Pharmaceutical Quality by Design: the Origins.

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This short and popular article aims to recall the important dates which marked the emergence of the pharmaceutical Quality by Design good practice.

At the very beginning there were Deming and Fisher... Most of the quality control procedures rely on statistical tools and in particular on the design of experiments (DoE). It is therefore natural to begin by citing R. A. Fisher, the “father” of modern statistics and experimental design (Fisher, 1936). But the concept of "quality control" was introduced a few years earlier by W. A. Shewhart (Shewhart, 1931). The latter notably introduced tools for statistical process control such as the control charts proposed for the first time in 1924.

And came Deming and Juran ... He 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. The latter collaborated a lot in the post-war years in Japan with J. J. Duran, inventor of the Pareto Diagram, also a specialist in quality control and at the origin of the name "Quality by Design" (Juran, 1992).

The Japonese school... Both have made it possible to create in Japan a dynamic centered on quality with on the one hand academics such as K. Ishikawa, inventor of the 5M diagram and G. Taguchi who democratized the methodology of design of experiments, and on the other hand manufacturers such as T. Ohno and E. Toyoda, within the Toyota automobile company, which will be one of the pioneering companies in terms of quality by design.

Lean & Six-Sigma. A few years later, this proactive approach of quality gave rise to two paradigms: (1) the Lean Manufacturing carried by J. Krafcik (Krafcik, 1988) by restructuring the concept of "muda" brought by the Japanese a few years earlier, and (2) the Six-Sigma approach based on the “Define, Measure, Analyze, Improve, Control” cycle and initiated by the Motorola company. These two trends ultimately gave rise to a synthesis entitled Lean Six Sigma in the early 2000s.

Design for Six Sigma. All these methods only address quality of the manufacturing process but did not consider the development of innovative products. The "Design for Six Sigma" paradigm was proposed in the early 2000s to fill this gap. As for all the previous approaches, it is based on a cycle made up of four stages: “identify, design, optimize and verify”.

and Pharmaceutical QbD. At that time, FDA officials drew on all this work to reform the way drugs were developed. A founding paper was published in 2004 (Department of Health and Human Services, 2004), which will lead to the international directive: ICH Q8 and the official birth of the pharmaceutical "Quality by Design", revised in 2009 (ICH Harmonised Tripartite Guideline, 2009). It includes a circular methodological structure and statistical risk assessment tools to ultimately reduce development delays and costs while optimizing the quality of pharmaceuticals since earlier steps of development. Today the pharmaceutical QbD concerns not only the preclinical development of drugs (ICH Q8 to Q11) but also that of new analytical methods (ICH Q14) as well as the implementation of good clinical practice (ICH E6 and

Figure 1: *Methods and Contributors of Quality Science*

E8).

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