Quality by Design (QbD) of Sterile Dosage Form Packaging

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Introduction

The International Conference on Harmonization (ICH) recently published the Q8 (R2) guideline for Pharmaceutical Development [1]. The key aspect of the pharmaceutical development process is to design a product and create a manufacturing process that consistently delivers the product with an intended performance – the rate and extent of drug delivery in vivo. The knowledge gained during the product development allows researchers to define specifications and manufacturing controls for the product. The guideline defines many key terms which have been quoted below.

Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding, as well as process control, which are based on sound science and quality risk management. Critical Quality Attributes (CQAs) are physical, chemical, biological or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality. Critical Process Parameter (CPP) is a process parameter whose variability has an impact on the CQA. The CPP should be monitored and controlled to ensure that the process produces products with desired quality specifications. Design space is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within this design space is not considered a change. Quality Target Product Profile (QTPP) is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality. QTPP also takes into account safety and efficacy of the drug product.

QbD has been discussed at length mainly for the manufacturing of pharmaceutical formulations. However, QbD applications are not sought widely for pharmaceutical packaging. This article focuses solely on the application of QbD to the subsection of pharmaceutical packaging – the packaging of sterile dosage forms (SDFs).

Sterile Dosage Forms (SDFs)

As the name suggests, these dosage forms have to be sterile, i.e., free of live bacteria or other organisms. There are various ways by which we can describe different types of SDFs.

Routes of Administration

Table 1 lists various types of routes of administration used to deliver SDFs. Based on the route of administration, the characteristics of the sterile dosage forms vary.

Injectable formulation

This is the biggest class of formulation in the SDFs. There are several kinds of injectable dosage forms. Some are listed in Table 2. The properties of the formulations vary based on the final form and application. As a result, the requirements of packaging material vary as well.

One can also classify Parental Dosage Forms as small volume parenterals and large volume parenterals.

In general, packaging of pharmaceutical dosage forms is divided in two parts – primary and secondary. Primary packaging comes in direct contact with the formulation. Table 3 lists the key functions of packaging in SDFs.

Table 1. Routes of administration for the SDFs.

Intravenous (IV)
Intramuscular (IM)
Subcutaneous (SC)
Intradermal (ID)
Intrathecal
Epidural
Intra-articular
Other routes of administration
Inhalation
Intranasal
Ophthalmic
Wound cleaning/irrigation solutions
Implantable pellets

Table 2. Various kinds of injectable dosage forms

Solution
Emulsion
Suspension
Lipid complex
Powder for Solution
Powder for Suspension
Lyophilized Powder for Liposomal Suspension
Lyophilized Powder for Suspension
Lyophilized Powder for Extended Release Suspension
Irrigants for Open Wound and Body

Table 3. Key functions of packaging in SDFs

• Protection: Physico-Chemical
• Protection: Microbiological
• Presentation: Appealing to patients
• Identification/differentiation
• Convenience: Administration to patients
• Ease of storage and transportation

Table 4. Commonly used primary packaging for SDFs

1. Vials Glass or plastic
2. Ampoules
3. Plastic bags
4. Bottles
5. Ophthalmic drop bottles
6. Inhalers
7. Prefilled syringes (PFS) As is or in an autoinjector

Table 4 lists various commonly used primary packaging used for SDFs.

Various dosage forms interact with the packaging components differently. In general, the SDFs have the highest propensity to interact with primary packaging. Table 5 lists various specifications used for the SDFs and describes how the primary dosage form may affect the specifications.

The assay value of the active can be affected in various ways. It can be reduced due to adsorption to the filter, degradation due to pH change associated with primary packaging aspects, and improper protection from light. Many of the effects are self-explanatory.

Quality by Design (QbD)

Quality is not just meeting the pre-established product specifications. The basic objective of a "quality" pharmaceutical dosage form is to produce a desired clinical effect, which is ensured by delivering the active(s) from the dosage form at a desired rate and to the desired extent. Quality is not an accident, but rather an outcome of a well-intended design and skilled efforts. As its name indicates, the QbD paradigm ensures that the quality is designed into a dosage form to meet patient needs and clinical performance. The key steps in QbD are creating a quality target product profile (QTPP), defining critical quality attributes (CQAs) and understanding the risk management during the lifecycle of the product.

Riley and Li [2] summarized the current status of QbD and PAT (Process Analytical Technology) for sterile product. The first step is to define the product performance upfront and identify CQAs. Sterility testing ensures sterility of that particular unit, but does not ensure sterility of the dosage form. Sterility is ensured only by process validation. This emphasizes an application of QbD to SDFs. As this article relates to packaging of SDFs, it is imperative to keep in mind the patient requirements to which the primary and secondary packaging have to be designed. The packaging process has to be developed to produce a

Table 5. Effect of primary packaging on different specifications used for SDFs.

Test/Specification	Effect of primary packaging
Assay	Adsorption issue, pH change, photostability
Uniformity of dose	Accuracy of dosing device
pH	pH fluctuation
Sterility	Exposure to air during multiple usage
Endotoxins/pyrogens	Leaching of plastic components from sterile bags, rubber closures
Particulate matter	Precipitation, leachables
Water content and penetration	Mainly for non-aqueous formulations
Antimicrobial preservative content	Adsorption to the plastic
Antioxidant preservative contents	Permeability to oxygen, heavy metal leaching in vials
Extractables and leachables	Different dosage forms
Functionality of delivery systems	Syringeability, pressure, seal integrity and piston travel
Osmolarity	Packaging altering the molar concentration of dissolved solids, dissociation of molecules and factors causing deviation from ideality
Particle size distribution	Induced crystallization
Redispersability	Shape of primary packaging
Reconstitution time	Transparency of primary package

product with desired quality attributes. During this process, one has to understand the impact of packaging material attributes and packaging process parameters on the product CQAs. It is important to understand the variables in the materials used and processes undertaken, and their impacts on the product quality and performance. For example, a change in the vendor supplying vials or vials manufactured at different sites may change the overall product stability.

Knowledge, design and control spaces are in three concentric circles, with knowledge space and control space being the outermost and innermost circles, respectively. It is important to develop a "knowledge space" in terms of formulation, primary packaging materials, labels, and secondary packaging materials. One has to create specifications for each material and define quality attributes. The "knowledge space" for packing aspects should also encompass storage of final packaged product at the manufacturing site, conditions during transportation and the storage of the product at the site of the medical service provider.

Feedback from physicians and nurses, while using the SDFs in terms of the ease and appropriateness of the delivery device, should be taken seriously. QbD is all about adopting proactive approaches for continual improvement. The feedback from physicians and nurses can be incorporated in establishing a design space. This will ensure a supply of "quality" pharmaceutical products with low risk of failing at the clinical setting. In the Biopharmaceutics and QbD conference held in Rockville, MD on June 10-12, 2009, the speaker echoed the same sentiment for the solid dosage form [3]. Currently, the product specifications are based on "check list" approach and batch history. It was recommended that future specifications be based on desired clinical (in vivo) performance.

Knowledge space is narrowed to a design space. Design space is, as defined earlier in this article, a multidimensional combination of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Control space dictates process control, the control of input materials and container closure system, and the control of the end point.

The following case studies describe few examples of the impact of primary packaging materials on the quality attributes of SDFs.

Case Study 1

Extractable/Leachables Assessment

The primary concern of any packaging is the extractable and leachables. It is more important for SDFs. The primary or secondary packaging material is expected not to provide toxic or harmful components in the formulation. Some of the commonly observed unwanted components are – plasticizers, heavy metals, phthalates, and polyaromatic hydrocarbons. Guidance for Industry titled – "Container Closure Systems for Packaging of Human Drugs and Biologics" provides guidance on the information of packaging materials needed on drug products [4]. Attachment C of the guidance provides information on various extraction studies. It is important to obtain qualitative and quantitative profiles on plastics and elastomers to be used as the packaging components. The following tests are recommended - USP <661> and USP <381> for the characterization of plastics and elastomers, respectively, and USP <87> and USP <88> for the biological reactivity of plastics and elastomers, respectively. The leachables can also come into the product from an indirect contact (e.g., imprinting on the bottle or adhesives, inks or varnish from labels) or from surrounding air.

D. Jenke [5] applied the concept of design space to the leachables in aqueous drug products packaged in a specific packaging system. The design space boundaries listed in Table 6 were used.

The QbD principles were applied to a packaging system which was utilized for 12 products. It was observed that when operated within the design space, the leachable profile was predictable.

Case Study 2

Silicone oil in syringes

Siliconized syringes are commonly used as a DDS. Majumdar et al. [6] evaluated the stability of 3 protein formulations – 1) The recombinant protective antigen for anthrax, 2) Abatacept, and 3) An antistaphylococcal enterotoxin B monoclonal antibody in siliconized,

Table 6. Design space boundaries in an experiment by Jenke D. [5]

Variable	Design Space Boundaries
A	Aqueous drug products, pH 2 to 8, no polarity impacting agents
B	Same packaging system meeting material specifications
C	Fill volume – 50 to 1000 mL
D	Subjected to terminal sterilization and stored at RT for up to 24 months

uncoated and BD-42 coated prefilled syringes. BD-42 is a proprietary coating produced by BD technologies. Uncoated glass and BD-42 coated syringes produced significantly lower the number of visible and subvisible particles. Siliconized syringes produced more particles and it was found not to be due to the loss of a soluble protein fraction.

In another research article, Badkar et al. [7] presented an approach to select a PFS system for the development of the monoclonal antibody (mAb) product. This included a compatibility with silicone oil, a PFS barrel and tip caps. The mAb product was observed to be sensitive to high levels of silicone oil, especially at high temperatures resulting in formation of protein-silicone particles. Although the tip cap resin was in direct product contact to a minimum extent, it was shown to affect the oxidation of mAb. Out of three tip caps chosen from 2 vendors, one tip cap material showed superiority. The mAb oxidation was the most impacted quality attribute.

Case Study 3

Syringeability, and Injectability

Syringes have been widely used to administer the injectable formulations. There are two key terms, which define the functionality of syringes. Syringeability is the ease of withdrawal of a formulation from a vial or an ampoule, a process which should be free of clogging and foaming. Injectability is the force required for injection. One expects an evenness of flow, which is free from clogging. In selecting a needle for an injection delivery system, the key parameters considered are the needle gauge and length. The higher the gauge number, the smaller the needle diameter. Ten and 30G needles have outer diameters of 3.404 mm and 0.3112 mm, respectively. Another parameter is the internal diameter of the needle. Cilurzo [8] defined three types of forces – plunger stopper break-loose force, maximum force and dynamic glide force. In general, by increasing the gauge # and needle length, all the three force values increased. Authors also studied the effect of formulations on these forces. As expected, viscous formulations needed higher forces. However, the type of formulation had an impact too. Authors determined the pressure required expelling formulation from a syringe as a function of extruded volume for various formulations - high viscosity lipid-based system, an aqueous suspension, w/o emulsion, and low-viscosity lipid based system, using 22G and a 44 mm needle. It is very important for a formulator to keep in mind such aspects in developing a formulation and in selecting an appropriate needle.

Case Study 4

Effect of radiation on the stability of formulations

The effects of temperature, light and humidity are commonly studied on the stability of formulations. Du et al. [9] presented the stability of formulations in space. The factors affecting the stability of medicines in space were different – increased exposure to radiations (ionizing radiations of protons and heavy ions), excessive vibrations, microgravity and carbon dioxide-rich environment etc. In this study, medicine kits containing 33 formulations were stored in the International Space Station for up to 880 days. Table 7 shows the time when the payloads were sent back to earth for analysis and the radiation doses to which these formulations were exposed.

It is very clear that the formulations were exposed to significantly higher doses of radiation at the Space Station. Table 8 lists the number of formulations failing the chemical potency requirement. As expected, a significantly higher percent of formulations failed the chemical potency requirement. Each kit contained 33 dosage forms including 22 solid, 7 semisolid and 4 liquid (ophthalmic and injectable) formulations. In the case of Ciprofloxacin and Promethazine, liquid formulations showed a greater effect of radiation on stability compared to the solid dosage forms. Certain APIs such as levothyroxine, dextroamphetamine, promethazine, trimethoprim, sulfamethoxazole and clavulanate appeared to be more susceptible to the radiation effects.

Keeping these results in mind, it is important to develop a packaging system which will protect the formulations from radiations, and at the same time, will fulfill constraints of storage in space. Parenteral formulations are mostly in liquid form and might be more susceptible to radiation effects. Commercial flights fly over 30,000 feet altitude and the exposure to radiation is higher. Work is needed to be done in this area in terms of stability of SDFs and role of packaging.

In a review article, Curry et al. [10] summarized problems and challenges involved in the selection of ready-to-use closures for parenteral products. Elastomers are defined as materials that can be stretched to twice their original lengths and that can quickly return to their original dimensions without permanent deformation. Butyl and halobutyl are the most common elastomers used to help to retain headspace inert gases and provide a good barrier for water vapor transmission. However, they tend to shed particulates after irradiation. Ethylene propylene material tends to cross-link and turns slightly yellow upon irradiation. Authors recommended a close collaboration between the closure manufacturers and with the pharmaceutical manufacturers.

Table 7. Comparison of cumulative radiation dose between the ground control and at the International Space Station.

Payload	# days	Radiation dose, Control, mGy	Radiation dose, Space flight, mGy
1	0	4.54	1.93
2	353	4.84	44.12
3	596	5.06	74.53
4	880	5.45	110.70

Table 8. Number of formulation (out of 33) failing the chemical potency requirement.

Payload (# days)	Control (%)	Space Flight (%)
1 (0)	0 (0)	1 (3)
2 (353)	2 (6)	11 (33)
3 (596)	8 (24)	17 (52)
4 (880)	16 (48)	24 (73)

The deep understanding of the details of the polymer(s), cure systems, and additives and their effect on the product would help "custom design" ready-to-use closure composition and sterilization processes of the closure.

Case Study 5

Glass flakes in injectable liquids

Appearance of glass flakes in the injectable liquids is not uncommon. The real problem is their transparent nature, which makes it difficult to detect them. In a study, Iacocca et al. [11] examined three carboxylic acid model drugs and stored them in 3 different types of Type I glass vials – A. Type I glass treated with Ammonium sulfate to reduce surface alkalinity, B. Uncoated Type I, and C. Type I coated with silicon dioxide. The vials were exposed to a depyrogenation temperature of 250°C or 350°C for 4 hours. The formulations were exposed to terminal sterilization cycles of 0 or 2 and the samples were stored at 5°C, 25°C, 40°C and 60°C. Some of the key observations in this study were as follows: Variation in the depyrogenation temperature did not affect the number of glass flakes in the product. The pH of formulation decreased from about 9.5 to about 8 during storage. In the ICP-OEC analysis, higher amounts of dissolved silicon were observed in Formulation A. The storage temperature also had an impact on the dissolved silicon – the higher the temperature, the higher were the dissolved silicon levels. SEM analysis showed breakage of glass flakes mainly in formulation A. Based on the Spectrex data, the greater number of particles were observed in A and at 60°C as compared to those generated at 40°C. The authors assigned the lack of glass durability to the combination of the nature of the drugs and the pH of the solution.

Case Study 6

Prediction of Lyophilization cycle parameters

The Lyophilization process provides unique advantages and has been used in many products. In this article, lyophilization is considered as a packaging step rather than a part of formulation manufacturing. In a research article by Mockus et al. [12], Bayesian treatment was added to the primary drying modeling. There are three critical steps in freeze-drying: 1) Freezing of the drug solution in partially stoppered vials, 2) Primary drying to produce a cake, and 3) Desorption phase for secondary drying. During the freezing step, the temperature at which the first crystals of ice appear is termed as a nucleation temperature. Nucleation temperature is affected by several formulation and process factors. In the primary drying step, temperature should not go beyond the eutectic temperature or else the cake could collapse. Some of the factors affecting the primary drying could be the composition of formulation, pressure differential, rubber stopper resistance for water vapor release, heating rate etc. The main goal of this study was to determine the duration of primary drying. The number of temperature gauges and their correct placements are critical in determining the exact primary drying end point. In this study, it was shown that the resistance of dry layer mass transfer was product specific and it was a function of the nucleation temperature. Authors developed a mathematical model to predict the end point of primary drying time. In general, for the freeze-drying process, the design space would generally vary for different products.

Cannon and Shemeley [13] studied the effect of vial design on the sublimation rate during the primary drying of lyophilization cycle. The sublimation rate was influenced by the heat and mass transfer rates. The composition of glass vials could affect the thermal conductivity. Other factors influencing the process were the vial diameter, the vial's bottom radius, and the fill volume. The bottom concavities did not substantially influence the sublimation rate.

Case Study 7

Packaging of liquid formulation

During the filling of a liquid product, the product showed a tendency to foam during the filling process, making it trickle down the outside. The composition of the formulation and container closure size could not be altered at that stage. The foaming could be reduced by slowing down the filling rate, which was still not sufficient. The problem could be resolved fully by using a slightly bigger filling needle.

Conclusions

Packaging aspects must be considered during the development of SDFs. The packaging process parameters may affect the final product quality. During the development of packaging for sterile products, it is important to understand the impact of material attributes and process parameters on CQAs. It is essential to identify and control the sources of variability. It is also critical to continue to monitor these throughout the lifecycle of the product.

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