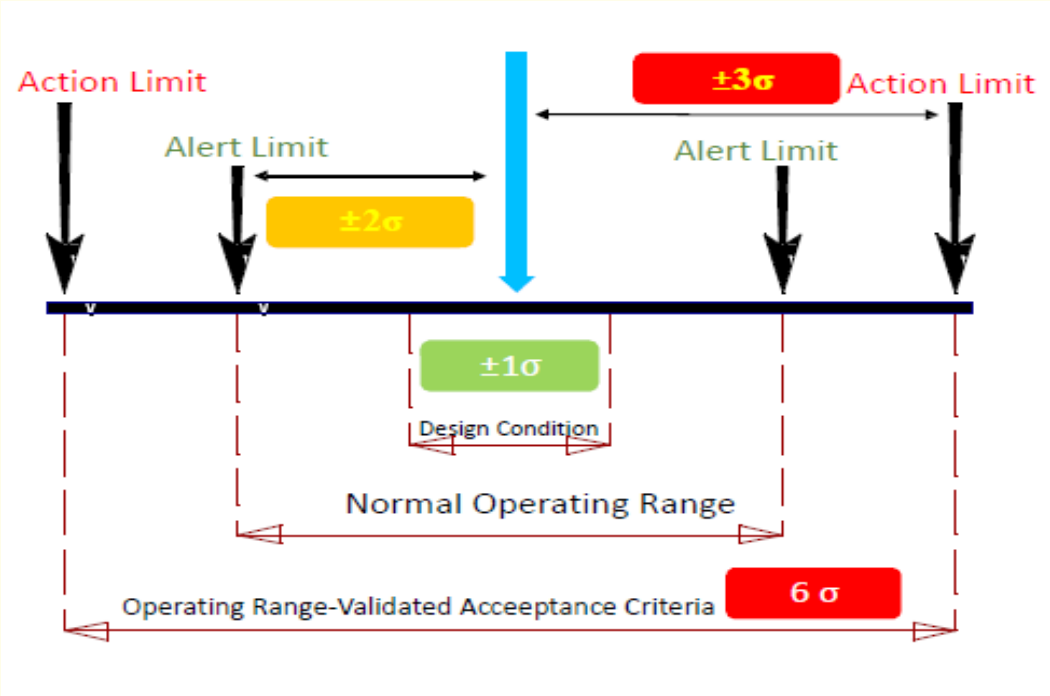

Figure 5: *Six Sigma Criteria [9,14].*

The Risk Analysis (or Criticality Assessment) consists in the identification of the possible sources of errors and quality variations that could result in drug non-conformity.

The goal is to ensure that the functional design specifications (FDS) are sufficient to maintain the possible systems defects at an acceptable level of criticality.

The related critical components and parameters having a direct impact on the integrity of the product are analyzed. In the case that the criticality of a defect would be too high, a modification or improvement of the FDS should be done to decrease the defect criticality to an acceptable level.

The risk analysis may also be used as a tool for further determination of the maintenance and calibration programs of the instruments.

Other risk analysis tool may also be used, such as FTA (Fault Three Analysis), HACCP (Hazard Analysis and Critical Control Point), HAZOP (HAZard and OPerability study), PHA (Preliminary Hazard Analysis), Risk Ranking and Filtering [1,2,10].

As illustrated on figure 6, the focus on critical aspects after evaluation of the risks was initially introduced by the ASTM E2500 [17,18].

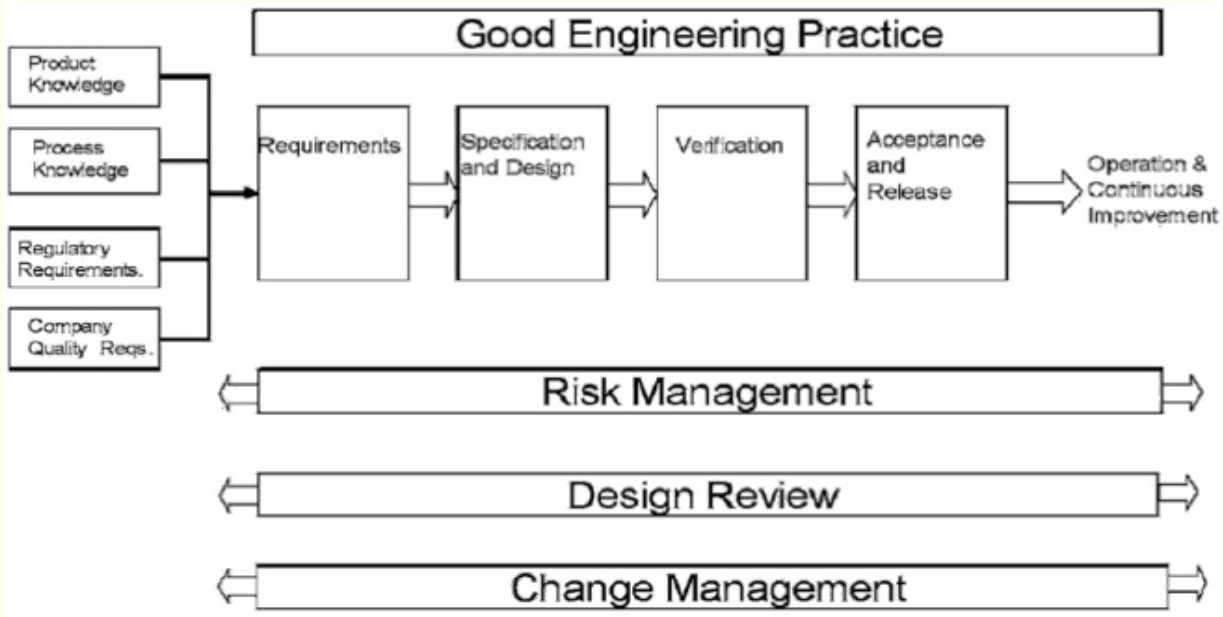

Figure 6: *ASTM 2500- specification, design, and verification process [17,18].*

ICH Q9 – Quality Risk Management operates according the following scheme. Risk assessment (identification, analysis and evaluations) leads to control measures and risk mitigation (reduction and acceptable) and loops are done until the risk is deemed acceptable (Figure 7) [1,2].

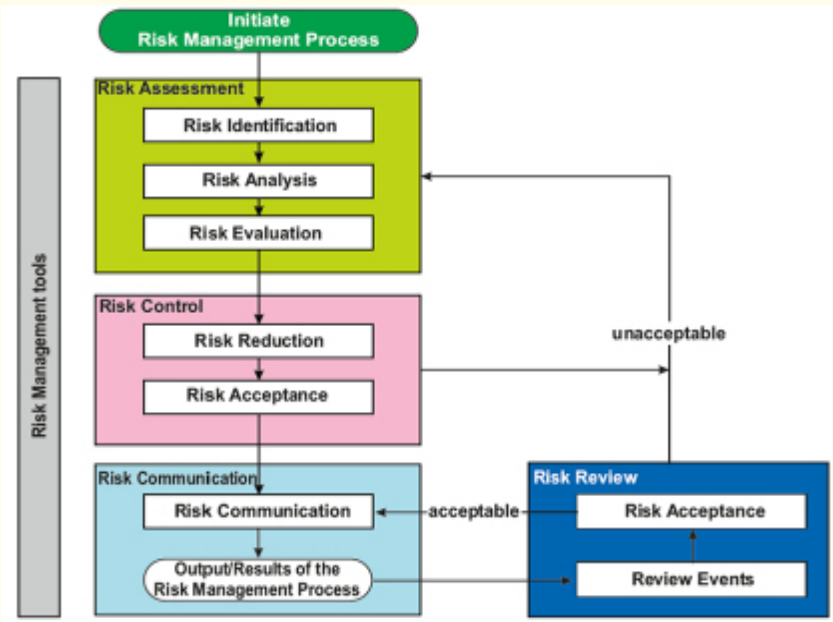

Figure 7: *ICH Q9 Quality Risk Management [1,2,9,10].*

ICH Q9 is part of the control strategy step of the life cycle approach involved in the updated process validation according to US-FDA 2011 and EMA guidelines, as shown below in figure 8.

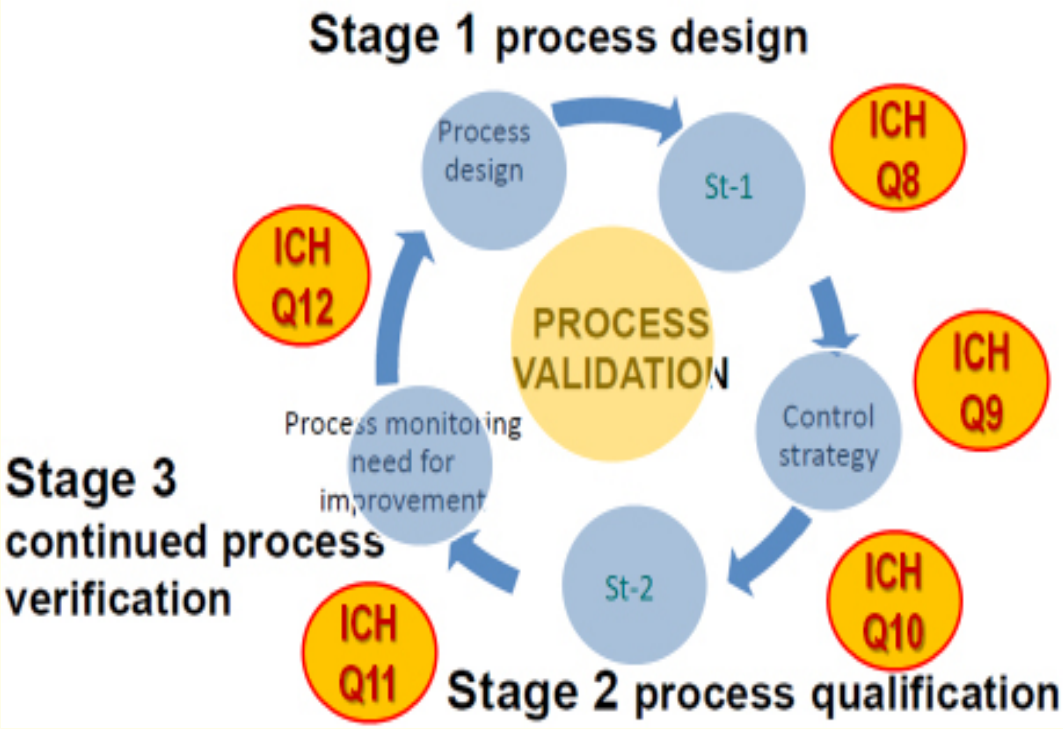

Figure 8: *ICH Q9 and Life Cycle Approach a part of updated Process Validation [3,4] (Developed by author).*

Given that 35% of the non-compliance are about controls, according to the CDER office of compliance and shown in figure 9 below, ICH Q9 is a very important part of validation [12].

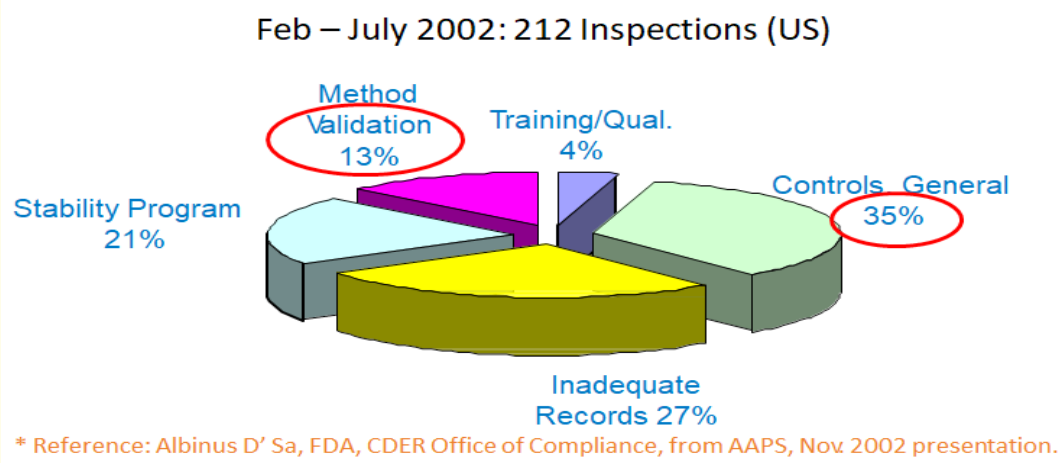

Figure 9: *ICH Q9 and Life Cycle Approach to Process Validation [1,2,5].*

More generally, impact assessment usually account for 1% of C&Q cost, which according to figure 10 has been decreasing over the years with the implementation of rationalized program, a major success.

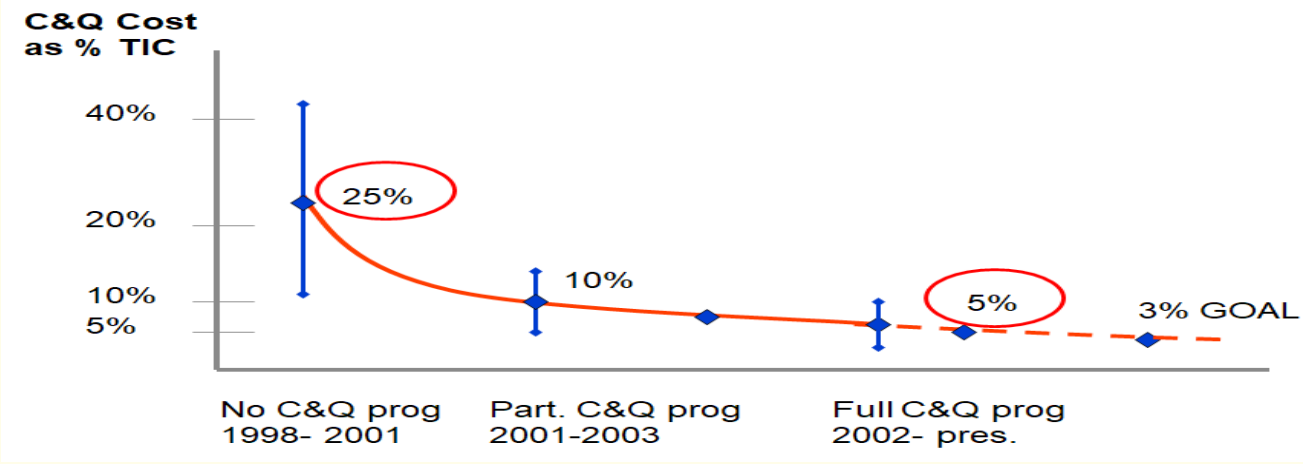

Figure 10: *Cost of Impact assessment and full C&Q [19].*

Methodology and Assumptions

Based on the FMEA methodology, there is three (3) possible defect parameters: gravity (G), occurrence probability (O) and probability of detection (D).

The gravity of an event (G), will be rated 1, 2 or 3. At level 1, there is a possible consequence on productivity but without disruption and no effect on quality. At level 2, there is a possible significant consequence that may affect the quality or system operability or that may lead to a production disruption. At level 3, there is a serious consequence that would affect the quality or operability or cause damage to the system.

The occurrence probability (O) will be rated 1, 2 or 3 according to the likelihood of the event. At level 1, it is unlikely. At level 2, it is possible. At level 3, it is usual (typical).

The probability of defection (D) will also be rated 1, 2 or 3 according to its detection possibility.

At level 1, a reliable detection device is continuously used on the system for direct parameter measurement and leads to alarm activation or automatic system safe state reconfiguration in case of the signal being over the threshold limit.

At level 2, there is a reliable detection procedure systematically used while operating the system but giving delayed information or there is a direct measuring device in line but with no alarm or no automatic system safe state reconfiguration (i.e. Ozone analysis).

At level 3: there is no reliable detection device or detection procedure part of system operation or monitoring.

The critical parameter C=D*O*G is the combination of all three parameters.

We assume the criticality level of a defect shall not exceed the value of 9 to remain acceptable. Otherwise specific preventive or monitoring actions shall be undertaken during system operation.

Case Study: Classified cleanrooms space

A case study of a risk analysis according to FMEA of a classified space is be presented here.

Other case studies such as: High Potent "HP" process, vaccine fermenter, purified water system, clean in place "CIP" system, will be presented at next publications.

Cleanrooms are very critical because they are innermost part of pharmaceutical systems in term of regulations as illustrated in figure 11.

Figure 11: *Schematic layers of regulation in a pharmaceutical plant (Developed by author).*

The table of the FMEA risk analysis of a classified space is presented below.

Furthermore, risk analysis related to some failures occurrences of air classification, HVAC operation and air change rate of the manufacturing cleanrooms is presented in table 1. FMEA approach is illustrated through these examples by setting up appropriate mitigation and risk reduction alternatives to acceptable risk levels.

Fault	Score	G	O	D	Risk Mitigation
Example #1: Upset of room air balance due to failure of control of variable air volume system on air supply.	**4**	**2.** Changes in airflow will change room particle counts and room pressures. Adverse pressure relationships may follow.	**2**. It does happen	**1.** DP alarms will detect change in room DP due to airflow change if there are no DP controls in the room to mask the problem. Daily in-operation particle monitoring should detect room count changes due to changed airflow.	Risk to patient is low: for good engineering practice, to avoid having the problem cause a loss of product; however, the use of low-quality variable air volume system boxes should be avoided. If air supply is held constant and double HEPA filters are used (primary HEPA in Air Heating Unit and terminal filters), variable air volume system boxes should not be needed. Airflow to each room will follow airflow from HVAC AHU (which is monitored for fan control); alarm low AHU airflow. Summary: risk to patient is low 'as-is.' However, changing the design (e.g., replacing CV devices with terminal HEPA) may increase confidence in the air filtration, while eliminating the potential for variable air volume system failure.
Example #2: Failure of Uni Directional Hood over Grade 5 (EU Grade A) area.	**12**	**3.** Product is exposed under the hood	**2.** Either the fan must fail to run (medium probability) or a HEPA filter must fail (low probability).	**2**. Operators may not notice a change in hood status.	Airflow switch on fan (not a motor current switch) or airflow velocity monitoring (hot wire) at the hood filter face, but not in the path to critical sites. Periodic scan testing of HEPA filters should include velocity check. Summary: 1-A hood flow monitor should reduce the risk and increase ability to detect. 2-Periodic HEPA integrity and velocity checks also are advised.
Example #3: Pressure reversals due to improper action of room pressure control damper	**18**	**3.** Pressure reversal may upset air balance in depyrogenation equipment or introduce large quantities of contamination from room to room.	**2.** Usually a small system can be tuned such that active pressure control will not adversely affect pressure relationships, but large systems may be more difficult to maintain in control. In additional, controls may reset wind up because of doors being open too long: when doors close pressure relationships reverse.	**3.** Pressure monitoring and alarm.	1-Calibrate and challenge DP monitoring periodically and ignore momentary DP changes because of doors opening and closing (validate acceptable time delay). 2-No further action will be needed, unless economics require minimal product loss due to upsets. 3-If further action is needed to avoid loss of product (GEP), use airlocks between air classes. Alarm if DP = zero through an airlock (two doors are open). Choose which. 4-DP control dampers should be "fast" and which "slow." 5-Consider eliminating automated pressure control by simplifying the air balance (no variable exhausts, constant supply, etc). Summary: if pressure monitoring can be trusted, no unacceptable product should result because of pressure control malfunction.
Example #4: Cross-contamination potential because of backflow in HVAC or residue from earlier product in air ducts or from other rooms running different product.	**6**	2. Power/HVAC failures are infrequent. Product contamination in air ducts is likely, but large amount are not expected as each room has local process exhaust to keep airborne level low	3. High if sufficient quantities of depositedmaterials break loose and contaminate other products	1	1. Put processes under protective hood or (better) inside pressurized containment device. If product is potent, consider a double wall barrier to also protect operator. Do not recirculate process exhaust from isolator. 2. Terminal HEPA filters will capture in-duct material and keep cross-contaminants from entering the room via HVAC, even if air supply power fails. Filters should be tested periodically. 3. Rooms should be held negative to building to help prevent airborne cross-contamination from other concurrent processes. 4. Optional: a central return air duct filter bank will keep AHU clean and capture airborne product closer to the room. An alternative would be return air filters at each room with volume controls (possibly DP control) to compensate for air filter loading. Summary: process containment and terminal HEPAs will do the most to reduce the risk to low, probability to low.

Table 1: *FMEA Risk Analysis for a classified space.*

Given example #1 outline that it is possible to maintain reduced risk level (G2xO2xD1) related to a given failure of control of a variable air volume system on air supply by means of an appropriate room DP monitoring and a daily in-operation particle monitoring.

Example #2 shows that a given failure of the Uni-Directional Hood (UDH) over Grade 5 area, used to protect sterile product and related aseptic activities, may impact the product quality and sterility, because the operators may not detect any change in hood status. In this case the risk of 12 is very high and was not mitigated (G3 x O2 x D2). An appropriate procedure should be developed and the involved operators trained to be aware and check continuously the proper UDH operation during the sterile activities.

Example #3 related to pressure reversals due to improper action of aseptic room pressure control damper presents a high risk of 18, which is not acceptable for depyrogenation equipment requirements and may impact the product sterility. A corrective action shall be set up to fixe and calibrate the related pressure probe and set up the appropriate alarm in the case of any pressure reversal.

Example #4 illustrate how the cross-contamination risk due to the backflow in HVAC may be mitigated to an acceptable level of 6 by setting up suitable alternative, such as operation under contained equipment (isolators, glove-box, installation of terminal HEPA filters, negative differential pressure in this room, …).

Through given examples, we may mitigate cross contamination and poor product quality risks by means of deep understanding the risk origin and process. The alternatives taken in place were very simple, not expensive, documented and effective. Therefore, initial risks were reduced to acceptable levels and low impact on product quality.

Conclusion

Regulatory agencies, such as FDA, HPFBI, EMEA, or others, request significant challenges to manufacturers, engineering professionals and equipment suppliers to meet c-GMP regulations as well as other standards, codes, regulations and laws throughout the life cycle of Biopharmaceutical facility projects (design, construction, commissioning and validation).

Complete structured documentation, adequate approaches such as 'Risk Assessment, Management, Analysis, and Mitigation', 'Integrated Project Management', 'Integrated Team Model', and 'Enhanced Design Review', as well as 'Good Engineering Practices (GEP)' should be implemented to meet the above-mentioned c-GMP regulatory and standards, and to ensure efficient and reliable new construction or revamping of biopharmaceutical plants, thus reducing schedule time and costs.

A case study using the Risk Analysis approach, is presented to illustrate how the GEP alternatives could reduce costs and related cross contamination risks of classified rooms, through the optimization of the requirements of critical equipment and instruments, while still meeting the performance criteria and the constraints set out by the regulatory requirements such as c-GMP, USP & ISPE standards, as well as by the client's performance, installation and operation URS. This risk mitigation approach based on updated regulations requirements should all the facilities and process validation life cycle activities to ensure reduced operation costs, reduced risks on product quality and operators.

Additional case studies such as: High Potent "HP" process, vaccine fermenter, purified water system, clean in place "CIP" system, will be presented and commented at next publications.

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