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Original Article

A PRACTICAL RISK-BASED APPROACH TO ASSESS VIAL'S DIMENSIONS DEVIATIONS EFFECT ON THE ASEPTIC FILLING PROCESSING, ACCORDING TO ICH Q9 GUIDELINE

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ABSTRACT

Objective: Qualitative risk assessment process is a new topic in the pharmaceutical industries. The main outcome of the risk assessment implementation is to help the manufacturers for a better decision-making, in a case that a quality problem arises. According to the ISO documents; vials used in the pharmaceutical industry have a special dimension specification and Quality Control analytical results should prove that the vial samples are in the defined range. Nevertheless, the value of these tests is not the same as defined ISO specifications; and this may have minor and/or significant impact on the final product quality.

Methods: The purpose of this qualitative study was to rank the results of the vial dimention tests based on quality risk assessment. Consequently, these rankings can help to decide whether the dimension deviation from quality specification of vials is acceptable and what will be the impact of accepting the risk on the final product safety and finally how to decrease the risk.

For this purpose, we consider the final product contamination could be one of the main indicators for the quality as the contamination from packaging materials in particular are more important when aseptic processing run.

Results: Dimensions that are directly associated with opening the vial containing d2, d3, d4 and h4 that they affect rubber sealing and capping. Other dimensions like h1, h2, h3 and d1 affect rubber sealing and capping indirectly. Therefore, these two groups of deviations have a very high probability of contamination.

Keywords: Quality Risk Assessment, Vial Dimension, Aseptic Filling Processing, ICH Q9, ISO 8362-1.

INTRODUCTION

Achieving a shared understanding of the application of Quality Risk Management (QRM) among diverse stakeholders is difficult because each stakeholder might identify different potential harms, place a different probability on each harm occurring and attribute different severities to each harm. In relation to pharmaceuticals, there are a variety of stakeholders, including patients and medical practitioners as well as government and industry. Here the protection of the patient by managing the quality risk was considered as the prime importance.

According to ICH Q9 harm defines as -damage to health, including the damage that can occur from loss of product quality or availability- and quality risk management is "a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle" [1].

An effective QRM approach can further ensure the high quality of the pharmaceutical product to the patient by providing a proactive means to identify and control potential quality issues during the development and manufacturing process. In this regards, an effective QRM model provides a positive and practical approach for implementing preventive actions [1]. In addition, utilization of QRM can improve the decision making whenever a quality problem arises. Effective QRM can also facilitate better and more informed decisions, provide regulators with greater assurance of a company's ability to deal with potential risks, and can beneficially affect the extent and level of direct regulatory oversight

As a result of the sanctions in the recent years, supplying the raw materials needed for pharmaceutical industries have become a thorny problem. Qualitative risk assessment for raw material chain supply can aid manufacturers to decide whether the deviations from ISO specifications have a major impact on product quality or not.

The purpose of this study was to offer a systematic approach to QRM for pharmaceutical vials as the first packaging materials in a high technology aseptic filling processing.

MATERIALS AND METHODS

Selection of QRM Working Team

QRM activities are usually, but not always, undertaken by interdisciplinary teams. Expert team for this study were selected from the appropriate working areas (Authorized person, Quality units [QA and QC], production operations, sales and marketing) in addition to individuals who were knowledgeable about the QRM process.

Definition of the possible risk types:

In this study, the main aim was to investigate the predictable risks, including higher risks leading to environmental contamination during filling operations, contaminations generated by human intervention (e. g., machine breakdown or component transfer), contaminations due to breakage in glass containers and presence of glass particles when vials are opened, contaminations that are caused by defective rubber sealing and malformed capping, and lower risks including vial imbalance during machine-run, difficulties in removing the fluid with a syringe from vial and etc.

According to International Organization for Standardization (ISO8362-1; 2009) [2] vial dimensions defined as shown in figure 1. Legally any value outside this range will cause unacceptable QC results.

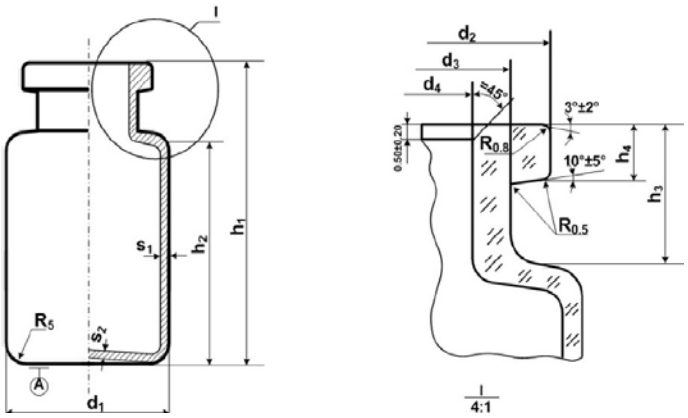

Fig. 1: Schematic view and dimentions of Injection Vials made of Neutral Borosilicate Glass Tubing according to the International Organization for standardization (ISO8362-1; 2009) [2].

Table 1: Scoring the Severity and Frequency of the deviations to define the risks.

Capacity mL	Diameter							Height							Thickness		
	d_1		d_2		d_3	d_4		h_1		h_2	h_3		h_4		S_1		S_2
	basic	tol.	basic	tol.		basic	tol.	basic	tol.		basic	tol.	basic	tol.	basic	tol.	
2	16.00	±0.20	13.00	+0.20 -0.30	≤10.50	7.00	±0.20	35.00	±0.50	≥23.00	8.00	±0.50	3.60	±0.20	1.00	±0.04	≥0.70
4								45.00		≥33.00							
6	22.00		20.00		≤16.00	12.50		40.00		≥27.00	8.50						
8								45.00		≥32.00							
10	24.00				≤16.50					≥31.00	9.00						
15								60.00		≥46.00							
20	30.00	±0.30			≤17.50			55.00	±0.70	≥35.00	10.00	±0.75			1.20	±0.05	
25								65.00		≥45.00							
30								75.00		≥55.00							

Score / Parameter	0	1	2	3
Severity (S)	not addressed explicitly or implicitly by the applicable GMP	Addressed by applicable GMP, but without possible impact on the manufactured product	Possible impact on the manufactured product but without risk for the patient (end user)	Possible impact on the manufactured product and with possible hazard for the patient (end user)
Frequency (F)	evident intervening with a frequency lower than 10e-6	accidental event, occurrence exceptional	frequent but not systematic event	event noted each time or almost

Quantification

Also the Factor (N) modules the expression of the risk and is defined by the following way:

- N=1.0: existence of documented evidence, established by an independent entity, proving the ongoing compliance to regulatory requirements during more than 36 months.
- N=1.1: existence of documented evidence, established by an independent entity, proving the ongoing compliance to regulatory requirements during more than 36 months.
- N=1.2: absence of documented evidence, established by an independent entity, proving the compliance to regulatory requirements or existence of non-addressed non-conformity.

After scoring the severity and frequency for each risk the systemic risk was calculated using the following equation:

$$Rs=S \boxtimes F \boxtimes N$$

To analysis the systemic risk of the following criteria are defined:

- Low, if: 0=<R<3
- Moderate, if: 3=<R<5

The method of quantification is according to QRM – implementation of ICH Q9 in the pharmaceutical field (3) as listed in Table 1:

- High if: R>=5

It is also agreed that a risk is acceptable if it is low or it is a moderate and detection is certain (D=d). "N" was considered equal to 1.1 for our production line.

RESULTS

Risk assessment analysis was performed and the results are summarized in Table 2 The most obvious critical point is vial entry surface that provides a good estimate to correlate with risk of contamination rather than the entire internal surface of the vial container. Dimensions that are directly associated with an opening of the vials are d2, d3, d4 and h4 which in turn affect rubber sealing and capping. Other dimensions like h1, h2, h3 and d1 affect rubber sealing and capping, indirectly. Therefore the deviations in the specification of these two groups of dimentions have a very high probability of contamination risk.

Another main surface that may potentially be contaminated is the external surface of container components. These surfaces are fully exposed to the laminar airflow and are in contact with equipment parts, such as the rails and ramps, which may transfer environmental contaminants.

Vial breakage caused entering such contaminations with glass particles into product container. On the other hand vial breakage during the filling process will lead to increased personnel traffic in the clean area to wipe off the rails from the glass particles , which in turn increase the possibility of contamination under laminar airflow. Almost all of the deviations from the standard dimensions can possibly lead to this risk.

The difference in amount of "t" -arc of vial stand- could be caused by an imbalance of the vial during the filling process and therefore increase the rate of fracture. Increasing the amount of "t" dimension might cause difficult removal of final pharmaceutical product filled in the vial by syringe.

"d1" dimension, Being outside of the specified range might lead to improper placement of vial for filling. It is more likely to break; and also may lead to improper filling volume.

Underweight vials, may increase the risk of contamination by increasing vial breakage probability. Any changes in the weight of vials might lead to improper filling volume, because the filler volume adjustment is done according to the standard vial weight. As specified in Table 2, weight difference deviation has the highest risk factor score for the aseptic filling process (R_s=9.9). Any significant weight distortion is very important especially when the standard deviation is too high. Risks resulting from this deviation couldn't be accepted in the filling production line. Deviations that are related to the h1, h4, s1 and s2 dimensions also showed high risk scores (R_s=6.6), and this risk might not be accepted.

Risk score for the h2 and h3 deviations was 3.3, and this was not accepted. Vial's defects i. e. breakage are detectable 100% but rubber sealing defects and malformed capping may not be detected by the visual inspection procedure. Deviations of r1, r2, t and d1-4 dimensions showed acceptable risk score (0=<R_s<3 or 3=<R<5 but D=d).

Table 2: Risk Assessment Analysis Results.

DISCUSSION

The Cut-offs of the risk scores , are useful to scale or fit the risk ranking for the quality management or policy objectives.

According to the obtained results, the final decision of risk assessment committee was to prepare a practical guideline for the commercial department management with the following topics:

Purchasing vials with vial weight or h_1, h_4, s_1 and s_2 dimensions deviations , will be unauthorized by the quality system.

- Vials with other dimension deviations can be purchased and used in filling production line; while the production personnel should increase certain controls applied to detect the defects.

- Interactive relation with domestic (national) vials manufacturers to correct and improve the products' quality and their manufacturing process, should be considered by the commercial department.

In order to ensure the quality analysis test results are validated, related QC laboratory equipments should be calibrated according to the written protocols. According to the ICH guidelines stability studies of thepharmaceutical injectable products are essential to repeat if supplier of any first packaging material like vial changed. On the other hand due to the recent sanctions of our country, the number of contracting companies are limited; so changing the source of vials has its own difficulties. Therefore, such a risk-based assessment plans to investigate the main causes of vial failure in the quality control test; dimensional deviations and vial weight are useful. Simulation of aseptic filling of inhectable pharmaceutical products is also helpful for confirmation of this conclusion [4, 5]. Although there are some examples of the quality risk management implementation in the pharmaceutical industries, these limited

practices do not represent the full contributions of practical risk management to the quality system. In addition, the importance of quality management systems has been recognized in the pharmaceutical industries, and it is becoming evident that quality risk management has a valuable role in this regards.

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