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Development of Control Strategy is Necessary to Ensure the Quality of Drug Products

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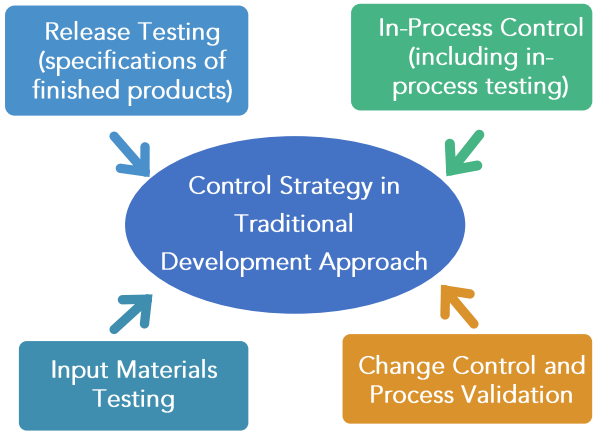
1 Introduction

The Quality by Design concepts

Moheb M. Nasr, CDER/FDA,2010

Drug quality control refers to a new drug, which is proved to be effective and less toxic through pharmacological screening and animal experiments. when it is recommended to clinical trial, it is necessary to develop certain specifications and standards for the quality of new drugs and control them. According to the ICH Q10 guideline, Control Strategy is a set of planned controls, derived from current product and processes understanding that assures process performance and product quality. Control Strategy must also take full account of patients and products, while showing how control measures ensure product safety, efficacy and quality.

2 Some Regulation About Control Strategy

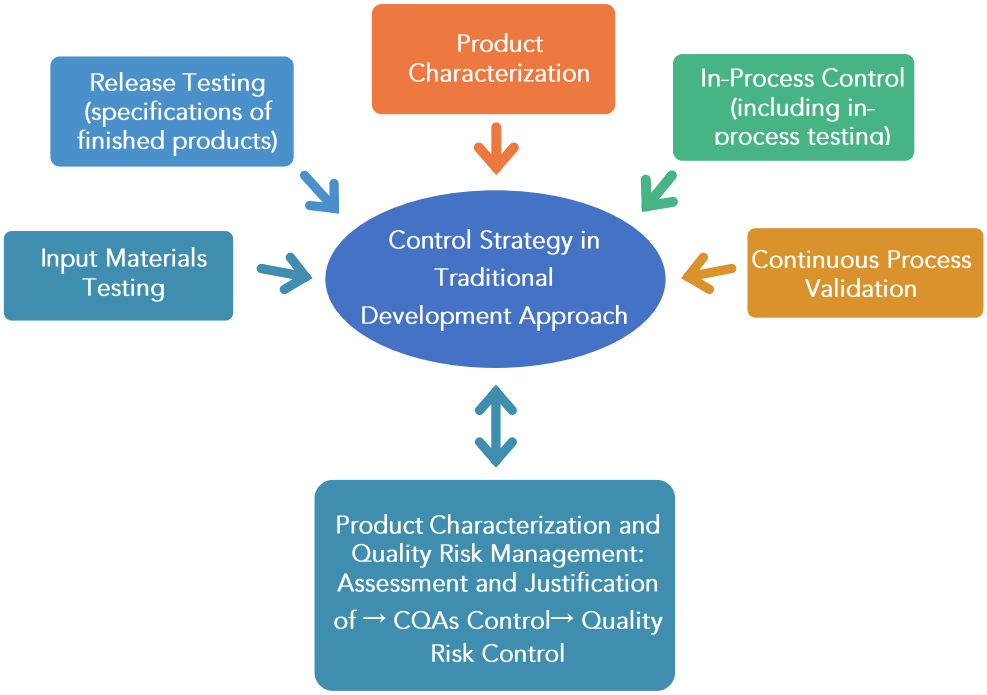


An example of Control Strategy in a traditional approach of development

With the increasing complexity of the process of new drug products, it is necessary to improve the Control Strategy to explain and prove how the product quality is managed. The necessity of improving the Control Strategy is emphasized in ICH guidelines Q8, Q9, Q10, Q11 and the reflections around their concrete implementation. ICH Q8 (R2) introduces the concept of Control Strategy and its relationship with product key attribute control. It is mentioned in the guideline "the process control strategies that provide process adjustment capabilities to ensure control of all critical attributes should be described."

The principle of this concept is further elaborated in ICH Q10, defining the control strategy as “a planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.”

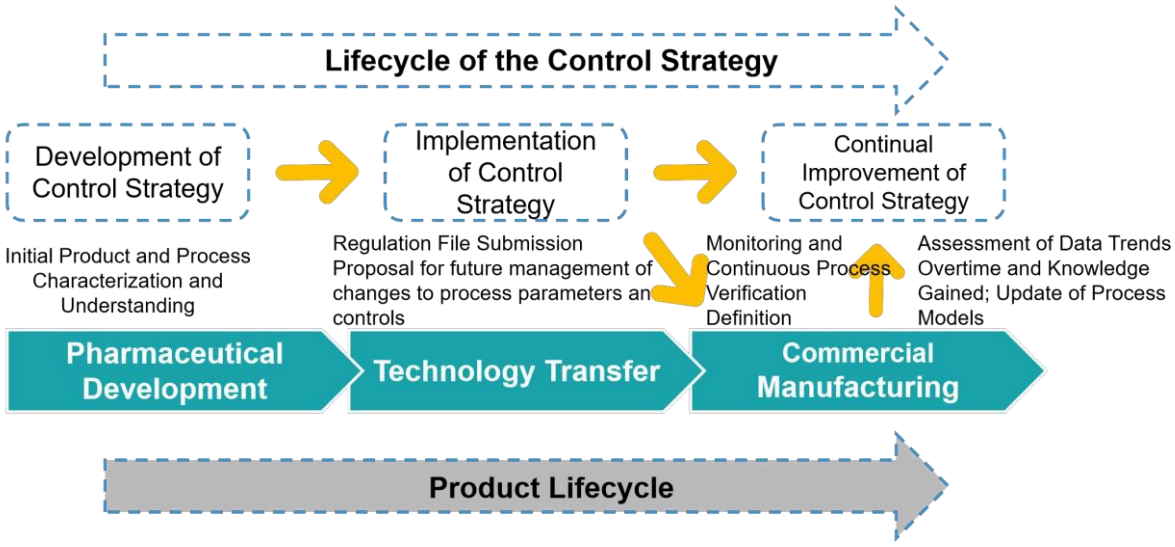
The ICH Q11 extends the application of Quality by Design concepts to drug substances. It clarifies the possibility of regulatory flexibility and enables Control Strategy to play a central role. ICHQ11 focuses on two approaches to pharmaceutical development: the "traditional" approach and the "enhanced" approach. The guide emphasizes that the combination of these two methods is possible.



An example of a Control Strategy in an enhanced approach of development (QbD)

3 Control Strategy is the Keystone of Product Lifecycle

According to ICH guidelines Q8, Q9, Q10 and Q11, the lifecycle of Control Strategy is supported by pharmaceutical development (QbD and initial knowledge management), Quality Risk Management (QRM), and Pharmaceutical Quality System (PQS). When new product/process knowledge is gained during manufacturing of the commercial batches, the Control Strategy must be improved. This improvement helps to maintain the link between control strategy and product/process understanding. The knowledge gained in the product life cycle about product/process components can continuously improve and maintain the Control Strategy, especially by updating the process model to adapt to the actual risks and variability encountered in the manufacturing process.



4 How to Optimize the Pharmaceutical Quality Control Strategy?

Based on good advanced process control (APC) concepts, Control Strategy can be divided into two categories:

- **Retrospective, feedback control** – These systems are based on monitoring quality attributes of the products produced and parameters of the manufacturing processes to provide corrective action to assure product quality.

- **Prospective, feedforward control** – Sometimes called anticipatory control, prospective control systems prevent upsets or poor performance by building intrinsically high-performing control strategies that take corrective action before upsets enter the process. For procedural control systems, the procedures can be prospectively designed, using quality by design methods.

Strategies for the pharmaceutical industry to improve product quality may include, the first strategy may be to increase the frequency of vendor inspections in the industry, using internal quality control (QC) procedures to check suppliers to ensure compliance with necessary supply agreements and compliance with appropriate manufacturing practices, including GMPs. The second strategy is consistent with good APC principles, and the most effective industry and regulatory control plan should be a coordinated effort to implement a cutting-edge strategy to ensure that suppliers have developed the necessary quality management system (QMS) programs before manufacturing materials for use. In the actual production process, it is necessary to understand the basic advantages and disadvantages of various control strategies and implementing appropriate methods, which can significantly improve product quality.

5 Quality Control Strategy of Modern Laboratory

As for how to design a good quality control (QC) strategy to meet the needs of the laboratory, most laboratory tests are carried out in batches. When batch testings are used in the laboratory, defining a QC strategy must answer two questions: how many QC samples should be included in the batch, and the QC rules to be applied to the results of the QC sample results to determine whether the batch is acceptable. The traditional method of designing laboratory QC strategy focuses on finding the answers to these two questions.

In the design of laboratory Quality Control Strategy, "determining when to test QC samples" is one of the hot topics at present. QC testings should be performed when events that may adversely affect the testing process occur (such as reagent batch number change, calibration, etc.), and if these events are planned and scheduled, QC should be performed again before and after the event.

6 Control Strategy of Impurities

According to the requirements of CTD submission data and the research concept of Quality by Design (QbD), the control of impurities can basically be divided into source control, process control and terminal

control. There are many indicators to be controlled, such as properties, crystal form, melting point, specific curl, isomers, related substances, residual solvents, chlorides, sulfates, pH values, solution color and clarity, burning residues, heavy metals, element impurities, genotoxic impurities, etc. In the test of each indicator, the control goal (what to test), the control method (how to measure) and the control limit (how to set the control standard) need to be considered.

- Source control includes the control of starting materials and excipients: The quality of the starting material often has a great influence on the synthesis process and the quality of the final product, especially when the chemical structure of the starting material is very complex or the synthetic route of the product is short; In the control of excipients, the research on the internal control standards has always been very important. For some drug products, the organic or inorganic impurities in the excipients may have an important impact on the product quality.

- The process control includes the control of production process and intermediate: the impurities caused by illumination, oxidation and hydrolysis in the pharmaceutical preparation production process should be analyzed and controlled in combination with the process. The control method and parameters should be determined according to the process parameters which are under the large production scale, and can ensure that the method is effective and reproducible. For key intermediates, if different scales and multiple batches of test results show that there are starting materials, by-products or degradation products in the intermediates., and the content of these impurities is large or may affect the next reaction, then, it should be studied and controlled in detail in the quality standard of the intermediate.

- Terminal control refers to the control in the final product. Usually, impurity control in the final product is to develop one or more reasonable and feasible impurity inspection methods and limits.

7 Quality Control Strategy for Starting Materials of APIs

The quality control of starting materials has always played an important role in the technical requirements of API registration. ICH Q7 defines the API starting material as "a raw material, intermediate or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API." In the process of API preparation process research, the quality of starting materials and solvents is the basis of API preparation research, which is directly related to the quality of the final product and the stability of the process, and can provide relevant impurity information for quality research.

It is also designed to the problems of labor protection and safety in industrial production. It is required that the quality of starting materials should be stable and controllable, and there should be sources, standards and inspection reports from suppliers. If necessary, internal control standards should be established according to the requirements of the preparation process. The basic principle of its internal control is that qualified API can be obtained without affecting the quality of API.

Key issues to be considered when developing internal control standards for starting materials:

- It is necessary to have a clear description of the name, chemical structure, physical and chemical properties.
- It is necessary to have specific sources, including manufacturers and simple preparation processes.
- A quantitative or qualitative description of the content and impurities (including toxic solvents).

8 Steps to Be Taken to Establish A Pharma Manufacturing Control Strategy With Considering the Patient

- **Defines the Quality Target Product Profile (QTPP)**

  Patients or healthcare professionals will provide comments on how to ideally design products. These comments are outlined according to the quality characteristics in the QTPP related to quality, safety and effectiveness, for example, consider route of administration, dosage forms, bioavailability and stability.

- **Identify the Critical Quality Attribute (CQAs)**

  Once the QTPP is defined, the potential CQA of the drug must be identified and graded by severity in order to study and control product characteristics that affect product quality. Then the proposed manufacturing process steps and the materials used are evaluated to evaluate their impact on different CQAs.

- **An Evaluation Using Scientific And Risk-based Principles**

  After identifying the CQAs, each identified process step needs to be evaluated using scientific and risk-based principles (process parameters may have a potential impact on a CQA). In order to determine the risk, it can be combined with a facility-dependent evaluation of the possibility of failure and the probability of detecting failure modes.

The development of drug product Control Strategy is a structured and iterative activity, involving a multi-disciplinary team of experts, which may include experts in formulation development, API development, process development, analytical development, quality control, quality assurance, regulatory affairs, etc., in order to connect pharmaceutical development with the manufacturing process and engineering controls of process equipment.

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