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Review

Application of quality by design in the current drug development

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ABSTRACT

Quality by Test was the only way to guarantee quality of drug products before FDA launched current Good Manufacturing Practice. To clearly understand the manufacture processes, FDA generalized Quality by Design (QbD) in the field of pharmacy, which is based on the thorough understanding of how materials and process parameters affect the quality profile of final products. The application of QbD in drug formulation and process design is based on a good understanding of the sources of variability and the manufacture process. In this paper, the basic knowledge of QbD, the elements of QbD, steps and tools for QbD implementation in pharmaceutics field, including risk assessment, design of experiment, and process analytical technology (PAT), are introduced briefly. Moreover, the concrete applications of QbD in various pharmaceutical related unit operations are summarized and presented.

1. Introduction

While medicine is well known as special goods, the development of pharmaceutical industry is based on innovation and manufacturing. However, there are lots of complaints from pharmaceutical industry about the strict rules. In current quality by test (QbT) system (Fig. 1a), product quality is ensured by following a sequence of steps, including raw material testing, fixed drug product manufacturing process, and end product testing. It is only when all the specifications of the FDA or other standards are complied with that the materials can be used for manufacturing or come into market. If not, they need to be reprocessed. Root causes for failure are usually not well understood due to the poor process understanding and uncertainty about how characteristics of substances impacts target product profile. As a result, the manufacturers have to restart the procedure until the root causes of failure are understood and addressed or FDA approves supplements to revise (e.g., widen) the acceptance criteria to pass the previously failed batches [1]. This causes poor cost-efficiency and product variation, which may lead to poor drug safety.

Fortunately, with the development of the concept "Quality by Design (QbD)", there will be a significant transformation in pharmaceutical quality regulation, from an empirical process to a more scientific and risk-based approach. QbD (Fig. 1b) is a systematic risk-based, proactive approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management. Comparison between QbT and QbD procedures is shown in Fig. 1.

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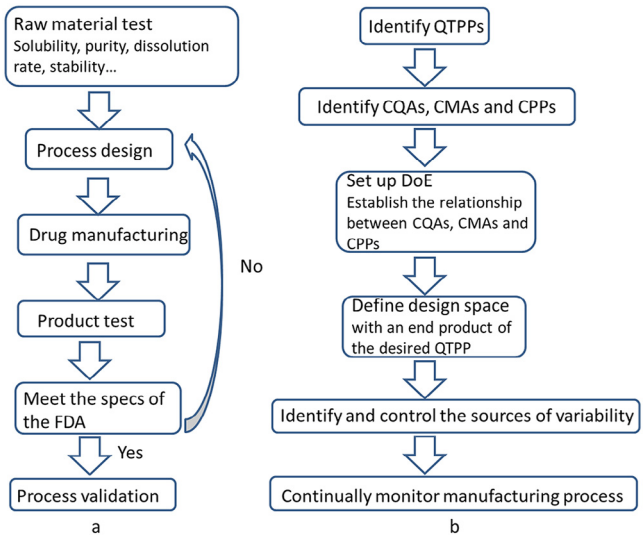

Fig. 1 – Comparison between QbT (a) and QbD (b). (QbT: quality by test; QbD: quality by design; QTPP: quality target product profile; CQA: critical quality attributes; CMA: critical material attributes; CPP: critical process parameters; DoE: design of experiments).

However, although there are some reviews about the theory of QbD [1,2], the papers about application of different analytical tools, such as Raman spectroscopy and near-infrared spectroscopy, in research and development of pharmaceutical dosage forms are also available [3–6]. References about the application of different analytical methods as monitoring tools in the framework of QbD are not available to the best of our knowledge. Nevertheless, good implementation of QbD in formulation and process design in pharmaceutical field is highly dependent on a good understanding of the sources of variability and the manufacture process, and Process Analytical Technology (PAT) is an indispensible tool in the QbD system. Therefore, the objective of this paper is to provide a whole picture about the application of QbD in pharmaceutical field by using PAT as a tool. Except for the basic knowledge of QbD, the elements of QbD, steps and tools for implementation of QbD in the field of pharmaceutics, and the applications of QbD in various dosage forms, which are summarized and presented as guidance. Moreover, PAT tools applied in different manufacturing processes in the QbD system have been summarized to provide an insight in the continuous manufacturing process.

2. Understanding pharmaceutical QbD

To overcome the limitation of GMP, FDA launched cGMP in 2002 [7,8]. cGMP places emphasis on the "software" during the manufacturing, namely management level, and specifies staff's responsibility strictly and clearly. In contrast, GMP attaches a great importance on the qualification and training details of the staff instead of their duties, and these relatively lower requirements are still broadly used in many developing countries. After the cGMP was carried out, there is still another problem, that is, in comparison with other industries, such as automobile, aircraft and electronic industries, the specification of pharmaceutical industry is much more rigid and fixed. However, it is almost impossible to keep all the parameters of the whole conditions constant and the environment may vary in small degrees inevitably. Then, the problem is in the approval documents for a new product to be handed over to FDA, the company can only write fixed number in the report, as 'details' and 'the authenticity of the process' are quite critical in cGMP, it may happen that batches of products fail to meet the rigid specifications. To solve this problem, the International Conference on Harmonization (ICH) and FDA began to learn from the other industries, and QbD was introduced into the chemical manufacturing control (CMC) review pilot program in 2004 with the objective of improving pharmaceutical drug quality and safety to achieve a desired state for pharmaceutical manufacturing on the basis of scientific and engineering knowledge. The function of QbD, Design Space and real-time release had been evaluated through the CMC project. Years later, a series of guidelines was published by ICH: ICH Q8 Pharmaceutical Development [9], ICH Q9 Quality Risk Management [10], ICH Q10 Pharmaceutical Quality System [11], and the ICH Q11 Development and Manufacture of Drug Substances [12].

Quality by Design (QbD) is defined in the ICH Q8 guideline 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' [9], which is in accordance with FDA's current drug quality system ideology of 'quality cannot be tested into products; it should be built-in or should be by design.' [13]

2.1. *Elements of QbD*

There are several statements about the elements of QbD, the most widely accepted is that, QbD consists of the following parameters [2,9]:

Quality Target Product Profile (QTPP): including dosage form, delivery systems, dosage strength(s), etc. It is a prospective summary of quality characteristics of a drug product to be achieved, taking into account dosage strength(s) and container closure system of the drug product, together with the attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) and drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product.

Critical Quality Attributes (CQAs): including physical, chemical, biological, or microbiological properties or characteristics of an output material including finished drug product. Potential drug product CQAs derived from the QTPP and/or prior knowledge are used to guide the product and process development and they should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Critical Material Attributes (CMAs): including physical, chemical, biological, or microbiological properties or characteristics of an input material. CMAs should be within an appropriate limit, range, or distribution to ensure the desired quality of that drug substance, excipient, or in-process material.

Critical Process Parameters (CPPs): parameters monitored before or in process that influence the appearance, impurity, and yield of final product significantly.