Pharmaceutical Quality by Design: a question of cycles.

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This short article aims to situate QbD in relation to other quality control approaches by analyzing and comparing their operating cycles.

1 Cycle of the Scientific Method.

In the ICH Q8 guideline (ICH Harmonised Tripartite Guideline, 2009), the "Quality by Design" approach is defined as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management". The term "sound science" can raise questions. How is this approach scientific ?

From Aristotle to some 17th century philosophers such as René Descartes and Francis Bacon, the scientific process is commonly described as a knowledge elaboration process based on a cycle endowed with at least four stages (Figure 1-1): the analysis of a problem, the formulation of the hypotheses to answer them, the experimental design and the evaluation of the hypotheses with regard to the results of these experiments (Bunge, 1967; Assar, 2015).

2 Shewhart's cycle of Quality.

The notion of quality control appeared in 1924 under the leadership of W. A. Shewhart (Best and Neuhauser, 2006). The latter is also recognized as the author of the quality cycle: Plan-Do-Check-Act, which will be popularized in the 1950s by W. E. Deming and used after in the Lean manufacturing approach of quality management. The first "Plan" step consists in planning or preparing what you want to achieve, then the "Do" step carries out the tests before evaluating the data in the "Check" phase to potentially react in the step "Act" also called "Adjust". This cycle is still used, in particular in the good practice for clinical trials based on the Quality by Design approach supported by the Clinical Trials Transformation Initiative[1] (Tenaerts et al., 2014).

3 Six Sigma cycle.

In the 1980s, another approach to quality control emerged under the name "Six-Sigma" (Bendell, 2006). The latter is also based on a cycle entitled: DMAIC for Define, Measure, Analyze, Improve and Control. If the first and last steps are equivalent to the "Plan" and "Adjust" phases of the previous cycle, the "Measure" and "Control" actions propose here to define the output and input variables of the system before carrying out experiments and analyze the collected data in the "Improve" step.

4 Design for Six Sigma cycle.

In the Design for Six-Sigma paradigm, dedicated to the development of new products(Chowdhury, 2003), at least six variants of cycle exist(Shahin, 2008), such as for example DMADV (Define, Measure, Analyze , Design, Verify), IDOV (identify, design, optimize and verify) or IDEAS (Identify, Design, Evaluate, Assure, Scale-up). Despite these naming differences, all versions of DFSS share fundamental strategies and tools

[1] https://www.ctti-clinicaltrials.org/

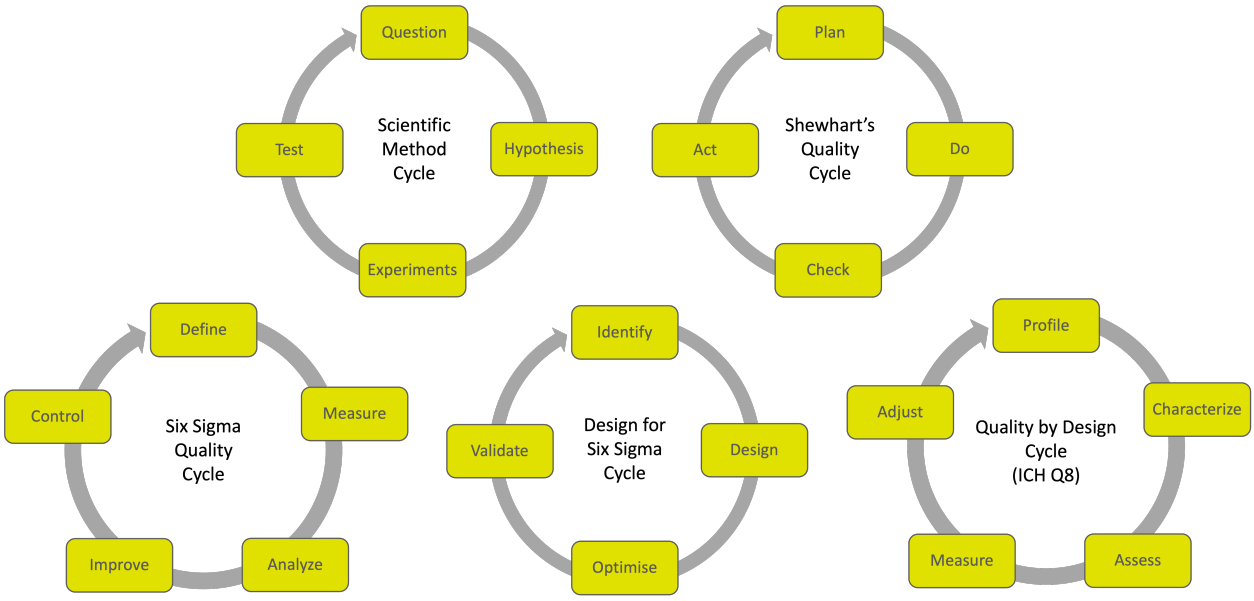

Figure 1: *Methods and Contributors of Quality Science*

that promote a common goal: to create a data-driven product development culture that efficiently produces winning products(Shahin, 2008).

5 Pharmaceutical QbD cycle.

The Pharmaceutical QbD approach, resulting from the ICH Q8 (R2) does not have an official cycle either, but there is a structure similar to the previous one which can be summarized in five steps:

1. Profile: defining of the main features of the desired product.
2. Characterize: identifying the input-output variables (causes and effects) of the product and its manufacturing process.
3. Assess: determining cause and effect relationships to assess risk regions (design space). This step can itself be broken down into two parts: one to design the experiments and the other to analyze the experimental data.
4. Measure: measuring the critical variables of the process using an adapted measurement technology online.
5. Adjust: automatically correct and adjust some input variables to stay within the quality region.

6 Conclusion

Whatever the differences between the cycles, they are still minor. All quality approaches are in fact inspired by the cycle of the scientific method in which the investigated question is that of the evaluation and control of non-quality risks.

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