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Review Article

Theme: Sterile Products: Advances and Challenges in Formulation, Manufacturing, Devices and Regulatory Aspects
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Quality by Design and Process Analytical Technology for Sterile Products—Where Are We Now?

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Abstract. Quality by design (QbD) and process analytical technology (PAT) have become priorities for the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). Numerous recent initiatives within CDER and FDA have had the objective of encouraging the pharmaceutical industry to utilize QbD and PAT in their product development and manufacturing processes. Although sterile products may be a minority compared to non-sterile dosage forms (*e.g.*, solid orals), their absolute requirement for sterility make design and control of the manufacturing processes extremely critical. This emphasis on the manufacturing process makes the sterile drug product an obvious target for QbD and PAT. Although the FDA encourages QbD submissions, the utilization of QbD and PAT for sterile products so far is still limited. This paper will examine the present state of QbD and PAT for sterile products and review some examples currently in use. Additional potential applications of QbD and PAT for sterile product development and manufacturing will also be discussed.

KEY WORDS: process analytical technology (PAT); quality by design (QbD); sterile product.

INTRODUCTION

Quality by design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding, based on sound science and quality risk management (1). Process analytical technology (PAT) is an important tool for the implementation of QbD; it can be utilized to monitor and control the manufacturing process with appropriate feed-forward and feed-back controls. PAT can also facilitate the tracking and trending of the process operations to support post-approval continual improvement efforts.

Food and Drug Administration (FDA) started to publicly discuss PAT at a Pharmaceutical Science Advisory Committee meeting in July 2001 and eventually led to the release of the FDA's PAT Guidance in 2004 (2). As the discussions about PAT were occurring, FDA's Center for Drug Evaluation and Research (CDER) was starting the Pharmaceutical Quality for the 21st Century Initiative (3). The Pharmaceutical Quality for the 21st Century Initiative encompassed both the fundamental concepts of QbD and PAT. At present, QbD continues to be a major goal in CDER's ongoing drug quality initiatives, and implementation is moving forward in CDER's Office of Pharmaceutical Science. "Technologies such as PAT are crucial to implementing the knowledge gained from quality by design in a meaningful and efficient way …", as CDER director Janet Woodcock said in a joint FDA/University of Rhode Island College of Pharmacy workshop in Bethesda, MD on May 11, 2010, "so FDA encourages adoption of these technologies for production processes" (Fig. 1).

Implementation of a QbD approach to pharmaceutical development utilizes modern scientific and quality risk management principles and quality control strategies based on product and process understanding. It is a way for the industry to share development and manufacturing information with regulators leading to regulatory decisions based on scientific and risk management principles. A QbD approach should provide a higher level of assurance of product quality, cost savings, and improved efficiency for industry and facilitate more efficient regulatory oversight.

To provide the industry with an opportunity to submit chemistry, manufacturing and controls information demonstrating QbD and to enable FDA to implement new QbD concepts, FDA has initiated several QbD pilot programs with the pharmaceutical industry. A pilot program for pharmaceuticals was recently completed by the Office of New Drug Quality Assessment in the Office of Pharmaceutical Science in CDER. To continue the QbD initiatives, the Office of New Drug Quality Assessment is now accepting QbD applications outside of a pilot program. A biopharmaceutical pilot program is currently proceeding in the Office of Biotechnology Products in CDER. The Office of Generic Drugs in

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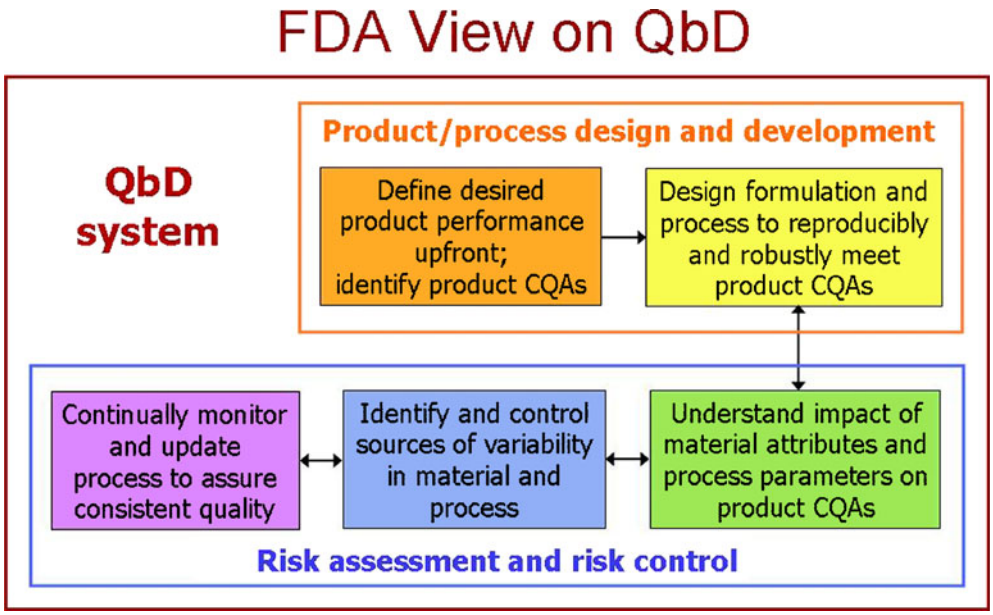

Fig. 1. A current FDA view of QbD

CDER implemented a program called the question-based review (QbR) for its chemistry, manufacturing, and controls evaluation of abbreviated new drug applications. This new QbR system incorporates some elements of QbD (4). It is a concrete and practical implementation of some underlying concepts and principles outlined by the FDA's Pharmaceutical Quality for the 21st Century and QbD initiatives (5). At present, the use of a comprehensive QbD approach for sterile drug products has been limited. Although submissions with components of a QbD approach have been submitted to the agency, a comprehensive QbD approach from product development to manufacture of the finished product has not been made available. This paper will examine some current approaches for QbD and PAT for sterile pharmaceuticals.

In order to provide a framework for a discussion of the current status of QbD for sterile products, a potential approach for the elements of pharmaceutical development (as described in ICH Q8R2) will be followed:

- Quality Target Product Profile (QTPP)
- Critical Quality Attributes (CQAs)
- Risk Assessment: Linking Material Attributes and Process Parameters to Drug Product CQAs
- Design Space
- Control Strategy
- Product Life Cycle Management and Continual Improvement

Although the QbD pharmaceutical development process described above seems to have a linear flow from one step to the next, the actual process is typically less linear than it appears (see Fig. 1), and the results of one element may cause the developer to revisit previous elements. Additionally, the final element in the process (Product Life Cycle Management and Continual Improvement) should lead to a continuous re-assessment of the process. The following sections will describe the potential pharmaceutical development process for a sterile product with emphasis on sterility assurance.

QUALITY TARGET PRODUCT PROFILE

The QTPP forms the basis for drug product formulation and process development. The target drug product profile may include the following (1):

- Desired product performance/target product profile, such as intended used in clinical setting, route of administration, dosage form, and delivery systems
- Dosage strength(s)
- Container closure system
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics appropriate to the drug product dosage from being developed
- Drug product quality criteria (*e.g.*, sterility, purity, stability, and drug release)

For a sterile product, special attention should be paid to the sterility, endotoxin content, container closure integrity, container closure extractables and leachables, and anti-microbial preservative for a multi-dose presentation.

DETERMINE CQAS

A CQA is defined as a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure desired product quality. Product CQAs can be determined based on prior knowledge and the target product profile, and they should always be considered during the formulation and process development. For example, sterility (and in most cases endotoxin content) is by default an essential CQA for all sterile products. Although every product will have multiple critical product quality attributes, this discussion will be focused on QbD approach to ensure sterility (and low endotoxin or pyrogen content) for a sterile product while not compromising other product CQAs.

RISK ASSESSMENT

According to ICH Q9 (6), "risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards." Risk assessment can be helpful to link raw material attributes and process parameters to drug product CQAs. For example, during risk assessment, it may become evident that to control the endotoxin level of a sterile drug product, it is important to control the endotoxin levels of all ingredients, since the endotoxin introduced in the formulation is unlikely to be removed by standard unit operations during sterile product manufacturing. Risk assessment is typically performed early during pharmaceutical development and may be repeated as more information and greater knowledge is obtained. Ishikawa diagrams, what-if analysis, and hazard operability analysis are some example tools for parameter screening, and failure mode, effects analysis and relative ranking are two examples of risk ranking tools used during risk assessment.

During risk assessment for a sterilization process, each component of the drug product should be carefully examined in terms of its potential impact on the CQAs of the final drug product. Relevant process parameters can be identified during the risk assessment for development of the design space. For example, if a drug product contains heat sensitive material, an autoclaving process would be considered a high-risk process. The autoclaving process parameters, such as time and temperature, should be thoroughly studied in terms of their impact on the CQAs, such as physical chemical stability of a drug product, and considered during design space development.

Risk assessment for the container closure system should be carefully performed to evaluate the impact of a sterilization process, especially a terminal sterilization process, on the container closure integrity as well as leachables or extractables. Pharmaceutical development studies need to address container closure integrity after the maximum stress of the sterilization process and to ensure that a terminal sterilization process will not produce unacceptable level of leachables or extractables.

For an autoclave process, the critical process parameters could include time and temperature as well as in-process bioburden limits (*e.g.*, bulk solution or container closure components). For an aseptic manufacturing process, the risk assessment should consider the potential for microbial contamination of the product at all stages of manufacture (from raw materials and components through finished product) and should include the manufacturing environment (7–9). Particular emphasis should be placed on the stages of the manufacturing process after sterilization (of the drug product, container closure components, or sterile product contact surfaces).

DESIGN SPACE

The design space encompasses the relationship between the process inputs (material attributes and process parameters) and the CQAs. Ideally, if design spaces are accurately developed and all essential aspects of the manufacturing process are within the design space, the CQAs are assured of being acceptable (10).

The design space can be developed via various approaches, such as first principles approach, empirical approach, scale-up correlations, *etc*. Design of experiments (DOEs) in combination with linear and multiple-linear regression is a typical way to develop design spaces via empirical approach. A good example will be to use factorial design studies to facilitate design spaces development when multiple variables have impact on the same CQA of a drug product. A scale-up correlation approach for the design space development can be convenient at times. For example, a design space for an autoclave cycle may be developed in a small scale autoclave in terms of heat input (F_0) and its effect on the physical/chemical stability of the drug product. This design space of F_0 can be transferred to a large scale production autoclave and translated into operating parameters, such as cycle time and temperature, of the production autoclave. However, the validity of the approach should be verified upon the scale-up. The design space for a sterile product could include such elements as bioburden limits for raw and in-process materials, sterilization/depyrogenation process parameters for container closure components and/or manufacturing equipment, and sterilization process parameters for bulk or finished drug product.

DESIGN AND IMPLEMENT CONTROL STRATEGY AND PAT

"Control strategy is a planned set of controls derived from current product and process understanding that assures 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 operation conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control." (11). PAT can be and preferably should be part of the control strategy

The critical sterilization process parameters (*e.g.*, temperature and time for a moist heat sterilization process) should be controlled to ensure sterility of the product. In addition to sterilization process controls, an aseptic filling process should have environmental controls to prevent microbial contamination. These environmental controls can include physical barriers for contamination (*e.g.*, isolators) as well as microbial monitoring of the air, surfaces, and personnel in the aseptic filling environment. Other non-microbial controls should be designed to minimize interventions which might compromise the aseptic environment. For example, PAT with minimal manual intervention would be preferable to manual sampling for in-process control. A good example is using automatic weight checking technology to replace manual weight checking during the filling process.

Bioburden control is a critical part of any sterile manufacturing process. In-process bioburden testing of the bulk drug product is performed prior to sterilizing filtration. Bioburden may also be monitored prior to terminal sterilization. Since in-process testing is most useful when the results are available in a timely fashion (*e.g.*, during processing), the use of test methods that provide results in real-time (or at least quickly) is particularly important. There are existing rapid microbiological methods (RMM), including both qualitative and quantitative microbiological methods, that can be

used for in-process testing (12–14). Some RMM rely on microbial proliferation using traditional growth medium but then use an alternate method of microbial detection (*e.g.*, ATP bioluminescence) to provide faster results (15,16). Other methods such as cytometry (flow or solid-phase) use a vital stain to count microorganisms and can detect single microbial cells within a few hours of sample collection (17–19). Another type of cytometer uses laser-excited auto-fluorescence combined with light scattering size determination to provide continuous real-time microbial detection and enumeration in air (20,21). The currently available RMM vary in their time to results depending on the test mechanism. Although real-time results are not an option for the majority of the existing RMM, these RMM are able to provide results significantly faster than the traditional microbiology methods and depending on how they are used they could be considered as PAT (22,23).

PRODUCT LIFECYCLE MANAGEMENT AND CONTINUAL IMPROVEMENT

The experiences gained from commercial manufacturing of a product can be used to improve product quality (11). The increased understanding of the product and process as well as advances in technology may enable improvements in control strategies or changes to the manufacturing process parameters. From a regulatory standpoint, the phrase "continual improvement" suggests enhancement of quality. However, from the standpoint of the manufacturer, increased production efficiency is more likely the desired goal. Fortunately, these two approaches need not be incompatible. The challenge for the regulatory authority is to enable "continuous improvement" without sacrificing regulatory oversight of safety issues. Several FDA and ICH guidance documents and initiatives exist with the goal of encouraging continuous improvement (2,3,11).

EXAMPLES OF QbD FOR STERILE PRODUCTS

There are examples of pharmaceutical development for sterile products that fit into the QbD paradigm. Some of these examples are currently being utilized to maximize sterility assurance. As was discussed previously, a terminal sterilization process (which will provide a sterility assurance level (SAL) of 10^{-6} or greater) is preferred for a sterile drug product. Product development studies should assess the stability of the drug product after a typical "overkill" terminal sterilization process such as autoclaving for 15 min at 121°C. If the drug product cannot withstand this "overkill" sterilization cycle (*e.g.*, unacceptable impurity levels), then a less rigorous sterilization cycle can be considered. For example, an autoclave cycle providing less heat could be validated to provide a 10^{-6} SAL by combining it with a rigorous bioburden control strategy. An extreme (but effective) example of a bioburden control strategy is to combine an aseptic manufacturing process with a reduced terminal sterilization cycle (*e.g.*, shortened exposure time and/or lower temperature). The reduced heat input can still provide a validated sterility assurance level of 10^{-6} when combined with the low (essentially zero) product bioburden after the aseptic process. This approach of combining aseptic processing and reduced terminal sterilization cycles is being used for approved sterile drug products. However, if the drug product cannot tolerate even a minimal terminal sterilization process, then an aseptic manufacturing process will need to be developed.

A QbD approach can be very useful in sterilization process development for a heat-sensitive sterile drug product. For example, an injectable drug product is formulated as a microsuspension which particle size is stabilized by phospholipids (24). It is identified that the particle size is one of the most important CQAs of the drug product. Since sterilizing filtration is not possible for this drug product, a moist heat sterilization process is desired. Trehalose is added as thermoprotectant to minimize the thermal degradation of the phospholipid during autoclaving. In this case, the design space for the concentration of phospholipid, the concentration of trehalose, pH of the formulation, and the level of heat input could be developed to ensure the physical/chemical qualities as well as sterility of the drug product. DOE, such as factorial design study, maybe helpful in the design spaces development in this sample case since multiple variables with possible interactions are involved. The design space should consider product quality both immediately after processing and over the shelf life.

An older example of a QbD approach for a sterile product is the use of parametric release for drug products terminally sterilized by moist heat (25). Sterility assurance is provided by controlling the sterilization process parameters within a range which was determined through validation experiments to provide a SAL of at least 10^{-6} and by validating container closure integrity after exposure to the maximum sterilization process. The sterile drug product can then be released without performing a sterility test on the finished product. The well-controlled sterilization process provides much greater assurance of sterility than does a sterility test of a limited number of drug product units. This version of real-time release has been safely utilized for over 25 years for millions of drug product units each year.

CONCLUSION

FDA quality initiatives are aimed at enabling a fundamental paradigm shift in pharmaceutical manufacturing via quality control strategies based on product knowledge and process understanding and a more scientific and risk-based regulatory oversight. Nowadays, much of the scientific basis is already in place for the implementation of QbD. Critical regulatory experience has been obtained via FDA's QbD pilot programs and communications between the agency and the industry. Continued dialogue and learning by both parties will help move the QbD concepts forward. Although the submission of applications for sterile products with a QbD approach is still limited at present, the tools exist to implement QbD for sterile drug products. The FDA would like to see more QbD submissions for sterile products in the near future.

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