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Quality-by-design of nanopharmaceuticals – a state of the art

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Abstract

Pharmaceutical Quality-by-Design is a risk-based approach of drug development relying on the understanding of both the product and the process. This state of the art analyzes 24 studies published during the last ten years. A risk modeling of the nanomaterial formulation and manufacturing is firstly presented. After a brief history of the QbD approach, its basic components are recalled in a second part. The most critical material attributes, process parameters, quality variables and measurement technologies are reviewed. Specific deficiencies are also emphasized such as the absence of prior risk assessment, production scale-up, process analytical technology and control strategy. Finally, perspectives and development priorities are drawn to improve the implementation of this integrative approach of quality and safety in nanomedicine.

Key words: Nanomedicine; Quality-by-design; Design of experiments

In a few years, the control of quality and safety of drugs containing nano-engineered materials has become a major issue.[1] The application of nanotechnology and nanomaterials to drugs concern a large spectrum of health challenges such as the increase of bioavailability, the change of biodistribution, the increase of drug action, the stabilization of degradable drugs and the targeted delivery of drugs. But the potential risks associated with those non-biological complex drugs are much more difficult to be assessed and we crucially need an integrative approach to address that issue.

To identify, analyze and control all causes that could alter quality and safety of a new drug, the United States Food and Drug Administration proposed in 2000 a risk-based approach of drug engineering, finally entitled *Quality-by-Design* in 2008 by the International Council for Harmonization of technical requirements for pharmaceuticals for human use (ICH).[1] Conversely to traditional approaches that only test the quality of product, QbD fundamentally aims at building quality and safety from the first design steps.[2] Up to now, no review has been conducted to deliver a comprehensive assessment of the major advantages and limits of QbD in nanomedicine. The only review proposed by Pillage et al. was focused on nasal administration of nano-sized formulations.[3] Nevertheless, during the last 10 years, more than 20 studies have applied the QbD recommendations to the formulation and the production of nanoparticles for drug delivery applications.

In this state of the art, we investigate a multi-parametric analysis of those studies and address several questions such as the ranking of the most critical factors, responses and technologies based on these 10 years of experience. The second objective is to outline some important deficiencies and inadequacies concerning the current implementation of QbD in nanomedicine.

This review is organized as follows. We firstly examine the reasons explaining why the quality and safety of nano-engineered drugs are more difficult to be controlled. A historical background of QbD is then recalled and its basic steps and components are explained. The review analysis is presented in section 5 before drawing conclusions and perspectives.

Nanomaterial formulation and manufacturing risks

There exists a wide variety of factors able to cause variations during the design and production of nanopharmaceuticals. Figure 1

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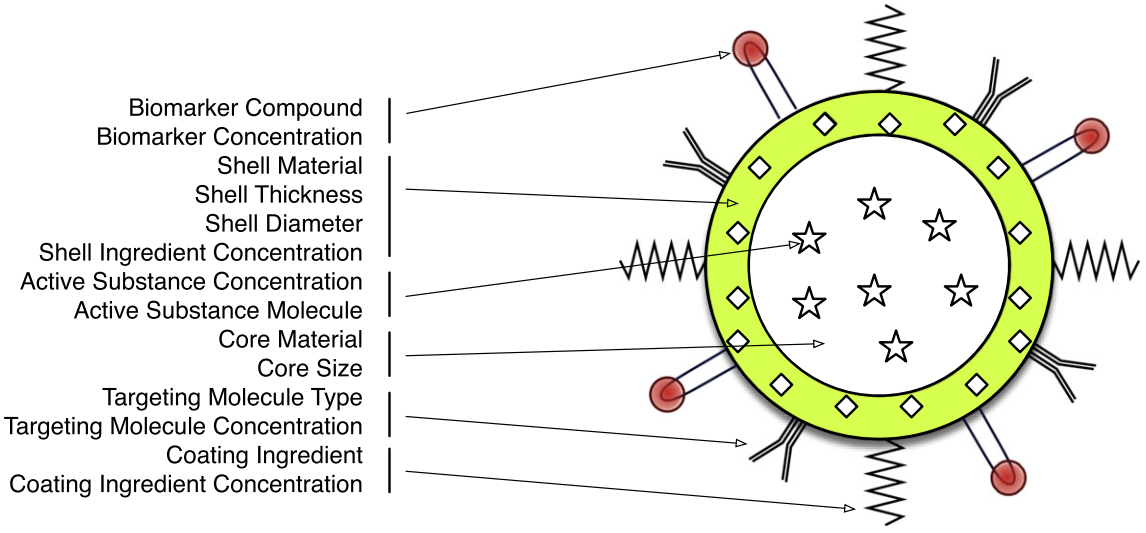

Figure 1. Generic prototype of an engineered multifunctional nanostructure.

presents the generic composition of an engineered multifunctional nanostructure. Let us denote X_d the number of ingredients. Each of them can be characterized by some design parameters such as the type of material, the size and the thickness of the shell, *etc.* Let us suppose the number Y_d of those parameters is the same for all the ingredients and each design parameter can take Z_d values. Finally, the total number N_d of possible formulations for the nanoparticle is given by:

$$N_d = Z_d^{X_d \cdot Y_d} \tag{1}$$

This combinatorial explosion problem also occurs for the production part, as illustrated in Fig. 2. Let X_p be the number of production units, Y_p: the number of controlled variable for each unit and Z_p: the number of tested values for each controlled variable. Then, the total number N_p of possible products for the nanoparticle is defined by:

$$N_p = Z_p^{X_p \cdot Y_p} \tag{2}$$

Finally, the complete number of possibilities over the design-manufacturing cycle is equal to $N = N_d \cdot N_p$. For instance, let us consider a nanoparticle composed of $X_d = 7$ components characterized by $Y_d = 2$ parameters taking each $Z_d = 3$ value. This nanoparticle is produced by a manufacturing process composed of $X_p = 6$ units controlled by $Y_p = 3$ variables taking each $Z_p = 3$ value. Finally, there can be about $400 \cdot 10^6$ different nanoproducts (NP) to be assessed. For each of them, testing quality and safety consists in carrying out two statistical tests:

$$\begin{cases} H_0: & \text{NP is not efficient} \\ H_1: & \text{NP is efficient} \end{cases} \& \begin{cases} H'_0: & \text{NP is not toxic} \\ H'_1 & \text{NP is toxic,} \end{cases} \tag{3}$$

A positive candidate is defined thereafter as a NP complying with H_1 and H'_0. Each test is coupled with two risks: false positive and false negative nanoproducts. In classical drug development, for about 10^4 identified molecules there is finally only one drug authorized to be placed on the market. In other terms, the risk for a candidate nanoproduct to be false positive is much more important than to be false negative. Unfortunately, testing all the nanoproducts is clearly impossible in practice and the challenge consists in selecting as soon as possible during the development process the most promising nanostructure that minimizes the risks of bad decisions in the two previous tests. Quality-by-design is a risk-based drug development approach addressing this issue.

Historical background of quality-by-design

Before QbD

Even though QbD is often regarded as a new drug development paradigm in the pharmaceutical industry, it is in reality the inheritance of the experience gained from manufacturing industry. In the 1970s, J.M. Juran created the QbD concept and popularized it in the 1990s.[4] In this book, he emphasizes the reasons and proposes a methodology to control quality in manufacturing processes. Nevertheless, neither is QbD the first approach aiming at controlling quality in systems engineering. The *Attribute-Driven Concurrent Engineering* method,[5] the *Total Quality Management,*[6] the *Lean Management*[7] and the *Design for Six Sigma*[8] have all proposed guidelines to facilitate the implementation of quality management in industry. All those contributions generally use common graphical, scoring and statistical tools such as the Ishikawa and Pareto diagrams, Failure Mode Effect Analysis, Design of Experiments and Statistical Process Control.

Genesis of pharmaceutical QbD

Juran did not consider drugs or medical devices in his book, and the United States Food and Drug Administration (FDA) was the first regulatory agency in 2004 to make the first steps towards integrating the QbD concept into *current good manufacturing practices* (cGMPs) to update the regulation of pharmaceutical