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Case Study

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

Aziz Chraibi* pbe@pbe-expert.com +1.450-600-0790 x253

Engineering and Compliance Director, Health Canada and MAPAQ Expert, CPMT Training Company Agreement, Canada

***Corresponding Author:** Aziz Chraibi, Engineering and Compliance Director, Health Canada and MAPAQ Expert, CPMT Training Com-

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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).

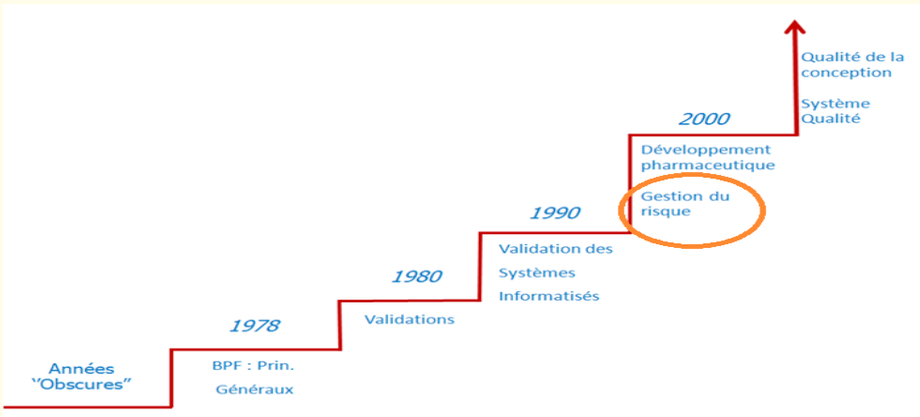

Figure 1: *History of the GMP [2].*

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).

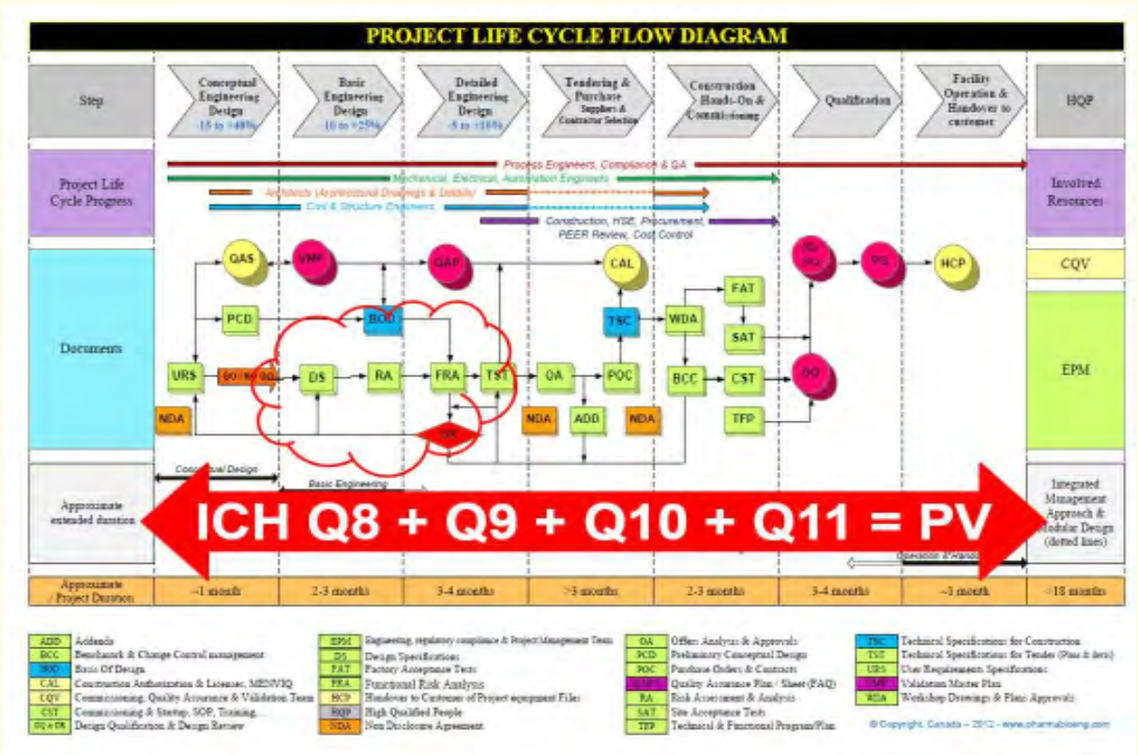

Figure 2: *ICH Q9 Quality Risk Management applied to pharmaceutical industries (Developed by author).*

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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pbe@pbe-expert.com +1.450-600-0790 x253