Regulatory challenges and solutions in implementing usfda microbiological standards in pharmaceutical manufacturing processes

Som Prakash Vats[1]*, Dr. Eshendra Kumar[2]

Research Scholar, Sunrise University, Alwar, Rajasthan

som_microbio@yahoo.co.in

Assistant Professor, School of Basic and Applied Sciences, Sunrise University, Alwar, Rajasthan

Abstract

The Food and Drug Administration (FDA) has gone to great lengths to ensure the safety and effectiveness of sterile product development. A lot of effort has been put into bettering medication development recently. Elements of greater technical engagement include Quality by Design (QBD) in product and manufacturing process development, safe usage and product design, and other related areas. Here we took a look at the big picture of the regulatory hurdles that sterile medicine quality assurance has so far faced. For the production of parenteral in bulk, the Food and Drug Administration has established current good manufacturing practice (CGMP) standards. Extending the research to include additional constituents allows for the assurance of API and excipient compatibility. Appropriate information on the drug product should be provided by the compatibility of the drug product. Both the drug's efficacy and the best way to take it should be covered. One of the FDA's reactions to nosocomial bacteremia's was a microbiological assessment that was carried out in 1970 and 1971 for the production of sterile drugs. Oral and topical drug product recalls and adverse events have prompted a reevaluation of the new drug microbiological review function's usefulness in non-sterile dosage forms. Whether the product is made in-house (as in the case of a non-chemical entity) or supplied externally (as in the case of a generic Active pharmaceutical ingredient -API), the process of proving the quality source for the active pharmaceutical ingredient is often laborious.

Keywords: USFDA, Sterile formulation, Active pharmaceutical ingredient, Compatibility, drug product, Recipients.

INTRODUCTION

Regarding microbiological laboratory inspections, the Guide to the Inspection of Pharmaceutical Quality Control Laboratories offered no direction. This article will assist with the examination of the microbiological analytical procedure, whereas that guide covers many of the concerns related to the chemical part of pharmaceutical laboratory analysis. An analyst (microbiologist) well-versed in the tests under scrutiny should, as is customary in any laboratory inspection, take part in these reviews.

It is common practice for many labs, including those affiliated with the USFDA, to use enrichment medium that include inactivators like Tween or lecithin in order to isolate certain microbiological contaminants. As a result, the preservatives in the product are rendered inactive, and the injured or slow-growing cells are provided with an improved medium. A longer incubation period and a lower temperature are additional growth factors that improve the survival conditions for injured or slow-growing cells.

In order to detect contamination in non-sterile drug goods, labs employed by the USFDA use the cosmetics test techniques outlined in the Bacteriological Analytical Manual (BAM), 6th Edition. A sample is enhanced in modified Lethean broth as part of this examination. Following incubation, MacConkey Agar and Blood Agar Plates are used for further identification. Next, we find the colonies that are on their own. Through this process, microbiologists from the FDA are able to maximize the recovery of all possible infections, as well as quantify and identify each organism that has been collected. Analyzing each medium for its growth-promoting properties is another critical part of the processes used by USFDA analysts.

It is the preservative and formulation of the product being evaluated that determine which neutralizing agents are most suitable. To proceed with identification, it may be required to move the growing organisms from the enrichment broth to a more selective agar medium or to a different kind of enrichment agar.

Colony identification is one possible outcome of microbiological testing, which involves the Total Aerobic Plate Count. Once again, the identification process shouldn't stop with the USP indicator organisms.

Isolate identification using Total Plate Count or enrichment testing is of varying value depending on the product and its intended usage. Testing oral solid dosage forms such tablets

may obviously allow for the acceptable identification of isolates when levels are high. Isolates from plate counts and enrichment tests should be identified for additional goods where there is a strong worry for microbiological contamination, such as topicals, inhalants, or nasal solutions.

LITERATURE REVIEW

Ali (2024) Several nations in the US, UK, ASEAN, SADC, Latin America, Australia, and New Zealand have standardized the regulatory status of drug substances and products to determine which categories traditional herbal products fall under for marketing purposes, and natural products play a significant role in drug development. Differences in the classification of excipients and components, as well as laws pertaining to safety, quality, and effectiveness, are stifling the development of herbal products across nations and regions in the context of their production systems, which disregards their potential medicinal value. In this chapter of the book, we learn about the many regulatory bodies that have recently adopted safety procedures and review practices that are harmonized worldwide. We also learn about the decrease in the use of animals and plants that indigenous peoples have shown to have beneficial properties, as well as the costs associated with this trend.

Challa (2022) Over the course of history, administrative organizations worldwide have consistently voiced significant concern over the composition of pharmaceutical products. Maintaining the medicine's quality is of the utmost importance due to the direct sale of pharmaceutical products and pharmaceuticals to consumers. Inadequate pharmaceutical quality poses a threat to public health and wellness while also addressing a waste of public and private funds. The pharmaceutical industry's first priority, therefore, is to implement a reliable quality system. One practical approach to achieving quality is the Quality Management Framework (QMS). Throughout the pharmaceutical industry, the Quality Management Framework (QMS) plays an important role, from the establishment of the company to the promotion and consumption of the advertised medicine. The pharmaceutical manufacturing sector employs a multi-stage process known as the quality administration framework, which involves applying quality standards at every stage of the production cycle. In order to help increase medication quality, this study will provide a comprehensive overview of the Quality Administration System (QMS) concept and the many administration tactics that contribute to it. Several approaches and procedures may lead to the actual implementation of this idea; two examples are quality by plan and quality gamble the executives. An overview of the various

processes and methods is provided in this survey report. This survey research will be very helpful for novice scientists trying to understand Value The board better, as it pertains to QMS, cGMP, Administrative Rules, QMS, and ICH Rules. In addition, the essay provides a high-level overview of the present quality management system (QMS) procedures and the many opportunities for mechanical innovations in quality administration that aim to improve the QMS's outcomes.

Sandle, Tim. (2017). In the years after these watershed events, pharmaceutical microbiology's scope grew to include both the laboratory and the industrial setting. An awareness of engineering, regulations, research and development, and manufacturing processes is essential for today's pharmaceutical microbiology. A more comprehensive strategy than just selecting technologies and disinfectants is needed for contamination control in pharmaceutical, healthcare, and pre-clinical drug development laboratories. Modern microbiologists are required to have a good grasp of cleanroom procedures, industrial processes, and the best ways to assess the potential human and environmental microbiological dangers to goods. The microbiologist plays a crucial role in meeting regulatory standards. On top of that, we need the opinions of engineers, process experts, and quality assurance staff. Although environmental monitoring and standardized laboratory testing will always be necessary, industrial pharmaceutical microbiology has come a long way in the last decade, adopting practices such as microbiological audits, rapid microbiological methods, risk assessments (both proactive and reactive), and "quality by design" principles to ensure that processes are free of contamination.

Talele (2023) The development and administration of pharmaceuticals rely heavily on Good Manufacturing Practices (GMP) to guarantee their quality, effectiveness, and safety. To keep regulatory clearance and fulfil worldwide standards, pharmaceutical businesses must comply with GMP criteria. Good Manufacturing Practices (GMP) are a collection of rules and regulations that control many parts of the pharmaceutical production process, such as the facilities, machinery, employees, paperwork, and procedures. Consistent production and management of pharmaceuticals according to established quality standards is the goal of these recommendations. From sourcing raw materials to distributing completed products, every step of the medication formulation and management lifecycle must adhere to GMP standards. The hazards of product contamination, cross-contamination, and manufacturing mistakes may be reduced by following GMP principles. Strong quality management systems, comprehensive documentation, well-trained employees, and validated vital procedures are all emphasized.

Pharmaceutical businesses may make their products safer, more consistent from batch to batch, and less prone to recalls and adverse occurrences by adhering to GMP. The inspections and audits conducted by regulatory bodies, such the European Medicines Agency and the United States Food and Drug Administration, ensure that GMP compliance. Regulator fines, product recalls, harm to one's reputation, and legal ramifications may result from failing to comply. Consequently, it is essential that pharmaceutical organizations foster a compliance culture and maintain robust quality assurance and control systems. To sum up, GMP guidelines are regularly revised to include new information, technological developments, and regulatory mandates, guaranteeing that pharmaceutical products are of the greatest quality and comply with all applicable regulations.

Sarkis (2021) New developments in pharmaceutical production and delivery are required to meet the growing demand for medicinal products with intricate and individualized characteristics. In order to make manufacturing processes more nimble, responsive, and repeatable, digital technologies are being used to facilitate communication between process units, plants, and distribution nodes. This article delves into the topic of how sensitive and new treatments are changing the game in the pharmaceutical sector. The pharmaceutical industry's supply chain architecture and operations, as well as new research directions in pharmaceutical production, are summarized here. We categories biologics as either patient-specific or non-specific, and we go over the current difficulties and potential benefits of both small molecules and biologics. Finally, we discuss how process systems engineering supports pharmaceutical distribution and manufacturing strategies by providing decision-making tools that help businesses reap the advantages of digitalization.

CHALLENGES IN PARENTRAL FORMULATION DEVELOPMENT:

The primary objective of developing various parenteral dosage forms is to ensure that the drug substances and excipients are compatible with one another, preventing the development of any new impurities through degradation or the creation of a chemical entity between the drug substances and excipients.

The drug ingredient in the product must be soluble and include a certain number of surfactants or prodrug, or utilise a solubility enhancer like cyclohexdrin, for the drug product to have a shelf life.

Last but not least, the parenteral preparations' properties should guide the sterilization technique selection. For example, sterilization by heat steam is appropriate for solutions that are mostly water, but dry heat is more appropriate for solutions that are mostly solid, but in any event, the main containers may provide justification for this. It shows decision trees for choosing a sterilization method for items that are either water-based or include non-water-based solutions, such as semi-solid or dry powder.

By conducting validation experiments with the appropriate biological markers, we can assess the efficacy of the sterilization procedure and guarantee an Assurance Sterility level (ASL) of 10-64.

RAW MATERIALS- SELECTION CRITERIA

It is crucial to understand the physiochemical characteristics of the active medicinal component. The main structure of biotechnology products, including solubility, molecules, water content, impurity kinds, and crystal structure, may be described using this knowledge. The secondary, tertiary, and quaternary structures can also be determined. In Q6A advice, it is specified what kinds of tests fall under these requirements.

For instance, although choosing the correct polymorph could shorten mixing times or cause other process variations, crystal shape might affect solubility, which is a problem for most small molecule products. Because solubility affects bioavailability, dosage and effectiveness in a solution may be unpredictable.

The raw material selection process also involves agonizing over the excipient choices. It is important to consider the use case while discussing API compatibility. Selecting it should be done with its intended purpose in mind. Antimicrobials, bulking agents, stabilizers, antioxidants, tonicity adjusters, and buffers are all on the list of excipients. The formulator or other characteristics should influence the viscosity.

If just a few of excipients are going to be interacting with the medicinal compound, then compatibility studies should reveal all the juicy details about how they'll work with the Active Pharmaceutical Ingredient (API). "To ensure compatibility with the API and each excipient, the investigations may then be extended to additional components. Preserving excipient levels within a functional concentration is crucial, since it mirrors the amounts that will be used in a formulation. Following this, investigations are conducted to prove that the selected level is suitable by investigating concentrations both above and below the suggested level.

MANUFACTURING PROCESS:

After the initial formula has been determined, the whole production procedure has to be detailed. It ought to handle the necessary component addition and mixing rates. It is recommended that drug items and principal packing materials be sterilized according to the suitable methods for sterile products.

"Creating a marketable product is the end aim of every process development endeavor. Therefore, it is essential to have a reliable process that can be easily scaled up to commercial size and carried out repeatedly. Process variations and out-of-spec test findings (i.e., rejected batches) are consequences of a process that is not resilient. Worse still, recalls resulting from an inadequately designed process might put patients at needless danger.

Therefore, the final result for the patient should be the primary focus of the process engineer and the formulator at all times. "Ongoing collection of thorough developmental data is a need for the formulator and process engineer. In order to ensure patient safety and be ready for regulatory inspection, it is essential to gather all relevant data and conduct all relevant actions throughout the whole development program. Always keep in mind the importance of properly qualifying, maintaining, and calibrating development equipment. The candidates may be employed in the non-chemical entity for the human phase 1 investigations, but all work must be done in a complying way. proper scientific methods, including equipment IQ/OQ, formal calibration, maintenance, and proper documentation, should be used even during pre-formulation work.

The logical conclusion is to,

- Oversee a safe and dependable supply network
- Continue to run a safe, dependable, and productive production process.
- Give a high-quality, safe, and detectable medication.

RAW WATER CHALLENGES IN STERILE FORMULATION:

1. All tests and assays mentioning water must also utilize purified water.
2. To be considered pure, water must not only be free of microbes but also meet certain standards for ionic and organic chemical purity.

3. In order to produce potable water, the water used as a feedstock must meet certain standards.

4. As an excipient, purified water is used in the manufacturing of non-parentral preparations.

Procedure to reconstitute the drug product (if applicable):

There should be a notice detailing the specific handling recommendations (shaking, shear) for the biological medicinal product.

In order to keep a medication product's concentration constant.

An IV container has to have the right size to keep a medication product fresh throughout storage.

The studies included in this part should address specific regulatory requirements.

CONTAINER/CLOSURE SYSTEMS:

Primary packaging components have the potential to impact product stability. Polymers include components that may dissolve into the mixture and induce precipitation or deterioration; the container/closure system is another potential factor influencing stability. The oxygen and moisture permeability of certain materials may influence their stability.

Issues like material selection, light and moisture protection, and so on should be considered while deciding on a main package. All building materials must be compatible with the dose form and be safe to use. It has to include an explanation for why the material utilised for the main package was chosen. Discussions should concentrate on research that proves the container and closing are secure. It is important to consider the potential interactions between the product, its label or container.

As a result, it has to be handled similarly to CCS for sterile finished medicinal products.

The sterile formulation must be stored in a container that is neutral to it.

There should be no mental or physical contact between the container and the material within.

CASE STUDIES:

"Your company has neglected to put in place and adhere to the necessary written protocols to ensure that drug products claiming to be sterile are not contaminated with microorganisms. These protocols should contain validation of all aseptic and sterilization procedures (21 CFR 211.113(b))".

A Laminar Airflow (LAF) unit with aseptic (b)(4) and tubing connections for the (b)(4) process experiences substantial airflow turbulence, which includes air travelling in a (b)(4) direction. The research also did not include any kind of dynamic modelling of this crucial intervention.

While manually aseptically transferring (b)(4) units into the (b)(4) utilised for transport to the (b)(4), no dynamic smoke studies should be detected by unidirectional airflow.

The airflow patterns in the region near your stopper (b)(4) and the turbulence around it were not well evaluated.

It is detrimental to sterility assurance when operators (b)(4) open filled vials while changing the stopper (b)(4).

To prove that your procedures are safe from microbiological contamination and provide sufficient guarantee of product sterility, you need smoke study data showing that all aseptic operations and processing stages have unidirectional airflows.

IN RESPONSE:

1. To avoid contamination of sterile drug products the room should be cleaned
2. Epoxy flooring should be there to avoid any dust particle storage
3. Dynamic airflow visualization study and smoke pattern testing should be conducted to minimize the risk
4. The stopper should provide proper airflow pattern
5. The open filled vials like ampoules should be closed perfectly without giving a chance of contamination

ANALYTICAL CHALENGES:

It is divided into the maximum dosage and the minimum dose to be administered in a clinical setting for the purpose of administration studies. "Although the upper concentration limit is typically not an analytical challenge because it is on par with the undiluted drug product's concentration, there are cases where the lower concentration limit is significantly lower than what can be measured analytically. From an analytical standpoint, the lower concentration limit of 0.05 mg/ml may provide difficulties for biological products like monoclonal antibodies. The dosage schedule or analysis should be adjusted accordingly in such cases. With the right concentration, the capacity of the intravenous container should be minimized for low dosage levels of delivery.

Individual copies of the sample. It is important that the samples used to optimize measurements provide accurate results. However, this might really cause a dramatic spike in the quantity of samples and the need for pharmaceutical products in the real world. Consequently, it's possible to use duplicate samples. Consideration of average sample composites may be warranted when the loads of duplicate samples remain too high. In this case, the analytical sample will really be a combination of many identically produced samples. It will be reflected1 when testing a single sample.

Analysis of sample preservation. It may be necessary to freeze samples in order to prevent any changes if they cannot be analysed right away or if they need to be transported to separate testing locations. Nevertheless, in order to assess how freezing affects sample stability, a probe research or previous experience is required.

Impurities in the diluent Some diluents may include contaminants that make it difficult to use certain analytical methods on admixture samples. The presence of 5-hydroxymethylfurfural and similar compounds in Dextrose Injection, USP solution may affect the accuracy of UV A280 concentration measurements since they are byproducts of dextrose's degradation and absorb light at around 280 nm.

REGULATORY REQUIREMENT:

The necessary steps for registering a pharmaceutical product have been deliberated by regulatory bodies. The following is described, for instance, in the "ICH Harmonized Tripartite Guideline—Pharmaceutical Development Q8": In order to provide suitable and supporting information for the labelling, it is necessary to address the drug product's compatibility with

reconstitution diluents (such as precipitation or stability). The suggested in-use shelf life, acceptable storage temperature, and expected concentration extremes should all be covered by this information.

It may also be necessary to handle the issue of product mixing or dilution before administration, such as when product is introduced to high-capacity infusion containers. 2009 ICH. Concerning the "Dosage and Administration Section of Labelling for Human Prescription Drug and Biological Products—Content and Format" (US Department of Health and Human Services and Drug Administration) referenced in the "Guidance for Industry" document titled "Dosage and Administration Section of Labelling for Human Prescription Drug and Biological Products" (21 CFR 201.57(c)(3)),

Discordant surfaces. The possibility of drug loss owing to adsorption (a little quantity of drug coming into touch with the whole surface of the container) is another issue with admixture solutions, and it becomes particularly important at low concentration levels. The likelihood of drug loss at surfaces increases with large dilution ratios because the concentration of surfactant, if present in the therapeutic product, may also decrease below critical micelle concentration. However, when surface driven denaturation adds instability to the mix, it becomes 12.

Option for diluents the clinical program's requirements should guide the conduct of the stability and compatibility investigations. In the event that incompatibilities arise throughout the administration studies, it assists in eliminating such options. The process of reformulation may also aid in the elimination of certain options in specific instances. To illustrate the point, prior to formulation, biologics may have shown signs of incompatibility with sodium chloride, such as a rise in opalescence, the production of particles, instability under shaking stress, and/or the development of soluble aggregates. Normal saline is not recommended as a diluent in such instances.

ICH Q8: PHARMACEUTICAL DEVEOPMENT:

The Health Authorities' parameters for ensuring quality during product registration are specified in the International Conference on Harmonization (ICH) guidance Q8 Pharmaceutical Development for Technical Requirements for Registration of Pharmaceuticals for Human Use (FDA Guidance for Industry 2009b).

The articulated aim of the Q8 advice is as follows.

The Q8 advice delineates the framework for presenting "the knowledge acquired through the implementation of scientific methodologies and quality risk management (as defined in ICH Q9 Quality Risk Management) in the development of a product and its manufacturing process." The part is first created for the approved original marketing application and should reflect comprehensive understanding. Achieved throughout the product lifetime. The Pharmaceutical Development section must address the critical elements of the product and manufacturing process for reviewers and inspectors.

The Q8 advice also identifies areas where enhanced comprehension of pharmaceutical and manufacturing sciences might provide a foundation for adaptable regulatory strategies. The Q8 guideline states, “The extent of regulatory flexibility is contingent upon the level of pertinent scientific knowledge provided.” Therefore, it should not pertain to preclinical and clinical phases. The information acquired from these investigations offers further help.

QUALITY BY DESIGN:

These guidelines address the different components of the Pharmaceutical Development report necessary for the Common Technical Document required for product registration. Each segment of the outline is grounded on essential principles of sound science that a formulation development expert typically considers. Furthermore, Q8 offers a proposed strategy for risk assessment by formulating studies to identify key process parameters (CPPs) and establishing suitable controls to guarantee consistent product quality. The often-used phrase is "Quality by Design" (QbD). The QbD concept emphasizes the significance of development scientists designing studies and prioritizing all aspects to ensure the maintenance of a high-quality end product.

QUALITY PARADIGM:

Product Overview

CQA's risk assessments

Design parameters Regulatory approach

Ongoing enhancement

ELEMENTS OF QBD:

Product process design and development:

Define desired product performance upfront and identify product CQA's

Design Formulation and process to meet product CQA's

Understand impact of material attributes and process parameters on product CQA's

Identify and control source of variability in material and process

Continually monitor and update process to assure consistent quality

Risk Assessment and risk control

ACTIVE PHARMACEUTICAL INGRIDIENT (API):

The formulator is probably informed about the selected API by the sponsoring business. The individual formulator is usually identified as an NCE and assigned the responsibility of generating the appropriate formulation in large pharmaceutical companies. Formulators in some smaller companies are tasked with identifying prescription components that have become old and reworking them to solve problems that have persisted from earlier formulations. In other companies, the formulator's job is to create a generic version of an established drug product by copying the original company's formulation.

It may be a tedious and time-consuming process to prove the quality source of the Active Pharmaceutical Ingredient, regardless of whether the product is generated internally (like a non-chemical entity) or purchased outside (like a generic API). A few of the primary characteristics assessed for small molecules are their impurity profile, salt form, and polymorph/solvate. Verification of the principal structural sequence of biotech compounds is required prior to their assessment. This sequence must include any secondary, tertiary, or quaternary structures as well as any labile connections.

Several parts of the formulation plan focus on the solubility of the small molecular product that is crystallized from salt. Stability might also be affected by the procedure's product. To create formulation solubility, it is essential to know where the active medicinal component is coming from.

The impurity profile of the active medicinal component must be considered. In conjunction with the Q6A guidance, ICH recommendations Q3A (FDA Guidance for Industry 2008b), Q3B (FDA Guidance for Industry 2006a), and Q3D (FDA Guidance for Industry 2009a) provide directives in this area. Impurities over 0.1% must be rectified. Actions range from identification to toxicity assessment, contingent upon the impurity level. Furthermore, ICH Q3C (FDA Guidance for Industry 2012) specifies permissible levels of residual solvents in pharmaceutical compounds, as does the USP.

The generic active pharmaceutical ingredients provide additional challenges in developing an impurity profile that meets the standards of the original product. Impurity levels must be evaluated against the branded product to confirm that no additional pollutants are introduced. Therefore, samples from many vendors must be obtained and assessed to determine which API providers can deliver the drug substance that conforms to the established impurity profile of the novel product. “Upon confirmation of the API source, routine Preformulation can commence to facilitate the characterization of the physicochemical properties of the drug substance.” These investigations include the augmentation of the solubility database across diverse solvent systems and varying pH levels, contingent upon the ionic characteristics of the medicinal molecule. The molecule's propensity for hydrolysis at different pH levels, thermal degradation, photodegradation, oxidation, and reduction is also analysed. Moreover, for biological molecules, Preformulation encompasses several studies, including amino acid sequencing, alpha-helix analysis, beta-sheet content analysis, sulphide linkage identification, glycosylation pattern characterization, and other assessments that may influence formulation strategies and overall stability. The FDA has controlled current good manufacturing practice (CGMP) standards. The investigations may thereafter be extended to other constituents to ensure compatibility with the API and each excipient.

CONCLUSION:

The research concludes that sterility must be preserved in accordance with quality standards inside the production unit, ensuring optimal compatibility of the medication product, hence adhering to quality criteria. This study has been undertaken to mitigate contamination in different sterilization processes. The production of sterile products must adhere to FDA regulations. The primary objective of the study is to reduce mistakes in the packing regions, manufacturing unit, and container closure system to create high-quality goods that meet

customer requirements. This discussion briefly addresses the regulatory constraints in sterile formulation.

Abbreviation

API: Active pharmaceutical ingredient

ASEAN: Association of Southeast Asian Nations

ASL: Assurance Sterility level

BAM: Bacteriological Analytical Manual

CCS: Closed Circuit System

CDER: Center for Drug Evaluation and Research

CFR: Code of federal Regulations

CGMP: Current Good Manufacturing Practice

CPP: Critical Process Parameter

CQA: Critical Quality Attribute

GMP: Good Manufacturing Practice

ICH: International Conference on Harmonization

IQ: Installation Qualification

IV: Intravenous

LAF: Laminar Airflow

OQ: Operational Qualification

ORS: Office of Regulatory Science

QBD: Quality by Design

QMS: Quality Management System

SADC: Southern African Development Community

UK: United Kingdom

US: United states

USFDA: United States Food and Drug Administration

USP: United States Pharmacopeia

USP: United States Pharmacopeia

Reference

1. Sarkis, M., Bernardi, A., Shah, N., & Papathanasiou, M. M. (2021). Emerging Challenges and Opportunities in Pharmaceutical Manufacturing and Distribution. *Processes*, *9*(3), 457. https://doi.org/10.3390/pr9030457

2. Talele, D., Talele, C. R., Shinde, Y., & Shaha, A. (2023). *Good Manufacturing Practices and compliance requirements in drug formulation and management*. In *Frontiers in Pharmaceutical Sciences*. Scieng Publication. which journal? Date?

3. Sandle, Tim. (2017). Pharmaceutical Microbiology: Current and Future Challenges. *Journal of GxP Compliance*. Volume 211-5.

4. Challa, Sri & Tilala, Mitul & Chawda, Abhip & Benke, Abhishek. (2022). Quality Management Systems in Regulatory Affairs: Implementation Challenges and Solutions. Journal for Research in Applied Sciences and Biotechnology. 1. 278-284. 10.55544/jrasb.1.3.36.

5. Ali, Faraat & Neha, Kumari & Ilyas, Anam & Ali, Hasan. (2024). Introduction, Challenges, and Overview of Regulatory Affairs. In book: Global Regulations of Medicinal, Pharmaceutical, and Food Products, Publisher: CRC Press Taylor and Francis, May 2024. 10.1201/9781003296492-2. which journal?

6. Angie D., 2009. Pharmaceutical Technology. 90. Available on http://www.pharmaceutical-technology.com. Accessed on 3.10.12.

7. Drakulich, A., & Van Arnum, P. (2010). *Solid dosage and excipients* [Supplement]. *Pharmaceutical Technology*, May 2010 Solid Dosage and Excipients Supplement. Pharmaceutical Technology. s24.e/month?

8. Lipuma, J. (2005) Update on the Burkholderia cepacia complex. Curr Opin Pulm Med. 11 (6): 528–33

9. Avgeri, S.G., Matthaiou, D.K., Dimopoulos, G., Grammatikos, A.P., Falagas, M.E. (2009). Therapeutic options for Burkholderia cepacia infections beyond co-trimoxazole: a systematic review of the clinical evidence. Int. J. Antimicrob. Agents. 33 (5): 394–404

10. FDA (2017) FDA advises drug manufacturers that Burkholderia cepacia complex poses a contamination risk in non-sterile, water-based drug products, U.S. Food and Drug Administration, U.S. Department of Health and Human Services, at: https://www.fda.gov/Drugs/DrugSafety/ucm559508.htm (accessed 23rd July 2017)

11. EudraLex Volume 4, EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Annex 1, Manufacture of Sterile Medicinal Products, Brussels, 2017

12. Jornitz, M. and Meltzer, T. H. (2011) Pre-use/post-sterilization Integrity Testing of Sterilizing Grade Filter: The Need for Risk Assessment, American Pharmaceutical Review, at: http://www.americanpharmaceuticalreview.com/Featured-Articles/36745-Pre-... (accessed 23rd July 2017)