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Advancing Cleanroom Contamination Control Strategies with Automation and AI: Current Status and Future perspectives in the Manufacturing of Parenterals

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Abstract

Contamination in parenterals affects products' critical quality attributes and patient safety. lapses are frequently noticed, leading to product recalls. The most recent Annex-1 guidance expects manufacturers of parenteral products to evolve with a holistic contamination control strategy covering unit operations, processes and activities. The operation segments in cGMP environment are described wholly under 6M's (Men, material, machines, Methods/processes, Mother nature/environment and Measurement/ controls) and their respective subfunctions. We discussed the role of critical controls to validate the process The need for automated equipment compliant with GAMP 5, the focus areas requiring technological advancement using artificial intelligence (AI) are discussed. Novel automation controls that can be installed in existing manufacturing units and the corresponding outcome for an improved CCS is summarized.

Keywords: Contamination Control Strategy, GAMP 5, ICH, GMP, Aseptic Process Simulation, Automation

Introduction

The most recently released Annex-1 draft guidance on the manufacture of sterile products (1) discussed the need for development of a comprehensive CCS. It emphasized the need for a top-down approach to understand the critical control points (CCPs) that affect product quality. The knowledge of process analytical technologies (PAT) (7) coupled with the principles of ICH Q10 (2) helps us to lay down the necessary controls. Regardless of the degree of controls laid down, we carry a residual risk. Among the various risk assessment techniques (2), the Hazard Analysis Critical Control Point (HACCP) is versatile and ideally summarizes the CCPs. In order to prepare a holistic contamination control strategy (CCS) document and apply the principles of HACCP in its entirety, we opted for the 6M approach (3-5). We graded the overall compliance requirements under the 6M tree. Based on the data of lapses reported for one or more of the CCS elements in various regulatory notices and/or warning letters, we summarized the vulnerable areas where redundancy of controls is required. Corrective and preventive actions (CAPAs) for lapses are usually tedious; however, modern automation tools can aid to effectively map the vulnerable areas on a real time basis and further correlate the root cause with existing data libraries thus helping to evolve with a more robust CAPA. Very often, product quality risk is eliminated by reducing manual intervention and improved automation. GAMP5 guidelines are designed to ensure that automated systems comply with the cGMP standards. (6). The advantages of automation and AI for achieving an improved CCS is presented.

6m classification & identification of CCPS in an aseptic environment

The 6M Technique aids in identifying process inefficiencies and helps to drive continuous improvement in the manufacturing environment (5-7). The scope of 6M for general aseptic operations is indicated in figure 1. CCPs for general aseptic operation are discussed. In instances demanding distinct attention to testing and controls, such as large-volume parenteral (LVPs) and powder injectables, we have dedicated sections within this review to address these specific areas.

Facility

Clean room controls

All intersection points through which materials, men and waste move are areas of concern. The guidance on the facility requirements for aseptic operations is widely available (8, 9). Facilities are qualified before their intended use. Equipment qualifications, simulation studies and validations are often conducted to identify the CCPs. Notably, the design must ensure the absence of uncleanable recesses (10, 11). Process areas are designed such that sink or drain provisions are absent in the Grade A/B areas. All other drains are microbially monitored for flora. Modern building designs ensured dedicated corridors for waste movement and separate passages for RM / FG movements to prevent contamination. A positive pressure variance with the surrounding is a vital CCP. Hence, a pressure differential of no less than 15 pascals between two distinct classified zones (regulation mandates NLT 12 pascals) and a pressure differential of at least 6 pascals (regulation mandates NLT 4 pascals) between two rooms with identical classification (regulation mandates NLT 4 pascals) is routinely upheld. Calibrated magnehelic gauges capable of recording and generating alarms are often placed to enhance monitoring capabilities. All the Cleanrooms are qualified and classified based on applications. Grade A (Filling area, sterile laundry receipt, LAFs area, Mobile LAFs, sampling area for pre-sterilized components), Grade B (filtration area, Receipt area for filtered liquid, blending area of sterile APIs, receipt area of filtered liquid, blending area for sterile APIs, peripheral area of filling), Grade C (laundry washing, Compounding area, equipment washing area, secondary change rooms, unloading pre-sterilized components, handling pre-sterilized components) and Grade D (Primary change room, equipment washing area, vial washing area, plug washing area) areas are equipped with terminal HEPA (H14) (12-21). CNC areas (Vial inspection, Packaging and labelling, RM stores, Microbiology waste disposal area, Quality unit, Finished Goods store) are equipped with 5µ filtered air. Lux level in the vial inspection area is a CCP and shall range from 2000 – 3750 lux depending on operation.

Men

Training, gowning qualification, health & hygiene

Human activity in the cleanrooms is the primary reason for particulate and microbial contamination (24). CCPs such as routine self-inspection, materials for apparels, garment sterilization, maintenance and the overall gowning processes are critical. Standards for cleanroom garments are described (22) and their quality can be assessed using various procedures (23). The Helmke Drum test (28) that verifies the particle shedding, especially when a garment is washed multiple times, is critical. The number of wash cycles for garments is hence validated. Sterilized garments shall have a definite validity period and the sterility assurance level shall be NLT 10^{-6} after sterilization

Gowning qualification tests the operator's proficiency to don and doff the garments correctly and conduct EM in Grade B areas. Re-qualification criteria, other than during annual frequency, is also required. No specified swab sampling locations were described in literature (1); hence, companies develop a risk-based approach to identify the locations for sampling (25).

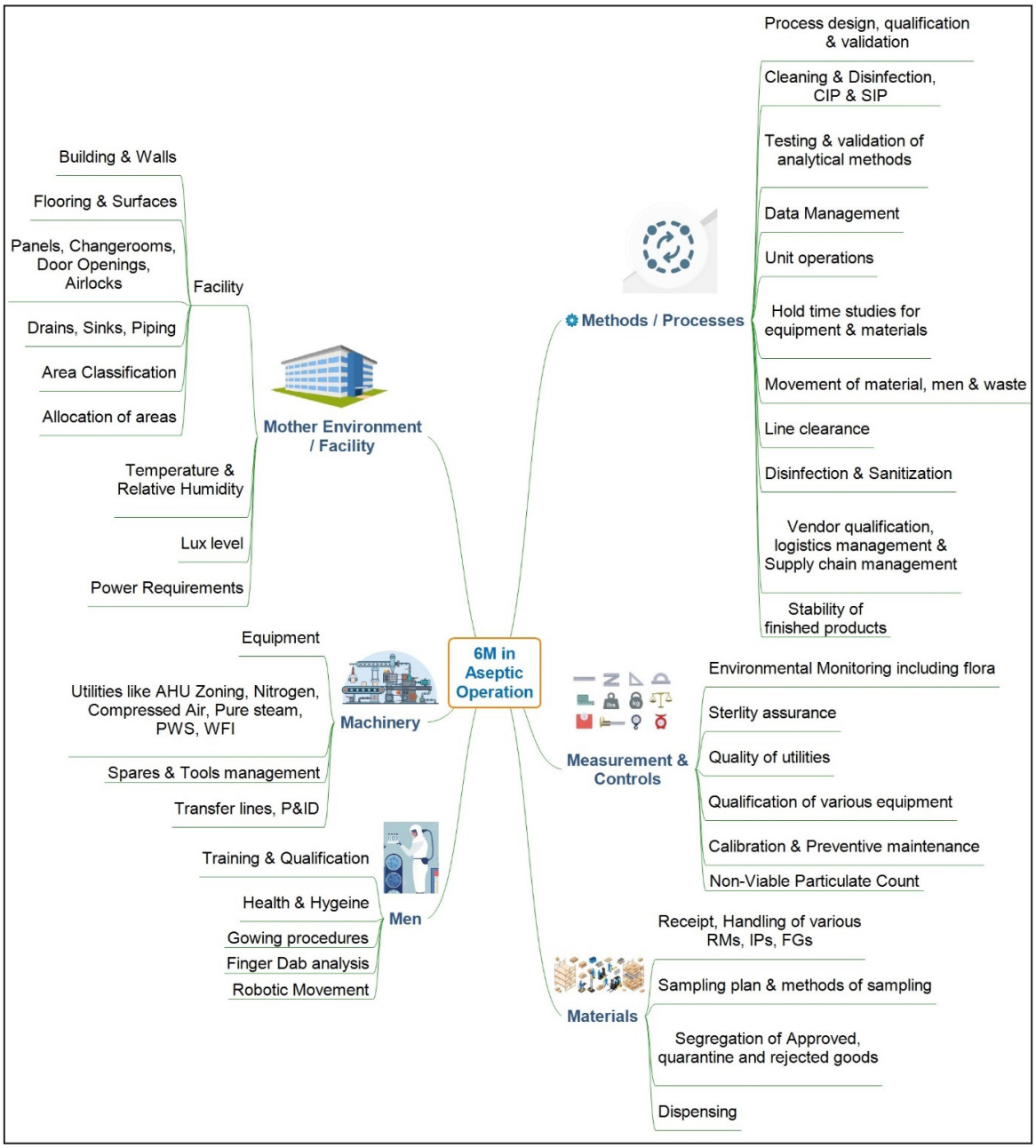

Figure 1: CCPs in an aseptic environment based on 6M classification.

Personnel suffering from communicable diseases such as tuberculosis, influenza, etc., including bruises and skin infections such as psoriasis and contact dermatitis, shall be prohibited (26). The health of the operators is monitored. Companies implemented thermal screening methods during the COVID-19 pandemic. Any undue absenteeism during the pan-

demic mandated the management to re-confirm that the personnel attended to the company in a clean environment.

Machinery (equipment, utilities & tools)

Control on the usage and maintenance of process equipment, utilities and spares is utmost critical as they are located in the Grade A area. A line clearance procedure enlisting the various CCPs is undertaken before the start of the activity. The handling of machinery, utilities and tools is video recorded for traceability during the operation.

Process equipment & utilities

Automation reduced human intervention and improved data integrity. All qualified process equipment is enabled with the highest degree of automation to prevent contamination (13, 28-30). Machinery equipped with data loggers and PLCs that are capable of real time recording and generating alarms, shall comply with 21 CFR Part 11 and GAMP5 recommendations (27). Filter membranes shall comply with ISO 16610-21 (31). Qualified utilities mostly undergo contact with the product solutions and hence filtered through 0.2µ porosity filters. A list of CCPs for various critical utilities is enlisted (see table-1). Purified water forms the input material for WFI generation and its quality is monitored continuously. The most recent water purification systems employed the use of variable frequency drive to meet flow velocity requirements (NLT 1.3 mt/sec). The most recent equipment are designed to give SMS alerts to the personnel concerned when the operating limits are deviated. Also, hooter alarms are equipped to alert the engineering personnel if there is a deviation in the set point conditions.

Tools & spares management

All tools introduced into core areas are sterilized and remain within, prohibiting their exit to maintain sterility. If a sterile equipment or tool accidentally drops to the floor, refrain from retrieving and using it. Instead, ensure that the room is equipped with extra sterile supplies. Additionally, all gloves and tools are designated for single use and subsequently discarded, upholding stringent cleanliness standards within the environment. Glove ports are sterilized and employed for contamination-free operations. Latex gloves, pre-sterilized through Ethylene oxide or Gamma sterilization, are tested for sterility in batches, ensuring their suitability for use. These gloves are also powder-free to prevent particulate contamination. Silicone tubes, integral for transferring gases and liquids, undergo autoclave sterilization and testing for leachates, compliant with USP <1663 & 1664> (32).

Materials and Methods

Receipt of raw materials (RM)

RMs shall be received from approved vendors only. Pre-shipment samples for sterile APIs, rubber stoppers and other gamma-sterilized materials, including sterile personnel protective equipment (PPEs), are received and tested for sterility. Upon confirmation of the sterility, the order quantity is requested for release from the supplier's site, and after receipt, it is verified against an inward checklist. Thermosensitive materials shall be adequately packed along with a temperature datalogger, and upon receipt, shall be stored in designated storage conditions.

Sampling & dispensing

Non-sterile APIs are subjected to 100% sampling while the excipients are sampled based on (Square root of N + 1) (9). For bulk receipts, AQL sampling methods can be followed (33). Sampling for sterile APIs shall not be done, and results of the pre-shipment sample are taken as final for approving the lot. For buffers, anti-oxidants and preservatives that are intended as powders for reconstitution separate procedural controls are required *(*see discussion under *CCPs for Powder injectables).* Sampling shall be done only after satisfactory visual inspection using dedicated and compatible tools. Clean and unclean equipment hold-time

studies shall also apply to the sampling tools. Reverse LAF systems complying with ISO 5 or Grade A/B requirements are used for dispensing. Line clearance is verified before carrying out the activity.

Controls for In-process materials

In-process materials shall only be prepared in the Grade B area until complete manufacturing. Hold time studies for solutions are done to study the effect of any unforeseen interventions during the process. The quality parameters at the end of the hold time shall be comparable with that of the finished product.

Storage & despatch of finished goods

Finished Goods (FGs) shall be stored in controlled environmental conditions with adequate protection from heat and light. The quantity reconciliation must be readily available, and despatch procedures shall follow the first-expiry-first-out methodology. Retention samples of each of the batches shall be stored at designated locations with physical lock and key to enable the investigation of complaints/queries that may arise after despatch. The retention period for finished goods batch samples is 1 year more than the designated shelf life. For RMs, the designated shelf life is up to 6 months from the date of receipt. The storage and despatch of intact sealed containers contribute very little to the overall contamination control strategy.

Methods (Processes & simulations)

Process qualification & routine unit operations

The process qualification shall involve the identification of CPPs with a challenge to consistently achieving the CQAs throughout the product life cycle. Ideally, procedural controls are established. The CCPs in the process are identified and documented. For filter membranes, the compatibility, integrity, adsorbent properties and filtration time often limit the batch size for viscous solutions. The overall process flow is described in figure 2.

Aseptic process simulation (APS)

Unlike in terminal sterilization, where parametric release of materials is permitted (47, 48)], the products manufactured by aseptic filling are exposed to a high degree of risk. Media fill studies (APS) are applicable for aseptically filled products only. Media fill studies are processes by which the product is not manufactured, but instead, media is prepared and filled into containers as though the product is made. The process undergoes all the steps that are there for a given product. All the unit operations involved in manufacturing the product must be carried out as part of media fill studies. These must be conducted under stress conditions to ensure the product can withstand any inadvertent contamination. The entire activity has to be carried out as though it is a routine process and not staged to have additional precautions than customarily practised. This may give a false negative result. Guidance on the number of containers to be taken for the media fill study was provided by the Parenteral Drug Association (34). The industry does not allow any failures in the APS. Any failure calls for thorough investigation and identification of the organism, at least to its genus level, its source and remediation to prevent recurrence. Three consecutive APS runs are usually done for the initial simulation. Based on the production load, the quality team can decide the number of runs for periodic confirmation.

Media fill studies are performed under various circumstances, including facility qualification, significant changes to the water system, facility, or air handling unit (AHU), the introduction of a new product, batch failures, or when environmental counts exceed alert limits. These studies are routinely conducted every six months to ensure aseptic processing integrity. In cases where the same product is filled in different volumes or weights, bracketing can be applied to streamline testing. Additionally, simulations are conducted for different dosage forms to validate sterility assurance across various manufacturing conditions.

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Filling of containers

The volume of product to be filled need not be the volume that is filled in a container. The reason is that, during incubation, the vials are kept so that the entire product contact surface area is covered, including the closure if applicable. (Up-right, Inverted, horizontal positions during the incubation period).

To simulate dry powder (lyophilized), sterile mannitol is filled into containers and sterile media is subsequently added and sealed as a part of unit operation. The mannitol dissolves immediately and does not alter the characteristics of the media.

For aqueous gels, the media is added into the gel without the active ingredient and the preservatives and filled.

Table -1: Controls for various utilities in parenterals, compendial requirements and best practices in the industry

	CCPs for various utilities	Compliance requirements	Routine Practice
Compressed Air	Oil content < 0.5 mg/m^3 Dew point -40°F NVP matter ≤ 90000 for 0.5µ and ≤ 1000 for 5.0µ Bio load = Nil Max discharge air pressure < 7 kg/cm^2	ISO 8573	For the service lines, a filter integrity test is done once every six months (± one month) during non-production days. The service line filter is replaced once in 2 years (± one month)
Nitrogen	Purity > 99.5% Oxygen < 0.5ppm CO / CO_2 < 1ppm Water < 3ppm Oil content < 0.5 mg/m^3 Dew point -40°F NVP matter ≤ 90000 for 0.5µ and ≤ 1000 for 5.0 µ Bio load = Nil	ISO 8573	Purity > 99.999% Oxygen < 2 ppm CO / CO_2 < 1ppm Total Impurities < 4 ppm Water < 3ppm The nitrogen line is built with a hydrophobic service line filter of 0.2µ porosity that is replaced once every 2 years. Filter integrity tests in service lines are also done once every 6 months.
Pure Steam	pH = 5.0 to 7.0 of condensate Conductivity < 1.1 µs/cm at 20°C of condensate Temperature, Pressure: Correlates with dry saturated steam Non-condensable gases < 40ml/kg Moisture < 5% Superheat < 50°C at atmospheric pressure Bacterial Endotoxins <0.25 EU/ml of condensate		pH = 5.0 to 7.0 of condensate Conductivity < 1.1 µs/cm at 20°C of condensate Temperature, Pressure: Correlates with dry saturated steam. Non-condensable gases < 4.0% Moisture < 5% Superheat < 25°C at atmospheric pressure Bacterial Endotoxins <0.25 EU/ml of condensate **Other practices** Controlling the % of make-up water < 15% to maintain steam quality. Pipeline velocity below 25 m/sec that allows effective removal of entrained moisture using steam traps Use of strainers to protect control valves and steam traps. Steam condensate should meet the current monograph of WFI.

Water Purification System	TOC (ppb) NMT 500 Conductivity (µS/cm) @ 20°C NMT 1.0 Nitrates (ppm) should be absent Heavy Metals (ppm) should be absent Aerobic Bacteria (cfu/ml) <100 / ml Pathogens: absent per ml	Pharm. Eur, USP JP	Reverse osmosis and ozonization coupled with Ultrafiltration are currently being used.
WFI	Same as Purified water additionally, Endotoxins (IU/ml) <0.25 EU/ ml	Pharm. Eur, USP, JP	Reverse osmosis, ozonization, ultrafiltration, and electrodeionization (EDI) are currently used. Multi-column distillation

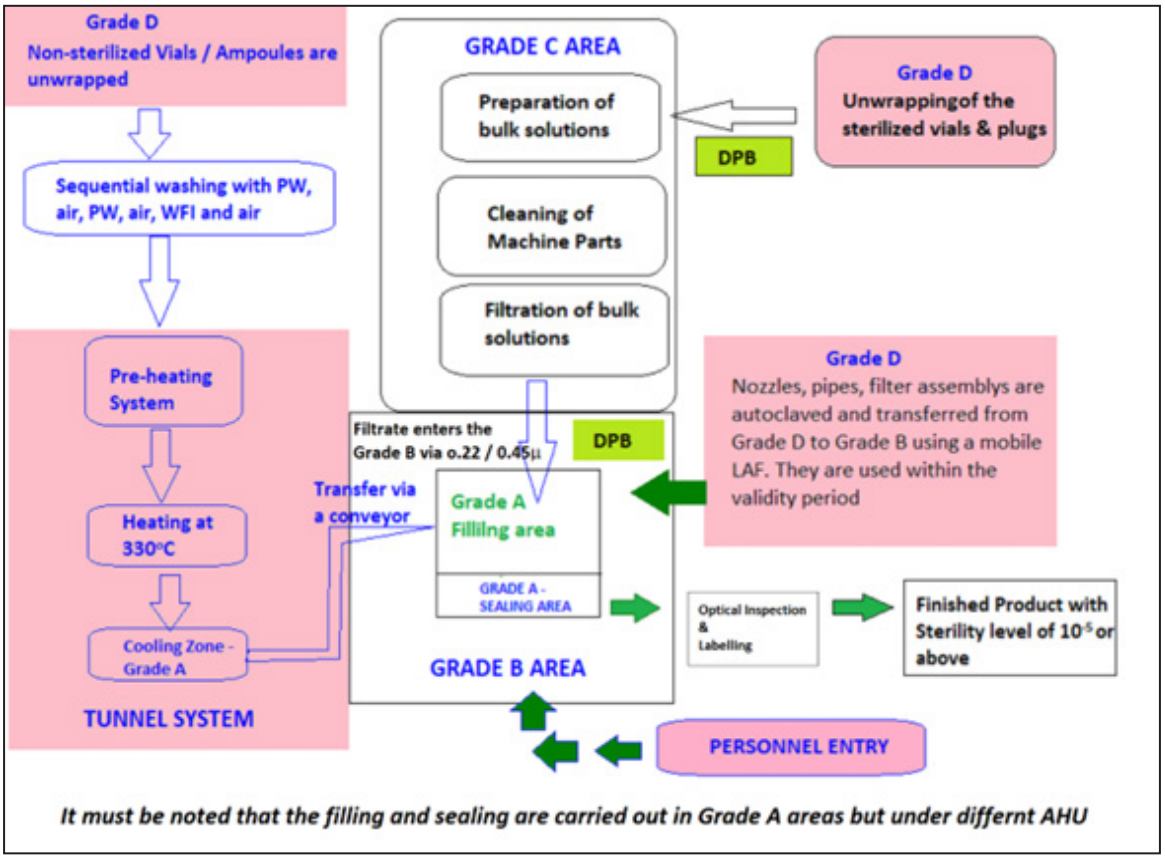

Figure-2: Processes in the aseptic area

Figure legend: the red background indicates zones of high risk. DPB – dynamic pass boxes are routinely equipped with 0.22 µ filters (H14 grade)

Media qualification

Soybean casein digest broth is the medium of choice for this activity. The media is qualified to ensure that the media can identify any single cell in the entire operation. The organisms used are prescribed in USP The lots used for media preparation shall be pre-qualified. The number of environmental isolates to be used may be more than one. All these organisms should have shown copious growth on incubation prior to the commencement of the study.

Cleaning, sanitization & disinfection

The primary methods for cleaning industrial equipment involve Clean-In-Place (CIP) and Steam-In-Place (SIP), which utilize chemical or heat treatments. Before this, it is essential to attempt the removal of process residues and particles using high-pressure water cleaning or steam. Alkali-based disinfectants and detergents are commonly employed in CIP systems, with sodium hydroxide being one of the most widely used options. It is crucial to validate the cleaning process for equipment to ensure its effectiveness.

Regular hand sanitization with an effective hand sanitizer is necessary for personnel engaged in Grade A/B areas. In Europe, established standards (EN 149913 and EN 150025A) describe the validation approach for hand sanitizers [35-38].

CIP & SIP

CIP and SIP are automated processes utilizing water, chemicals, and heat to sanitize equipment effectively. One CIP cycle will usually take between 60 and 90 minutes and generally operate at 100^{o}C. SIP enhances the sterilization achieved through the CIP process by employing steam at temperatures ranging from 120°C to 135°C for 30 minutes. An important factor affecting the SIP is the quality of steam (See table-1).

Factors that influence the CIP & SIP are the operating temperature and pressure, the concentration of the chemical, the heating duration, and the viscous nature of the material to be cleaned. Several chemicals used in the CIP process have been found incompatible with elastomeric seals. In most CIP and SIP applications, VMQ silicones and hydrogenated acrylonitrile butadiene rubber (HNBR) are unsuitable due to their limited compatibility. Fluoroelastomer (FKM) materials also exhibit weaknesses when exposed to alkaline and acidic substances. Ethylene propylene diene monomer (EPDM) is generally suitable for sealing aseptic technology but falls short when confronted with more rigorous CIP procedures. In contrast, Perfluoroelastomer is resistant to chemical media and high temperatures, making it the universally preferred material for CIP and SIP processes.

Hold time studies for equipment and materials

According to the WHO Technical Report Series No. 992, 2015, Annex 4, hold-time studies determine the permissible duration for holding materials at various production stages to ensure product quality remains within acceptable limits. The study design must accurately represent the holding times at each stage, as they directly impact the final product's overall quality, making hold time a critical control point (CCP) in the industry. Various routine and unforeseen interventions can extend hold times, including filter assembly blockages, volume or fill weight corrections, crew changes during shift transitions, intermittent sampling, component adjustments, operational delays, periodic replenishment of materials, sensor replacements, conveyor or guide rail modifications, spillage, container replacements, temporary increases in personnel, and simulations of failures such

as UPS or AHU malfunctions. Additionally, exceeding the allowed frequency for opening entry doors in Grade B areas and non-robotic human movement for short durations can also influence hold time. These events are commonly simulated during process validation to assess their impact on production and ensure compliance with quality standards. During the interventions, batch production time can be extended to a few hours, during which bio-load can increase. Hence, material hold-time studies are done during process validation.

The clean equipment hold time involves verification of microbial load on the contact surfaces, while the unclean equipment holds time verifies both chemical and microbial load. Swab samples are collected from designated locations, and the residue per unit area is calculated. The unclean equipment hold time is of pivotal importance. Formulation residues left over on the surface of the equipment can undergo degradation due to one or more factors, such as temperature, humidity, oxidation, or hydrolysis. It is important to note that, during the selection of a cleaning aid, operators rely on the solubility of the active ingredient. In principle, no data is available on the solubility of impurities or degradation products likely to be formed during exposure. Hence, deviating from the established unclean hold time can cause the carryover of the chemical residues into subsequent batches. A checkpoint here is to verify the TOC of the swab sample and ensure that it is comparable to WFI limits. On several occasions, the regulatory agency requested that unknown peaks due to extended hold time be identified. Analysts relied on advanced HPLC-based techniques for identifying and quantifying such impurities or referred to the stability-indicating methods to see if such peaks occurred during product development or due to the stress conditions during product storage (40,41).

Cleaning validation

An efficient cleaning procedure allows the contaminants to be effectively removed below acceptable levels. Residue levels not exceeding 10 ppm are considered reasonable, and a safety factor of 0.001 is recommended in the current PDA guidelines; however, the industry follows the least of the two (42, 43)., In routine practice, detergents are prohibited as their composition and surface compatibility is unknown. A suitable sodium lauryl sulphate (SLS) concentration either alone or in combination with suitable ICH class 3 solvents (44) with a fixed number of rinse cycles shall be done with final WFI recirculation at 80^{o}C. The residue of SLS can be quantified. The TOC of the final rinse samples should not exceed 500 ppb. The residual carryover can be more prominent with sterile powders, wherein insoluble residues may stick to the inner surfaces of long pipes and bends. Solubility information is paramount in such cases.

Measurement (*routine controls and monitoring*)

Sterility assurance

Sterility assurance is the degree of certainty that a given product or unit, which is claimed to be sterile, indeed meets the criteria of sterility. The test is destructive, and several controls over practices, utilities and the environment. Besides controls over the elements described in the 6M environment, additional aspects such as reducing or eliminating the number of interventions, implementing a closed, restricted access barrier system (RABS), and adequate process simulations that include preventive testing and periodic vendor qualifications contribute to sterility assurance.

Environmental monitoring **(EM)**

The readiness of the environment shall include compliance verification over Viable and non-viable particulate matter (14, 15). The air quality correlates with the product quality. Periodic performance verification for air quality are given in Table 2.

Table -2: Performance verification tests for AHU/HVAC

Utilities	Performance verification tests and Frequency
AHU / HVAC	Airflow velocity, volume and Air changes test Filter integrity test Differential pressure test (Real Time basis) Airflow pattern test Airborne non-viable count (Particle count) Particle Recovery test Temperature control and humidity test Airborne viable count (Microbial quality of air)

Environmental flora

Why should these isolates be included in GPTs? The rationale is that if organisms are indeed present in the product, the utilized media should be able to detect their presence. Environmental isolates may be sporadic or predominant and vary with seasons. The predominant isolates must be identified up to the species level by available software – VITEK 2. These organisms need to be maintained as a part of the library with its details of morphology and photographs. Once the organisms are identified, it has to be ascertained that the media used – Reasoner's 2A (R2A) agar (if the isolate is waterborne), Soyabean casein digest agar (if it is from environment or people), and Fluid thioglycolate (if water, environment and people) will be able to identify its presence. So, these organisms form a part of Growth promotion tests (GPTs). GPT should encompass one organism from each family in the isolates.

Non-viable particulate count

In a study conducted by the NIH (45), the Continuous monitoring of non-viable airborne particles shows a correlation with airborne colonies and serves as an acceptable proxy for the daily evaluation of cleanroom performance. However, the USP still mandates using agar contact plates for particle counting in ISO 7 areas. Continuous monitoring of the non-viable particles can help monitor the trend, and such equipment will work as an early warning system. ***Specific CCPs for Powder injectables***

Apart from the active pharmaceutical ingredient, the powder injectables have buffers, antioxidants and preservatives. In order to test the microbial load, the inhibition properties of buffers, anti-oxidants and preservatives are neutralized such that the microbial recovery is maximum (46). Powder injectables are either blended and filled or filled as such. The vials are sterilized in a tunnel system validated for non-viable particulates (NVP) and BET, ensuring contamination is avoided. The entire quantity of the API or the excipients are consumed in once instance and left overs are discarded.

Routine quality control testing of the finished product involves reconstitution of the contents using filtered WFI under LAF. The vials are inspected to ensure that particles of definite micron sizes are within limits. The particulate matter shall comply with the limits prescribed under USP <788>. The powder injectable product process is simulated by filling pre-sterilized mannitol powder. As powder injectables are generally moisture sensitive, the temperature in the classified area is maintained below 20˚C and RH below 35 %. Controlling moisture is essential for controlling microbial burden.

Specific CCPs for large-volume parenteral

Any volume of more than 100 ml is known as LVP and are terminally sterilized. As the product does not have preservatives, the bio-burden has to be least. Polypropylene (PP) granules made under ISO 8 conditions are used for LVPs and glass is prohibited.

Gamma sterilized granules are blown into heating and blowing with filtered and qualified compressed air. Other required parts of the bottle are also made of PP and are pre-sterilized. The solutions are prepared under ISO 7

tions, personnel control, contamination prevention, and overall compliance with quality standards.

Achieving enhanced efficiency through automation

Automation and robotics, combined with single-use systems, are transforming aseptic processing by streamlining operations, minimizing human intervention, and reducing the risk of contamination or errors. Advances in analytical testing, such as rapid sterility testing can yield results in under seven days, a significant improvement over the traditional 14-day incubation period required by compendial sterility standards. However, regulatory guidelines for viable particulate monitoring are based on CFUs, which do not easily correlate with results from fluorescent particle counting. Manufacturers need to validate new methods against existing standards to prove their equivalence or superiority.

Rapid microbial methods, using biofluorescent particle counters instead of settle plates, offer real-time microbial data during aseptic processing, enabling immediate responses to EM failures and reducing the risk of batch losses. Further innovations in EM systems now allow for real-time differentiation between viable and non-viable particles, capturing viable particles on a growth medium as they are detected. This advancement shortens the timeframe for identifying EM excursions, crucial for preventing delays and shortages in parenteral supplies.

Automation and robotics are also revolutionizing visual inspection in drug manufacturing. Automated visual inspection (AVI) combined with AI for image analysis [66] enhances defect and particle detection, reduces false reject rates, and improves process efficiency. The use of standardized, ready-to-use components, such as pre-sterilized vial nests, has also streamlined production by eliminating steps like vial washing and sterilization, reducing glass vial damage, and enabling more efficient filling processes.

Despite these advancements, robotics still face challenges, particularly in handling unexpected events. Future innovations may involve integrating vision systems and AI to enable robots to respond to unplanned interventions, further reducing human involvement and enhancing operational flexibility. To fully leverage these technologies, manufacturers must adopt flexible implementation strategies that maximize the benefits of automation and robotics. Some automation tools that can enhance cleanroom performance metrics are listed in table-3.

Table 3: Some automation controls that need to be implemented in the Grade A / B areas

Automation control	Intended purpose	Expected improvement in CCS
Implementation of differential pyro-electric Infrared sensor [51] and a camera at entry points of Grade A/B Area	To capture real-time data about the number of operators inside the critical area (Grade A/B).	This process can limit the number of operators inside the Grade A/B area and thus help reduce contamination. Linking this device with the interlocking doors can provide restricted access into the Grade A/B areas.
Implementing wearable Performance metrics monitoring devices [52, 53]	To monitor the working personnel's real-time health status, stress levels, fitness, etc.	Failure to meet the fitness and hygiene norms will prevent operators from entering the sterile environment.
Implementation of Real-time attention monitoring and behaviour recognition systems [54, 55]	To enable monitoring and recording of behaviour in the clean rooms.	Any deviation in the operator's behaviour can alert the quality personnel immediately. Improving the awareness of the pupil working in the Grade A areas can be easy with the help of recorded videos.

Implementation of screeners to verify the training [56]	Only qualified and trained operators are allowed inside the cleanroom	While this is already in place, monitoring the real-time readiness of the personnel and enabling access to qualified personnel has to be implemented.
Installation of capacitance proximity sensors for the detection of waste [57]	To detect and remove any leftover material in the dispensing, labelling and packaging areas	In the dispensing area, it provides electronic evidence of thorough line clearance. Currently, this is done manually. Implementing this system in the labelling and packaging areas will prevent mix-ups and mislabelling of products.
Quick response coding systems on the labels [58]	To verify the accuracy of labelled contents	This practice is already being followed in India by manufacturers of APIs. Implementation by formulation manufacturers is pending.
Real-time Temperature data logging and transmission system [59]	To ensure that the goods are transferred to the destination under controlled conditions.	This will support generating data for transportation validation and provide trend data on logistics and supply chain control.

Ai for an efficient CCS

AI tools can extract the key drivers that facilitate the identification of CCPs and work as enablers for knowledge management (50). Developing process performance dashboards that act as enablers for statistical decision making is possible. Ideally AI can enhance the throughput during real time monitoring and predictive analytics, automated surface decontamination, defect detection during packaging, process optimization, automated EM, training simulation and smart CAPA implementation. This is a herculean task. By integrating the real-time and historical data points and personnel behaviour trends, the next challenge is to build a robust CCS strategy. A straightforward framework involves mapping all vulnerable unit operations, areas, and controls that could lead to non-compliance while providing real-time trend data for monitoring. Establishing performance metrics for each operator in core areas is required. Performance metrics coupled with analysing historical events aids in identifying root causes and assessing the effectiveness of corrective and preventive actions (CAPAs). Integrating data sets to compare actual practices with established procedures through real-time audio and video monitoring enhances oversight. Operators' movements and health status within Grade A/B facilities can be monitored using thermographic cameras, while infrared or optical sensing devices help regulate the number of personnel in critical areas. Environmental monitoring (EM) locations should be strategically determined based on room design, personnel movement, and airflow direction. Additionally, continuous improvements in isolator and equipment design can further enhance compliance and operational efficiency.

AI-powered algorithms must be designed to gather data within the 6M framework of the manufacturing processes and integrate data from disparate sources and formats, including sensor data, laboratory results, hypothesis testing and historical records. AI algorithms can then be used to build predictive manufacturing process models. As optimization progresses, AI algorithms learn from past iterations and refine their strategies to converge on optimal solutions more efficiently. Once optimized process parameters are identified, AI systems can continuously monitor manufacturing operations in real time to ensure that the process remains within specified limits. Sensor data and feedback from monitoring systems are fed back into the AI algorithms, allowing them to adjust to maintain optimal conditions and respond to changes or disturbances in the process environment. These algorithms use techniques

such as gradient descent, genetic algorithms, or reinforcement learning to search for the best set of parameters within the vast space of possible combinations. By leveraging AI-powered optimization algorithms, pharmaceutical companies can significantly improve manufacturing efficiency, leading to higher productivity, lower production costs, and better-quality products.

Future scope

The recent advancements in automation that reduced the process and product risks are discussed. Applications of novel automation devices for trending the behaviour, real time health and fatigue status of personnel in the core areas are presented. The role of AI in process optimization, continuous process improvement and implementing an effective CCS to minimize the risk of rework and/or recall is discussed.

A granular understanding of each of the processes is a pre-requisite for AI to percolate. Integration of the existing data libraries and refinement of the critical data is quite challenging. Yet, with technological upgrades, it must be possible to compound products without interventions in much smaller cleanrooms where the risk of contamination is considerably lower. Automation should be coupled with artificial intelligence (AI) to recognize and decontaminate vulnerable equipment surfaces. Such systems may take the support of real-time monitoring devices. Also, fully automated gloveless isolators can mitigate the risk of contamination.

Technological advancement aimed at reducing manual intervention, building accurate and rapid analytical methods, automatic alert systems, faster or automated screening of defects in primary packaging materials, filter membranes etc is due.

Current rapid test methods such as VITEK-2 systems are helpful in EM (61-65). This process is only indicative but needs to be more conclusive. Rapid detection and instant characterization of infected surfaces, such as finger dab tests, can be developed, but environmental flora challenges persist. The flora, along with mutant variants, may keep changing with seasons. Hence, detection is only probabilistic and not confirmed because data on such mutant strains may need to be updated. If the database is updated, the performance qualification needs to be redone. Such challenges prevail even with the support of AI.

Conclusion

A novel method of identifying the CCPs using the 6M framework is presented. Quality lapses in the CCPs leading to product recalls and/or warning letters are presented. Novel and emerging automation devices that find applications in reducing process / product risk are presented. Key areas where the support of AI and automation needs technological advancement are discussed. A guidance for integrating AI with existing processes is presented. This can very much help industry for building a robust CCS compliant with regulatory requirements.

Declarations of Interest

None

Declaration of Generative AI and AI assisted technologies in the writing process

None.

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Abbreviations used:

Active Pharmaceutical Ingredients: API

Air changes per hour: ACPH

Air handling unit: AHU

Annual product quality review: APQR

Artificial intelligence: AI

Aseptic process simulation: APS

Bacterial Endotoxin Test: BET

Bill of materials: BOM

Clean but not classified: CNC

Clean-In-Place: CIP

Colony forming units: cfu

Contamination control strategy: CCS

Corrective action & preventive action: CAPA

Critical control points: CCPs

Critical material attributes: CMAs

Critical process parameters: CPPs

Critical quality attributes: CQAs

Environmental Monitoring: EM

Finished Goods (FG)

Growth promotion tests: GPTs

Hazard Analysis Critical Control Point: HACCP

High density polyurethane: HDPE

High efficiency particulate air: HEPA

Human-machine interface: HMI

Institute of Environmental Sciences and Technology: IEST

Key performance indicators: KPIs

Laboratory information management sys tem: LIMS

Laminar Air Flow: LAF

Large volume parenteral: LVP

Non-viable particulates: NVP

Not less than: NLT

Out of specification: OOS

Out of trend: OOT

Polypropylene: PP

Polyurethane Foam (PUF)

Process Analytical Technology: PAT

Programmable logical controls: PLCs

Quality management system: QMS

Quality by Design : QbD

Raw materials: RM

Restricted access barrier system: RABS

Relative Humidity: RH

Steam-In-Place: SIP

Uninterruptible Power Supply: UPS

User Requirement Specifications: URS

Water for Injection: WFI

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