Quality by Design in Single Use Systems

Single use systems (SUSs) are replacing stainless steel systems in biopharmaceutical industry, for need of higher flexibility, faster turnaround, lower documentation and lower energy consumption. Customized multi-component polymeric assemblies, which has resulted in new challenges for the bioprocess owners with regards to leachables, biosafety, sterility, integrity and particulate matter. As an end user, the bioprocess owner usually does not have expertise to verify these single use assemblies. So, it has thus become imperative for SUS supplier to address these challenges through a well developed system that assures quality at every step in production of such assemblies. Quality by Design (QbD) with its basic elements helps to ensure consistent quality of SUSs. QbD elements includes Quality Target Product Profile (QTPP), Critical Quality Attributes(CQA), Critical Material Attributes(CMA), Design Space and Critical Process Parameters(CPPs). Incorporating the elements of QbD at every step helps mitigate the risk of failure and improve process efficiency. This white paper discusses the impact of QbD on quality of single use fluid management systems critical for biopharmaceutical processes.

Keywords: Quality by Design (QbD), Quality Target Product Profile (QTPP), Critical Quality Attibutes (CQAs), Critical Material Attributes (CMAs), Design Space, Critical Process Parameters (CPPs)

Authors: Vipasha Sharma, Vivek Sheel Gupta

We are witnessing an industry wide shift in biopharmaceutical manufacturing processes from reusable stainless steel systems to single use disposable systems, for need of higher flexibility which leads to faster turnaround times and lower documentation and energy costs. Single use systems also reduce the demand for arduous and expensive cleaning, alteration, and validation processes, which minimizes required processing time. However, Single Use Systems (SUSs) are customized, multi-component, assemblies with components such as membrane filtration devices; bags; connectors; tubing; and fittings; and range from simple transfer systems to complex disposable filling lines. This has resulted in new challenges for the bioprocess owners with regards to leachables, biosafety, sterility, integrity and particulate matter. These major concerns need to be addressed for efficacious outcomes (1).

The bioprocess owner as an end user, usually does not have the infrastructure or expertise to verify these single use assemblies for such regulatory and functional concerns and to ensure compliance. It has thus, become imperative for the SUS manufacturer/supplier to address these challenges through a well developed system that assures quality at every step to design, development, qualification, validation and manufacture of these single use fluid management systems.

Quality by Design (QbD)

According to ICH Q8, QbD is defined as "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and Quality Risk Management (QRM)". QbD consists five practical elements which integrate quality considerations throughout the lifecycle of a product, from design to production (2).

These basic elements are:

- Quality Target Product Profile (QTPP)
- Critical Quality Attributes (CQA)
- Critical Material Attributes (CMA)
- Design Space
- Critical Process Parameters (CPPs)

Quality by Design (QbD) with its basic elements, helps ensure consistent quality of SUSs and every single use component that goes into realization of these SUSs. It ensures quality right at the, conceptualization of the product with definition of its Quality Target Product Profile(QTPP), which is done

by establishing the Market Requirement Specifications (MRS) for the product. The MRS establishes product specifications and help design products that meet or exceed functional and regulatory requirements.

This is followed by design and development of new product, including selection of materials, based on Critical Material Attributes (CMAs) and Critical Quality Attributes (CQAs).

Critical Material Attributes

One of the key aspects of quality in SUS is ensuring that the materials used are of high quality and meet industry standards. The components of SUSs, such as bags, tubing, connectors, and filters, must be made of materials that are compatible with the products being processed and free from contaminants that could compromise drug product quality and consequently patient safety. It is essential to use high-quality, medical grade materials that are compatible with the intended use of the system. The materials should be of broader chemical compatibility, biosafe, nitrosamines free, animal origin free, with low extractables and gamma sterilizable to ensure product integrity and patient safety. It is requisite for manufacturers to work closely with suppliers to ensure the materials meet stringent quality requirements and are tested for compatibility with the processes they will be used in (3).

Critical Quality Attributes

Critical Quality Attributes (CQAs) are determined based on the desired quality standards and the needs of the end users. An understanding and control of these CQAs, ensures that the product meets the desired quality specifications consistently (4).

Some of the Critical Quality Attributes are:

- Low bioburden
- Sterility Assurance Level (SAL) of 10^{-6}
- Integrity Testability
- Bacterial Endotoxin < 0.25 EU/ml
- Particle/Fiber free
- No Microbial Ingress
- Shelf Life

Ensuring Consistent Quality

In addition to material quality, design and testing, the manufacturing process plays a major role in quality of SUSs. It is essential to have robust measures in place to monitor and control every step of the manufacturing process.

One of the core principles of the QbD is to design and develop processes and products with an understanding of how variation affects product quality. By understanding the Critical Process Parameters (CPPs) and their relationship to product quality attributes, manufacturers can design robust processes that consistently produce products that meet the desired quality standards (5).

At MDI, once initial prototypes are tested, the productionization program which involves definition of various process steps involved in product realization along with CPPs at each step, is initiated. This program culminates with machine qualification, validation of CPPs and process/product validation, and helps establish, not only a robust manufacturing process to deliver consistent quality but also to define test methodologies and specifications for in process and final product quality control.

All single use components undergo a well defined on-boarding program where in compliance with various regulatory as well as functional requirements are assured through extensive testing of validation lots and documentation including characterization and validation reports, validation guides, certificate of analysis, etc. These include but are not limited to testing and verification of bio-reactivity, cytotoxicity, non animal origin, bacterial endotoxins, particulate matter and bio-burden.

Design of customized SUSs

The design of the SUS is another important factor in ensuring it's quality. The design must be appropriate for the intented application and must meet industry standards and regulatory requirements.

MDI works closely with the process owners to understand their applications and requirement in terms of working environment, volume range, temperature conditions, fluid pressure, size and number of connections, transfer lengths, sampling needs, chemical compatibility etc.

Subsequently technical feasibility of the system is established based on available **approved** single use components and an initial SUS drawing is proposed. Product prototyping and final approval lead to realization of the customized SUS.

Realization of Customized SUSs

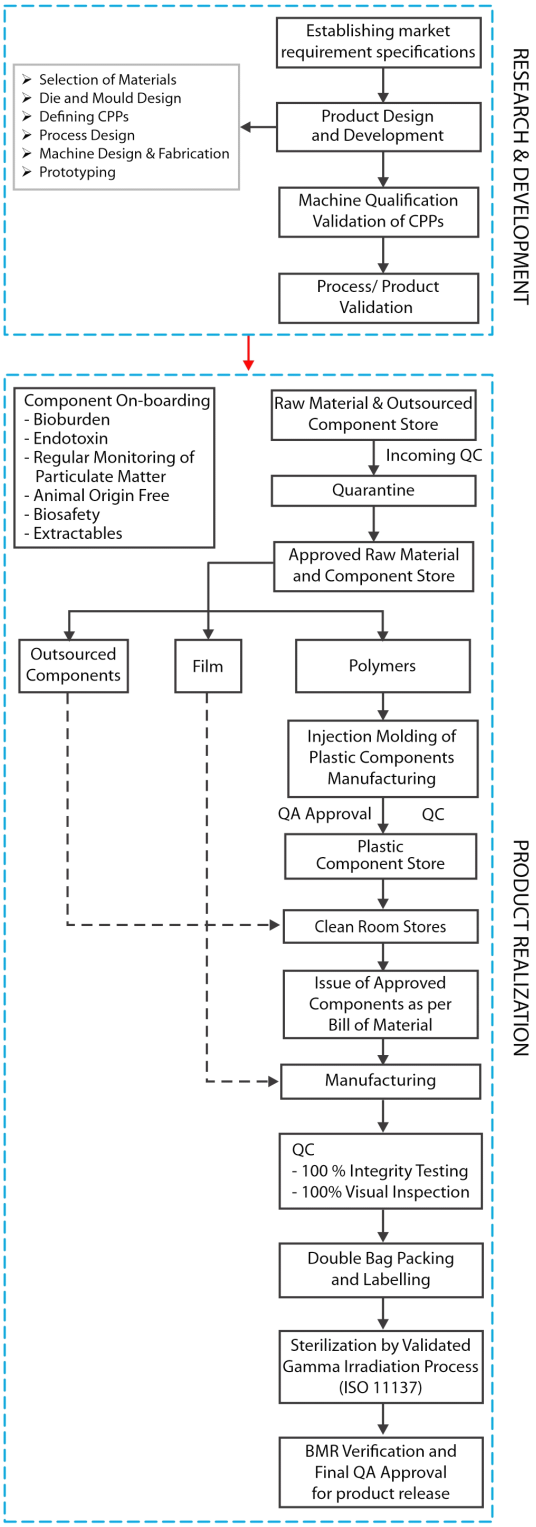
Realization of a single use system involves assembly of approved components as per customer approved drawings.

This assembly process is required to ensure:

- No leaks
- No microbial ingress
- Low bio-burden
- Bacterial endotoxins exhibit < 0.25 EU/ml as per USP <85>
- Particulate matter as per USP <788>
- Sterility with a Sterility Assurance Level (SAL) of 10^{-6}

Therefore, it is critical that these SUSs are assembled in cGMP compliant clean room facilities (ISO Class 7) by trained personnel using validated assembly processes. This helps ensure control over bio-burden and particulate matter.

cGMP Compliant ISO Class 7 facility



Another challenge for SUS manufacturers is to ensure integrity of each and every customized assembly, designed to meet user specific process requirements. This is critical as any failure can lead to leakages causing loss of high value process fluids or microbial ingress resulting in sterility failure.

As the assembly process involves various critical steps such as film slitting, bag sealing, port sealing, tube cutting, and making secure connections between different components, in order to realize an integral SUS, these are required to be validated.

Also, each and every lot of single use assemblies needs to be 100% integrity tested. The integrity is tested by pressure decay using a differential pressure gauge method. It involves an automated integrity test system to pressurize the assembly up to a defined pressure using filtered air and measuring the pressure decay.

Single use assemblies are highly customized fluid management systems used in critical applications. It is critical to establish the integrity test specifications for each customized single use systems/assemblies by correlating the same with maximum allowable leak limit (MALL).

MALL is established conducting microbial ingress studies on assemblies with different controlled leak sizes.

In addition, the SUSs, need to be visually inspected and verified at various stages of the assembly process to not only ensure that the components used, their dimensions and orientation are as per the approved drawing, but also check for any defects or particulate contamination in the fluid pathway or packaging.

Packaging

Double bag packaging and labelling in approved packaging materials with chemical indicator ensures proper safety of the system. MDI SUS are double packed in polyethylene bags to ensure package integrity in the course of shipment as well as to prevent contamination while transferring to cleanroom assembly or process areas.

Sterilization by Gamma Irradiation

SUSs are sterilized by gamma irradiation and it is critical to ensure that the sterilization process provides the required sterility assurance level of 10^{-6}. This program includes continuous monitoring and control of bioburden levels as well as the sterilization process by gamma irradiation. It involves qualifying gamma irradiation service provider, gamma irradiation dose mapping, gamma irradiation dose substantiation, quarterly dose audits for dose verification.

Finished gamma sterile single use systems are released into the market after Batch Manufacturing Records verification and approval by Quality Assurance.

Conclusion

Quality in SUSs is essential for ensuring the safety, reliability, and consistency of the drugs being produced which inturn can impact patient safety as well as process economies.

QbD promotes a holistic approach to quality management that focuses on understanding the product and process, designing for quality, and continuously improving through data-driven decision making. By focusing on understanding and controlling critical quality attributes, optimizing process parameters, and managing risks effectively, single use system manufacturers can ensure consistent quality through high-quality materials, product design, robust manufacturing process and validated quality control methods.

References

1. https://mdimembrane.com/blog/2024/07/05/quality-by-design-enhancing-biopharmaceutical-manufacturing/
2. https://www.ich.org/page/quality-guidelines
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4070262/
4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4674654/
5. https://www.sciencedirect.com/topics/engineering/key-process-parameter