Journal Pharmaceutical Science and Application
Volume 6, Issue 2, Page 65-73, December 2024
E-ISSN: 2301-7708

QUALITY ASSURANCE OF SMALL VOLUME PARENTERAL PRODUCT WITH QUALITY BY DESIGN APPROACH: A REVIEW

Anietta Indri Nur Ramadhani[1*], Sri Yuliana[1], Teuku Nanda Saifullah Sulaiman[2]

[1]Master Student of Magister Management of Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta-Indonesia
[2]Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta-Indonesia

Corresponding author email: aniettaindrinurramadhani@mail.ugm.ac.id

ABSTRACT

Background: Nowadays, many small-volume injection products are circulating on the market. Small-volume parenteral (SVP) products are usually designed for treatment purposes that provide systemic effects. If it is not produced strictly, the product will be hazardous and even life-threatening. Quality assurance is one of the primary tools used to ensure the acceptable performance of SVP products. Quality by design (QbD) represents a systematic strategy for product development that starts with setting a target product quality and emphasizes product process control based on a scientific approach and quality risk assessment. The purpose is to ensure SVP product quality from design to production process. **Objective:** This review will determine generally Critical Quality Attributes (CQA), Critical Material Attributes (CMA), and Critical Process Parameters (CPP) in terms of explaining the quality assurance of SVP products with a quality-by-design approach. **Methods:** All articles were obtained by electronic search using ICH guidelines, Science Direct, and Google Scholar. **Results:** From the literature review, it was found that using a quality-by-design approach through integrated CQA, CMA, and CPP can produce SVP products that comply with QTPP (Quality Target Product Profile) and regulatory requirements. **Conclusion:** QbD has been established as a valuable scientific approach for ensuring quality assurance within the pharmaceutical industry. Pharmaceutical companies prioritize obtaining regulatory approval before introducing any product to the market.

Keywords: Critical Process Parameter; Critical Quality Attributes; Quality by Design; Parenteral; Small Volume Parenteral.

INTRODUCTION

Precision and accuracy are essential when handling certain medications, including potent drugs with narrow therapeutic margins, ophthalmic formulations, and pediatric dosages, to safeguard patient well-being. In the context of pharmacy compounding, syringes play a crucial role in accurately measuring small volumes, particularly when preparing sterile products for injection and infusion[1]. A small-volume parenteral is any sterile pharmaceutical preparation packaged in 100 ml or less volume, such as a vial, ampoule, or prefilled injection syringe[2]. Small-volume parenteral are usually designed for treatment purposes that provide systemic effects. If it is not designed strictly, the product will be very dangerous and even life-threatening. Quality assurance is one of the primary tools in

DOI : https://doi.org/10.24843/JPSA.2024.v06.i02.p02

ensuring the acceptable performance of small-volume parenteral products. Therefore, intrinsic statements regarding certain quality attributes (QA) are significant for small-volume parenteral products that provide systemic effects. Thus, the quality has to be built into the product.

Nowadays, pharmaceutical industries use Quality by Design to develop their product and ensure quality with a scientific approach[3]. Quality by design starts by defining a list of quality requirements: Quality Target Product Profile (QTPP). To accurately characterize the various components of the QTPP, it is essential to define Critical Quality Attributes (CQAs) in the initial step. To attain a final product with desired Critical Quality Attributes (CQAs), it is essential to incorporate quality into the product design by considering Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs). These concepts developed through the Quality by Design (QbD) approach[4]. Implementing Quality by Design (QbD) concepts will support the creation of high-quality products and their continuous evaluation across the lifecycle of the product, ultimately leading to enhanced patient outcomes[5]. The basic principle of QbD is that quality cannot be tested in products, but quality should be built into the product by design [4].

This review study will discuss the quality assurance of small-volume parenteral products with a QbD approach, including the CQAs, CMAs, and CPPs. It integrates the QbD framework with quality assurance for Small-Volume Parenteral (SVP) products. It provides a structured, proactive approach, emphasizing critical quality attributes, critical process parameters, and real-time monitoring through Process Analytical Technology (PAT). This study aligns with key regulatory frameworks like ICH Q8-Q11 and global agency expectations, offering practical insights for compliance.

METHODS

All articles were obtained by conducting an electronic through guidelines, Science Direct, and Google Scholar. The search used the following keywords: ‘quality by design,’ ‘small volume parenteral’, ‘pharmaceutical quality assurance,’ ‘risk-based approach,’ and ‘critical quality attribute (CQAs).’

RESULTS AND DISCUSSION

QUALITY BY DESIGN (QBD) IN ASSURING PARENTERAL PRODUCT QUALITY

Parenteral drug products are administered through routes other than the gastrointestinal tract. These routes include injections through the skin or other external boundary tissue and implantation within the body. The goal is to deliver the active drug substance(s) directly into blood vessels, organs, tissues, or specific lesions. Parenteral dosage forms encompass various formulations, such as solutions, suspensions, emulsions, sterile powders for solutions and suspensions (including liposomes), and implants (including microparticles). Additionally, combination products include both a drug and a medical device, such as drug-eluting stents. Based on filling volume, the parenteral dosage form was divided into two categories: Large Volume Parenteral (LVP) and Small Volume Parenteral (SVP)[2,6].

The utilization of QbD in the development of parenteral drug formulation confers significant advantages. By applying QbD, manufacturers can create the desired product quality, mitigate batch error, and increase patient safety and efficacy[7]. These CQA of parenteral attributes encompass parameters such as stability, potency, purity,

DOI : https://doi.org/10.24843/JPSA.2024.v06.i02.p02

and drug release profiles. Additionally, QbD proposes a lifecycle perspective, spanning the entire product journey from development through post-approval modifications. This needs continuous process verification, monitoring of product performance during production, and quality control strategies to ensure consistency and reliability. Implementing QbD in parenteral drug formulations provides a robust, scientifically grounded approach to ensuring the product's safety, quality, and efficacy[7]. Small-volume parenterals have more or less the same characteristics and treatments as parenterals. It is just different in volume and size.

QbD focuses on ensuring quality assurance of parenteral products built into the product's design. Determination of Quality by design (QbD) represents a systematic strategy for product development that starts with setting a target product quality and emphasizes product process control based on a scientific approach and quality risk assessment[4]. QbD consists of several parameters [4,8]:

- Quality Target Product Profile (QTPP)
- Critical Quality Attributes (CQAs)
- Critical Material Attributes (CMAs)
- Critical Process Parameters (CPPs)

The initial stage of QbD involves establishing the product's intended use and determining its routes of administration. Subsequently, Critical Quality Attributes (CQAs) are defined. These CQAs define the physical, chemical, biological, or microbiological properties that impact the product's purity, strength, release characteristics, and stability. After defining CQAs, a risk assessment is conducted. Finally, a control strategy is designed, incorporating ongoing product management for continuous improvement.

The tools most commonly utilized for performing various activities include the following: Risk Assessment (RA) employs methodologies such as the Ishikawa Diagram, Failure Mode and Effects Analysis (FMEA), and Risk Estimation Matrix (REM). Emerging trends in the field emphasize an increasing focus on quantifying and managing the variability in raw material attributes and their influence on processes and products. Additionally, there is notable progress in developing Retrospective Quality by Design (rQbD) approaches to complement traditional Quality by Design (QbD) practices[9].

QUALITY TARGET PRODUCT PROFILE (QTPP)

Quality Target Product Profile (QTPP) is the first stage of QbD. It summarizes the quality characteristics of a drug product to be achieved, related dosage strengths, container closure system, and attributes that can affect pharmacokinetic characteristics (for example, dissolution, aerodynamic performance) and drug product quality criteria (for example, drug release, stability, purity, and sterility). It includes dosage forms, delivery systems, dosage strengths, and others.

QTPP for parenteral products establishes the desired quality characteristics of a specific parenteral formulation and references formulation development, process design, and quality control. The QTPP includes information such as release profile, stability, route of administration, dosage form, strength, and other relevant attributes. It emphasizes the overall quality of the product and patient safety. The differences between the QTPP of LVP and SVP can be seen in Table 1.

CRITICAL QUALITY ATTRIBUTES (CQA)

Critical Quality Attributes (CQAs) are product characteristics that include chemical, physical, biological, or microbiological characteristics that should be within an appropriate limit or range to ensure the

DOI : https://doi.org/10.24843/JPSA.2024.v06.i02.p02

desired quality of the product[4]. The CQA references of small-volume parenteral products can be adopted from compendial and non-compendial. Compendial refers to USP, Indonesia Pharmacopeia, or other compendial.

Table 1. The QTPP Differences between LVP and SVP[2,6,7]

Items	Large Volume Parenteral (LVP)	Small Volume Parenteral (SVP)
Volume	volume ≥ 100 mL	volume < 100 mL
Purpose	Typically used to administer fluids, electrolytes, and nutrients intravenously.	Used for the administration of certain medications, such as antibiotics
Packaging	Glass bottle packaging or large-capacity flexible containers (ex, glass or glass-like, Polyvinylchloride (PVC), Ethylene vinyl acetate films (EVA), Blow-Fill-Seal Technology)	Small capacity (ex: prefilled syringes, ampoules)
Characteristics	Sterile, pyrogen-free, particle-free, without antimicrobial agents, and isotonic	Sterile, pyrogen-free, and QTPP compliant
Examples	electrolyte solutions, nutrients, and contrast agents	solutions, suspensions, emulsions, and dry powders

Non-compendial refers to the pharmaceutical industry itself. CQA is usually about the active ingredients, excipients, intermediates, and the finished product. The critical quality attributes of a finished product significantly impact its performance, ensuring it meets the desired standards of quality, efficacy, and safety. These attributes influence product specifications, such as impurity levels, potency, stability, drug release, and microbiological properties. Additionally, they include characteristics of the active ingredient that affect the product's performance or reproducibility[21]. In general, CQA in small-volume parenteral is assay, impurities, particulate contamination, pyrogens, endotoxins, sterility, identification of a product, and batch number, as is shown in Table 3.

CRITICAL MATERIAL ATTRIBUTE (CMA)

Critical Material Attributes (CMAs) are an input material's physical, chemical, biological, or microbiological properties. It should be within an appropriate range, limit, or distribution to ensure the desired quality of drug substance or active pharmaceutical ingredients, excipient, or in-process material[4].

The material component of the drug product consists of drug substances and excipients. The drug's physicochemical and biological properties, such as insolubility, water content, particle size, crystal properties, biological activity, and permeability, should be identified and discussed because they can influence the product's performance and manufacturability. These properties also could be interrelated and might need to be considered in combination[4].

The excipients' characteristics can significantly impact a drug product's performance, affecting aspects such as stability, bioavailability, and manufacturability. It is essential to discuss these characteristics concerning the specific function of each excipient.

DOI : https://doi.org/10.24843/JPSA.2024.v06.i02.p02

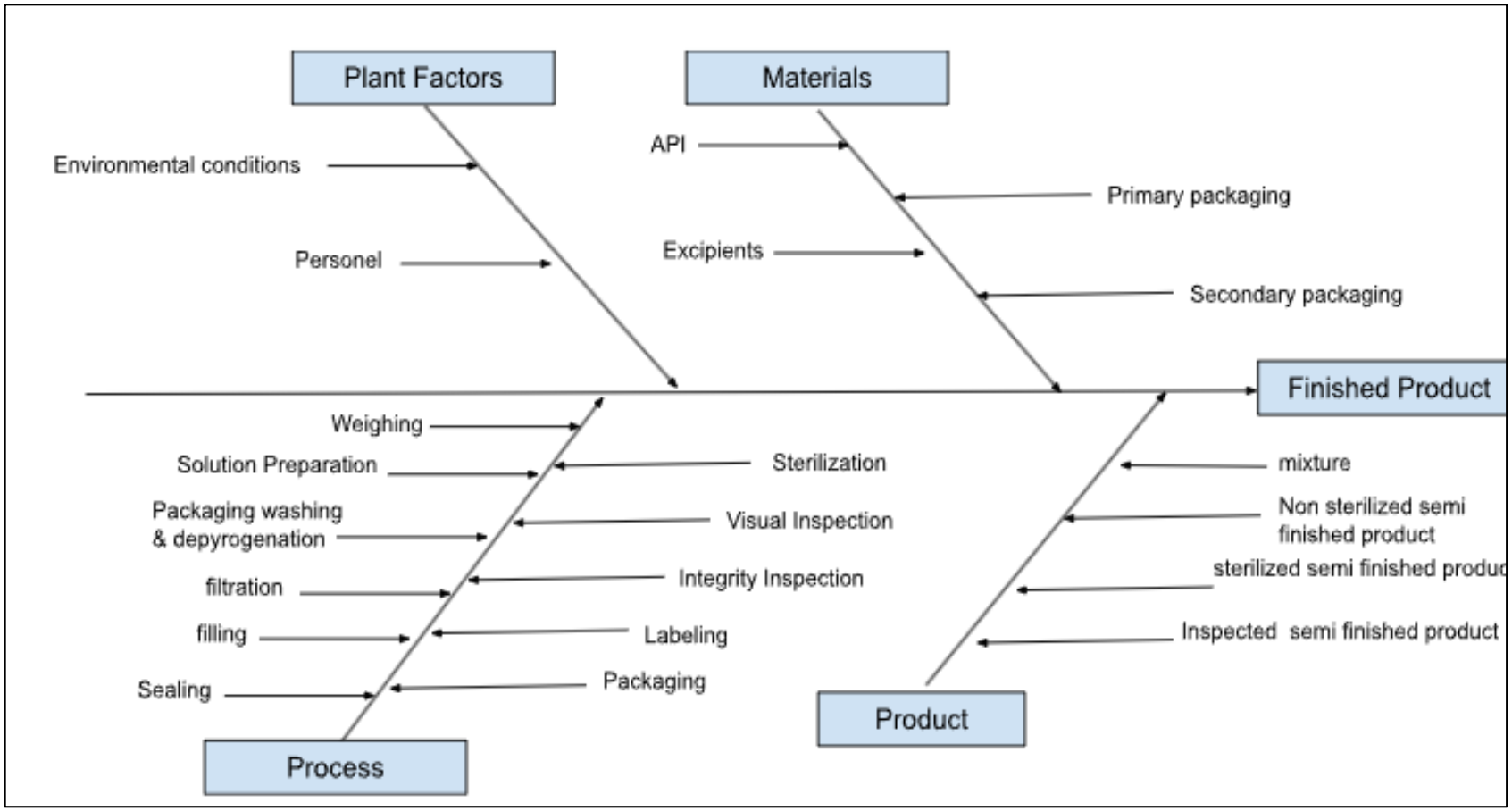

Figure 1. Ishikawa Diagram of Small Volume Parenteral Process [10]

DOI : https://doi.org/10.24843/JPSA.2024.v06.i02.p02

Table 2. Critical Process Parameter of SVP

Unit Operations	Critical Process Parameters	Justification
Weighing[10]	Only APIs and Excipients approved can enter the weighing rooms and should be tested according to their specifications.	Should be performed under the Laminar Air Flow (LAF) with a Class D background
Solution Preparation[10]	- Mixing API+ Excipient - Stirring Process	The solution should be homogeneous Time and speed of stirring influence the dissolution of API
Filtration[10–12]	Flow rate Temperature of filtration Use time Pressure	Using 0,22 um filter sterilization The filter should be integrity tested before
Ampoules[10]	It can be clear or amber with type I glass, type C form (according to ISO 9187-2)	Ampoules glass must comply with compendial requirements for type I glass containers and comply with light transmittance (for amber glass)
Ampoules Washing[10]	Water temperature Water Pressure Washer Velocity	Water temperature pressure and washer velocity influence the efficiency of washing
Ampoules Depyrogenation[10]	Conveyor belt velocity Chamber temperature	Conveyor belt velocity influences the stability of the ampoules in the tunnel, affecting the exposure to the sterilization temperature Chamber temperature should be high enough so that ampoules are efficiently sterilized and dehydrogenated.
Filling[10]	Solution flow Volume to fill	The solution should flow properly to fill the container Volume will influence the intended use of the dosage form and influence dosage uniformity
Sealing[10]	Flame temperature Ampoules height	The sealing temperature must be adequate. Ampoules height will influence the ease of opening
Sterilization (Autoclave Method)[10,13]	Time: 15 minutes Temperature: 121^{0}C	Time and temperature influence the F0 of the sterilization process. It should be taken at least 15 minutes in 121^{0}C.
Visual inspection[12]	Absences of foreign particulate matters	The inspection process should be designed and qualified to ensure that every lot of product is essentially free from visible particulates
Packaging[4,10,14]	-Free from leakage -Container closure system integrity	Refers to the sum of packaging components (container closure system) that together contain and protect the dosage form.
Labeling[10]	Label Barcode Batch & Expiry date printing	Label and barcode is essential to the identification of the product The correctness of printing will allow the correct traceability of the batch

DOI : https://doi.org/10.24843/JPSA.2024.v06.i02.p02

Table 3. Critical Quality Attributes of SVP

Critical Quality Attributes	Acceptance Criteria	Justification
Sterility[15]	meet the sterility test requirements	Incubate a portion of the medium at a suitable temperature for 14 days without microbial growth.
Endotoxin level[16]	Maximum 5 UE/mL (Gendal Gel Test)	Ingredients qualify if they contain endotoxin levels less than the value stated in each monograph.
Particulate Matter (751)	Light Obscuration Test: ≥ 10 µ: 6000 ≥ 25 µ: 600 per container Microscopic Method: ≥ 10 µ: 3000 ≥ 25 µ: 300 per container	Light obscuration test: count the number of particles present in each specific unit tested or each combined sample tested. If the average particle number exceeds the limit, test the preparation with the Microscopic Particle Count Test. Microscopic method test: the test requirements are met if the number of particles present (real or calculated) in each specific unit tested or in each composite sample tested does not exceed the values listed in the monograph.
pH (1071)[17]	Based on product	Measure pH using a suitable potentiometric device (pH meter), which has been standardized accordingly.
Osmolality (941)[18]	- Osmotic pressure depends on the number of particles in the solution, according to the colligative properties of the solution.	Osmotic pressure depends on the number of particles in the solution, as per the colligative properties of the solution.
Chemical and Physical Stability (1351)(51)	- Chemical stability: each active substance maintains the chemical integrity and potency stated in the etiquette within the specified limits. - Physical stability: maintains initial physical properties, including characterization, conformity, uniformity, dissolution, and ability to be suspended - Microbiological: sterility or resistance to microbial growth is maintained in accordance with the stated requirements. Antimicrobial agents present maintain effectiveness within established limits.	Additional ingredients may be added to the injection preparation to improve stability or effectiveness.
Appearance and Clarity (881)	The solution is clear, not cloudy, with no sediment, and fog-free	Visual method: make the determination using flat-top test tubes with an inner diameter of 15-25 mm, colorless, transparent, and made of neutral glass.
Fill Volume (1131)[1,19]	Volume not less than the volume indicated on the container. The mean percent error ranged from 1.4% to 18.6% (manufacturer specification ±5% accuracy).	Each container is filled slightly over the amount indicated on the etiquette or the volume to be drawn. The recommended excess volume is indicated in the Determination of Injection Volume in Containers.
Glass container[20]	Type-I glass, chemically inert and an effective container closure system (CCS)	The evaluation of the container was performed using a mechanical and chemical durability testing platform: freeze-thaw, lyophilization, compression, scratch tests; visual inspection, pH, particle size analyses, extractable, leachable, and imaging studies that were conducted under normal (4 and 25°C), and stress condition (60°C).

DOI : https://doi.org/10.24843/JPSA.2024.v06.i02.p02

The assessment should encompass all substances used in the drug product's manufacturing process, regardless of whether they appear in the final product. Evaluating the compatibility of excipients with one another is crucial.

Additionally, demonstrating the ability of excipients to fulfill their intended functionality throughout the drug product's intended shelf life is essential. Information on excipient performance can be leveraged, as needed, to justify the selection and quality attributes of the excipient, supporting the overall drug product specification[4].

CRITICAL PROCESS PARAMETERS (CPP)

Optimizing the critical process parameters was important, as these parameters significantly influence the quality of the final product. The FDA encourages the use of advanced optimization software, such as Design of Experiments (DoE), to streamline the optimization of critical process parameters (CPPs). These tools assist formulators in identifying the most critical CPPs that significantly influence product quality, and factors with minimal impact that can be deprioritized. By leveraging such software, formulators can concentrate on CPPs that directly affect critical quality attributes (CQAs), thereby enhancing the overall efficiency and effectiveness of the development process.[22]

Critical Process Parameters (CPPs) are monitored before or during the process, which significantly influences the appearance, impurity, and yield of the final product[4]. The Ishikawa fishbone diagram (Figure 1) was developed to verify which aspects can influence the finished product quality. The fishbone diagram also explains the critical parameter of the process and it is described in Table 2. The Ishikawa diagram will identify some potential variables that impact the desired quality attributes [4]. Thus, the critical process parameters should be evaluated together with the CQAs.

CONCLUSION

The application of Quality by Design (QbD) in drug development enhances the quality of medications for patients, manufacturers, and regulators. By integrating science and risk management in the development process, manufacturers can ensure that their products meet stringent quality standards. Regulatory requirements significantly impact the adoption of QbD, which has emerged as a valuable scientific approach for ensuring quality assurance within the pharmaceutical industry. Pharmaceutical companies prioritize obtaining regulatory approval before introducing any product to the market.

Furthermore, implementing QbD needs a deep understanding of the production process and materials used, as well as continuous monitoring to ensure product consistency and reliability.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ACKNOWLEDGEMENT

There are no conflicts of interest in this research. This research article was written independently. All authors have no financial or personal relationships with other individuals or organizations that could inappropriately influence this research.

REFERENCES

1. Jordan MA, Choksi D, Lombard K, Patton LR. Development of Guidelines for Accurate Measurement of Small Volume Parenteral Products Using Syringes. Hosp Pharm. 2021;56:165–71.

DOI : https://doi.org/10.24843/JPSA.2024.v06.i02.p02

2. FI VI KR. Farmakope Indonesia Edisi VI. 2020.
3. ter Horst JP, Turimella SL, Metsers F, Zwiers A. Implementation of Quality by Design (QbD) Principles in Regulatory Dossiers of Medicinal Products in the European Union (EU) Between 2014 and 2019. Ther Innov Regul Sci [Internet]. 2021;55:583–90. Available from: https://doi.org/10.1007/s43441-020-00254-9
4. ICH Q8. Pharmaceutical Development Q8 (R2). ICH Harmon. Tripart. Guidel. 2005.
5. Print I, Online I, Tambe K, Bonde S. A review on: Applications of pharmaceutical quality by design in product development. World J Pharm Sci. 2017;
6. Jenke D. An Introduction to Large Volume Parenterals(LVPs) as a Pharmaceutical Dosage Form and an E&L Challenge. Nelson Labs. 2021;
7. Ergin A, Uner B. Quality by Design for Parenteral Formulations. 2024. p. 217–42.
8. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, et al. Understanding pharmaceutical quality by design. AAPS J. 2014;16:771–83.
9. Grangeia HB, Silva C, Simões SP, Reis MS. Quality by design in pharmaceutical manufacturing: A systematic review of current status, challenges and future perspectives. Eur J Pharm Biopharm. 2020;147:19–37.
10. Rita A, Cabaco C. A Validation Master Plan for Small Volume Parenterals. 2014;93.
11. Acucena RW. Defining a strategy for the Validation and Qualification of Sterile Filtration Processes of Investigational Medicinal Compounds Traditional Definition of Sterilizing Grade Performance. Presentation. 2014;45.
12. Kolhe P, Shah M, Rathore N. Sterile Product Development. 2013.
13. European Medicines Agency. Guideline on the Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container. Eur Med Agency [Internet]. 2019;31:1–25. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-sterilisation-medicinal-product-active-substance-excipient-primary-container_en.pdf
14. Amrit A, Pande L. Development and Manufacturing of Injectable (Parenteral) Drug Products. Pande World J Pharm Res [Internet]. 2020;9:1047–67. Available from: www.wjpr.net
15. FI VI KR. UJI STERILITAS <71>. 2024;
16. FI VI KR. ENDOTOKSIN BAKTERI <201>. 2024;
17. FI VI KR. PENETAPAN pH <1071> MIKROSKOPI OPTIK <1076>. 2024;2066–7.
18. FI VI KR. Osmolalitas dan osmolaritas <941>. 2024;2046–8.
19. FI VI KR. Penetapan Volume Injeksi Dalam Wadah. 2024;2073–4.
20. Srinivasan C, Ma Y, Liu Y, Wang Y, Hengst L, Liu X, et al. Quality attributes and evaluation of pharmaceutical glass containers for parenterals. Int J Pharm. 2019;568.
21. Mesut B, Özsoy Y, Aksu B. The place of drug product critical quality parameters in quality by design (QBD). Turkish J Pharm Sci. 2015;12:75–92.
22. Pipada V, Joshi SK, Bikkina DJ, Zade S. Scaling Injectable Pharmaceuticals : Roadblocks And Strategies. 2024;2:1598–605.

DOI : https://doi.org/10.24843/JPSA.2024.v06.i02.p02