U.PORTO

FACULDADE DE FARMÁCIA
UNIVERSIDADE DO PORTO

Mestrado em Controlo da Qualidade

Especialização em Produtos de Cosmética e Higiene Corporal

Quality Control into the Production Process of Cosmetic Products

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2026

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Relatório de Estágio do 2º Ciclo de Estudos Conducente ao Grau de Mestre em Controlo da Qualidade na Faculdade de Farmácia da Universidade do Porto.

Trabalho realizado sob a orientação de Doutor Hugo Almeida e Prof. Doutora Beatriz Oliveira.

2026

Abstract

The present report describes the curricular internship carried out at Mesosystem, S.A., a global reference company in the development and manufacturing of advanced medical cosmetics and medical devices. Conducted within the scope of the Master's Degree in Quality Control, the internship primarily aimed to develop activities within the company's production and quality control departments. This path sought the development of competencies across all phases of the production process for various cosmetic products and medical devices, the monitoring and execution of all activities ensuring the quality control of the manufactured products, and the implementation of a new internal water analysis process, all within an industrial environment strictly regulated by ISO 9001:2015, ISO 13485:2016, and ISO 22716:2007 standards.

Initially, the work involved the transversal monitoring of the entire production cycle, closely following conformity validation and quality control between the different stages of the process. This stage encompassed the execution of various routine assays (such as pH, viscosity, density, volume and microbiological control, stability studies, and Container Closure Integrity Testing - CCIT), alongside rigorous microbiological evaluations and environmental monitoring within classified cleanrooms.

The core project of the internship consisted of internalizing the quality monitoring protocol for purified water, the most critical resource across the entire production facility. Based on the strict specifications of the European Pharmacopoeia, the internal protocol covered regular assays for conductivity, pH, oxidisable substances, nitrates, and microbial quantification.

The implementation of this system provided the company with essential technical autonomy, optimizing operational costs and laboratory response times. In conclusion, this intervention enabled a structural transition from a reactive troubleshooting approach to a predictive maintenance strategy, guaranteeing data integrity and clearly reinforcing the company's philosophy of continuous improvement.

Keywords: Quality Control; Medical Cosmetics; Mesosystem, S.A.; Water Quality Monitoring; Good Manufacturing Practices (GMP); Continuous Improvement.

Resumo

O presente relatório descreve o estágio curricular realizado na Mesosystem, S.A., uma empresa de referência global no desenvolvimento e fabrico de produtos cosméticos e dispositivos médicos. Inserido no âmbito do Mestrado em Controlo da Qualidade, o estágio teve como principais objetivos o desenvolvimento de atividades nos departamentos de produção e de controlo da qualidade da empresa. Este percurso visou o desenvolvimento de competências em todas as fases do processo produtivo dos diferentes produtos cosméticos e dispositivos médicos, o acompanhamento e execução de todas as atividades que asseguram o controlo da qualidade dos produtos e, por fim, a implementação de um novo processo interno de análise da água, num ambiente industrial rigorosamente regulado pelas normas ISO 9001:2015, ISO 13485:2016 e ISO 22716:2007.

Numa fase inicial, o trabalho incidiu no acompanhamento transversal de todo o ciclo de produtivo, acompanhando a validação de conformidade e o controlo de qualidade entre as diferentes etapas do processo. Esta etapa compreendeu a execução de diversos ensaios físico-químicos de rotina (tais como pH, viscosidade, densidade, controlo de volume e microbiológico, estudos de estabilidade e testes de integridade do fecho das embalagens - CCIT), bem como avaliações microbiológicas e monitorização ambiental rigorosa em salas limpas.

O projeto central do estágio consistiu na internalização do protocolo de monitorização da qualidade da água purificada, o recurso mais crítico de toda a unidade de produção. Com base nas estritas especificações da Farmacopeia Europeia, o protocolo interno abrangeu ensaios regulares de condutividade, pH, substâncias oxidáveis, nitratos e quantificação microbiana.

A implementação deste sistema conferiu à empresa uma autonomia técnica essencial, otimizando os custos operacionais e o tempo de resposta do laboratório. Conclui-se que esta intervenção permitiu uma transição estrutural de uma postura de resolução reativa de problemas para uma estratégia de manutenção preditiva, assegurando a integridade dos dados e reforçando de forma clara a filosofia de melhoria contínua da empresa.

Palavras-chave: Controlo da Qualidade; Cosmética Médica; Mesosystem, S.A.; Monitorização da Água; Boas Práticas de Fabrico (BPF); Melhoria Contínua.

Agradecimentos

A concretização desta tese de mestrado e de todo o percurso que a antecedeu não teria sido possível sem o contributo, o apoio e o carinho de diversas pessoas a quem expresso a minha mais profunda gratidão.

Ao Doutor Hugo Almeida, por todo o apoio e pela excelente orientação ao longo de todo o processo de escrita. Agradeço a sua disponibilidade constante para ajudar e a oportunidade de publicação do artigo científico, uma conquista que nunca imaginei alcançar.

À Prof. Doutora Beatriz Oliveira, pela excelente coorientação, por todo o apoio prestado e por estar sempre disponível para me guiar e aconselhar durante esta etapa.

Aos colaboradores da Mesosystem, S.A., onde tive o privilégio de realizar o meu estágio. O meu muito obrigada a todas as pessoas que, com sorrisos, palavras de carinho e apoio diário, me ajudaram a crescer e tornaram o ambiente de trabalho tão leve, divertido e acolhedor.

Ao João, meu namorado, que acompanhou toda a minha trajetória no ensino superior. Foste, com toda a certeza do mundo, o meu maior pilar de apoio. Obrigada por seres a pessoa que sempre acreditou no meu potencial, mesmo quando eu própria achava que não iria conseguir, e, acima de tudo, por todo o amor, paciência e carinho que me dedicaste.

Aos meus pais, que durante toda a minha vida foram, e sempre serão, as pessoas mais corajosas e admiráveis que já conheci, sendo as maiores bênçãos da minha vida. Obrigada por todos os ensinamentos, por confiarem que eu daria o meu melhor nesta fase tão importante e porque sei, no fundo do meu coração, que se pudessem me dariam o mundo todo nas mãos. Tudo o que sou, devo-o a vocês.

À minha sobrinha Valentina, que neste ano de 2026 completa os seus três aninhos. Mesmo sendo apenas um bebé, ensinaste-me a ver a vida com outros olhos, a dar valor aos atos mais simples e a compreender que a nossa presença é o presente mais valioso que podemos oferecer a alguém. Não existe, com toda a certeza, sensação melhor do que o amor que sinto quando chego à casa e me dás o melhor sorriso do mundo.

Aos meus irmãos, pelo amor, companheirismo e por todo o apoio que sempre me dedicaram.

Por fim, a mim mesma. Por não ter desistido, pela resiliência nos momentos de dúvida e por ter a certeza de que me dediquei a 100% a toda esta experiência universitária e profissional que tive o enorme prazer de realizar.

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List of Abbreviations

ALCOA+. Attributable, Legible, Contemporaneous, Original, and Accurate

CAF. Chloramphenicol

CAPA. Corrective and Preventive Actions

CCIT. Container Closure Integrity Testing

CE. European Conformity

CFUs. Colony Forming Units

CoA. Certificate of Analysis

CPNP. Cosmetic Products Notification Portal

CPSR. Cosmetic Product Safety Report

EC. European Commission

GLP. Good Laboratory Practices

GMP. Good Manufacturing Practices

HEPA. High-Efficiency Particulate Air

INCI. International Nomenclature of Cosmetic Ingredients

ISO. International Organization for Standardization

LAF. Laminar Air Flow

MCE. Mixed Cellulose Esters

MDR. Medical Device Regulation

MO. Manufacturing Order

OOS. Out-Of-Specification

Ph. Eur.. European Pharmacopoeia

PRRC. Person Responsible for Regulatory Compliance

PW. Purified Water

QA. Quality Assurance

QC. Quality Control

R2. Reasoner's 2

RABS. Restricted Access Barrier Systems

RO. Reverse Osmosis

RODAC. Replicate Organism Detection and Counting

RPM. Revolutions per Minute

TAMC. Total Aerobic Microbial Count

TSA. Tryptic Soy Agar

TYMC. Total Combined Yeasts and Moulds Count

UV. ultraviolet

WFI. Water for Injection

1. Introduction

Quality Assurance (QA) in the cosmetic sector transcends the mere verification of final specifications; it constitutes a preventive ecosystem that ensures the biological and physicochemical integrity of the product from its inception (1,2). In a market where the convergence of dermatology and cosmetics, so-called medical cosmetics, dictates increasing standards of rigour, Quality Control (QC) acts as the guarantor of compliance with demanding regulatory frameworks, such as the European Commission Cosmetics Regulation (EC) No 1223/2009 (3) and the International Organization for Standardization (ISO) 22716:2007 standard (4). The galenic complexity of modern products requires continuous monitoring to mitigate risks of cross-contamination, emulsion instability, or microbiological deviations that could compromise the safety of the final consumer (5).

It was under this paradigm of rigour that the curricular internship was developed, as part of my master's degree in QC, with a specialisation in Cosmetic and Body Hygiene Products. The project, based at Mesosystem, S.A. (Vila Nova de Gaia) between September 2025 and February 2026, allowed for the transposition of academic knowledge into an international reference production unit.

The experience at Mesosystem was structured to mirror the actual product flow, beginning with a production perspective. This initial immersion in the factory floor was essential to understanding the rheology of formulations, ranging from liquid to semi-solid and solid states, and identifying critical control points during the complex stages of manufacturing and filling.

The internship transitioned into a laboratory and normative perspective, dedicated to the analytical testing of raw materials and finished products, alongside rigorous environmental monitoring. This phase extended to cleanroom control and operator hygiene validation, ensuring strict adherence to the ISO standards. The core objective of this industrial experience was the integration of QC into the production flow, aiming not only for compliance but for the continuous improvement of the company's internal processes.

In line with this goal of operational excellence, the main focus of the internship evolved into the implementation of a new analytical process. It was determined that a critical area for improvement lay in the autonomy of the laboratory regarding water quality. Consequently, the project was directed towards the adaptation and implementation of internal weekly water analysis protocols. This intervention sought to reinforce surveillance over one of the most critical components in the manufacture of medical devices and high-performance cosmetics, while simultaneously optimising the supply chain and ensuring a more proactive response to potential deviations.

2. Characterisation of Mesosystem, S.A.

2.1. Corporate Identity and Organisational Workflow

Mesosystem, S.A., established in 2006 and based in Vila Nova de Gaia, Portugal, is now a global leader in the medical cosmetics and advanced aesthetics sector. The company's core is built upon a symbiosis between scientific research and technological innovation, with the clear objective of developing high-performance solutions for health and aesthetic professionals. Beyond its proprietary portfolio, which features flagship lines such as MCCM Medical Cosmetics, alongside Mccosmetics, MS Mesopharma, and Mesocross, Mesosystem also leverages its industrial capacity to provide bespoke contract manufacturing (private label) services. In this business-to-business model, clients benefit from the company's high-quality formulations while retaining full control over their own packaging and design customization. Under its flagship brand, MCCM Medical Cosmetics, the organisation has expanded its presence to over 95 countries, consolidating a portfolio renowned for the sophistication of its formulas and the safety of its results (6).

The trajectory of Mesosystem has been marked by a constant evolution of its infrastructure, and it has developed a complex industrial structure that integrates pioneering Research and Development laboratories, quality control laboratory and production units equipped with state-of-the-art technology. This evolution has been accompanied by rigorous adaptation to regulatory requirements, enabling the company to manufacture not only cosmetics but also medical devices of high complexity. Mesosystem's identity is defined by its commitment to QA. The company does not limit itself to complying with current standards, it integrates them as the driving force behind its productivity. Certification in international reference standards, such as ISO 9001:2015 and ISO 13485:2016 (internationally recognized standard for quality management systems in the design and manufacture of medical devices), attests to the organisation's ability to manage risks and ensure full traceability for every batch produced (7,8). Also, compliance with ISO 22716:2007 Good Manufacturing Practices (GMP) guidelines for the production, control, storage and shipment of cosmetic products, ensures that every stage of the production flow, from the weighing of raw materials to final packaging, is executed under conditions of strict industrial hygiene, technical rigor, and robust contamination control (4).

Currently, Mesosystem positions itself as a strategic partner in the aesthetic health sector, where the efficacy of its active ingredients, such as hyaluronic acid, vitamins, and peeling acids, is supported by a QC system that monitors, with surgical precision, all critical variables of the industrial process. To sustain this high level of operational excellence and regulatory compliance, the organisational structure of Mesosystem reflects an institutional maturity deeply

focused on risk management, stringent quality standards, and consumer safety. The company is governed by an Executive Board supported by specialised advisory bodies, such as the Legal Department, Strategic Consultant, Clinical Advisor, and Statutory Auditor, ensuring that top-level decisions are grounded in both legal and scientific expertise.

The Regulatory Compliance Nucleus acts as a fundamental pillar to meet international standards, integrating Technical Direction, Regulatory Affairs (including the central figure of the PRRC - Person Responsible for Regulatory Compliance, for medical devices), and the Quality Department, which is divided into Quality Management and QC. The company's operational efficiency is sustained by four major management pillars that ensure the workflow from conception to market. The Administrative and Finance Department manages vital support functions, such as administrative services in Portugal and Spain, Human Resources, Accounting, and Invoicing/Logistics Control. Production Management ensures the execution of the manufacturing cycle, covering processing and formulation, filling, packaging, and sanitisation protocols, while also supervising flow logistics and inventory management to maintain an uninterrupted supply chain. R&D acts as the innovation engine of Mesosystem, operating across two distinct laboratory sites at Mesosystem (Vila Nova de Gaia) and Spinpark (Guimarães), allowing for specialised focus on new medical cosmetic formulations. Complementing this, the Strategic Management and Communication area is responsible for the brand's global presence, managing Marketing and Design for content and trade fairs. This comprehensive organisational structure and its key areas of responsibility are visually summarised in Figure 1.

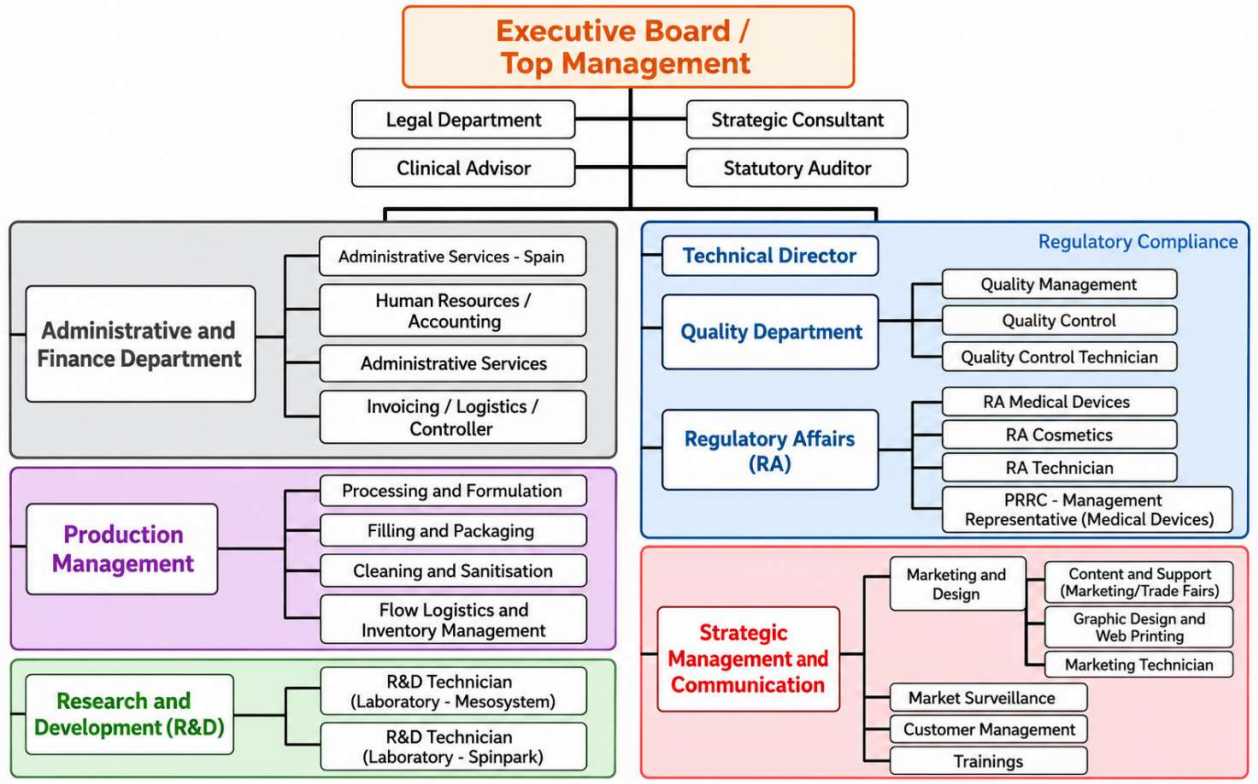

Figure 1 - Organizational structure and key areas of responsibility at Mesosystem, S.A.

2.2. Infrastructure

Excellence in the production of medical cosmetics and medical devices at Mesosystem is based on an industrial infrastructure designed to mitigate contamination risks and ensure batch reproducibility. The industrial plant is organised to ensure continuous and unidirectional flows of personnel and materials, aiming to optimise the movement of resources and employees while minimising the possibility of cross-contamination and ensuring full traceability (4). The company's facilities feature a strict physical separation between the cosmetics and medical devices areas, reflecting the distinct environmental and regulatory requirements of each sector (9).

2.2.1. Water Treatment and Purification System

Water serves as the most critical component in Mesosystem's production flow, necessitating a sophisticated internal infrastructure to achieve distinct grades of purity tailored to specific regulatory requirements. The process begins with potable water supplied by the public grid. The quality of which is periodically monitored by an external entity to ensure compliance with World Health Organisation guidelines, national legislation, and ISO standards (10). This potable source serves as the raw intake to produce Purified Water (PW), which is intended for the manufacture of cosmetic products and non-injectable medical devices (11).

The transformation of potable water into PW involves a multi-stage sequence designed to ensure chemical and microbiological integrity. The process commences with filtration through a Progard filter, followed by Reverse Osmosis (RO), where high pressure forces the water through a semi-permeable membrane to separate it from organic and inorganic compounds, as well as suspended particles (12). Final disinfection is achieved via ultraviolet (UV) radiation (200–280 nm), which destroys the cellular components of microorganisms to prevent replication and the formation of biofilms (13). For the most sensitive applications, specifically injectable medical devices, the system produces Water for Injection (WFI), also known as ultrapure water. This superior grade is derived from PW through a distillation process by heating the water to boiling point, the resulting steam rises free of impurities while non-volatile contaminants, such as salts, heavy metals, bacteria, and endotoxins, remain in the liquid phase to be discarded. The subsequent condensation generates water of the highest chemical and microbiological purity - WFI (12).

Once treated, the water is managed through a distribution network designed as a closed-loop system, constructed from sanitary materials such as specialised plastics and stainless steel that inhibit bacterial proliferation (10). This loop maintains the water in continuous circulation, delivering it directly to the classified cleanrooms while preventing stagnation. To uphold long-term system integrity as mandated by GMP, the infrastructure undergoes preventive maintenance, and scheduled disinfection cycles (10).

2.2.2. Critical Control Environments: Cleanrooms

The production support at Mesosystem relies on specialized cleanrooms, which are defined as highly controlled environments where the concentration of airborne particles, temperature, relative humidity, and differential pressure are rigorously managed to ensure absolute product safety. These rooms are classified according to two complementary frameworks: the GMP guidelines, which range from Grade A to Grade D (9), and the international ISO 14644-1:2015 standard, which defines classes from ISO 1 to ISO 9 based on strict maximum permitted particle limits (14). To establish the regulatory baseline for air cleanliness, Table 1 presents the standard particle thresholds per cubic meter defined by ISO 14644-1:2015 (14), while Table 2 details the specific particulate boundaries enforced under the GMP framework during both "at rest" and "in operation" states (9).

Table 1 - ISO classes of air cleanliness by particle concentration.

ISO Class Number	Maximum allowable concentrations (particles/m^3) for particles equal to and greater than the considered sizes, shown below[a]					
	0.1 µm	**0.2 µm**	**0.3 µm**	**0.5 µm**	**1 µm**	**5 µm**
1	10[b]	[d]	[d]	[d]	[d]	[e]
2	100	24[b]	10[b]	[d]	[d]	[e]
3	1 000	237	102	35[b]	[d]	[e]
4	10 000	2 370	1 020	352	83[b]	[e]
5	100 000	23 700	10 200	3 520	832	[d, e, f]
6	1 000 000	237 000	102 000	35 200	8 320	293
7	[c]	[c]	[c]	352 000	83 200	2 930
8	[c]	[c]	[c]	3 520 000	832 000	29 300
9[g]	[c]	[c]	[c]	35 200 000	8 320 000	293 000

Note: ([a]) All concentrations are cumulative (e.g., the limit for 0.3 µm includes all particles of this size and larger); ([b]) Requires large air sampling volumes; sequential sampling may be applied; ([c]) Concentration limits are not applicable due to excessively high particle concentrations; ([d]) Classification is inappropriate due to statistical limitations at very low concentrations; ([e]) Not applicable for particles >1 µm in low concentrations due to potential particle loss in the sampling system; ([f]) For ISO Class 5, the macroparticle descriptor M should be used alongside another particle size; ([g]) Applicable only in the "in operation" state.

Table 2 - Maximum allowable airborne particle concentrations during "at rest" and "in operation" states.

Grade	Maximum Limits for Total Particle (≥ 0.5 µm/m^3)		Maximum Limits for Total Particle (≥ 5 µm/m^3)	
	At Rest	**In Operation**	**At Rest**	**In Operation**
A	3 520	3 520	Not specified ([a])	Not specified ([a])
B	3 520	352 000	Not specified ([a])	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined ([b])	29 300	Not predetermined ([b])

Note: ([a]) Classification including 5.0 µm particles may be considered if historical trends indicate a need; ([b]) Limits are not predetermined. The manufacturer establishes these internally based on quality risk management and historical data.

Environmental control is managed with surgical precision. Parameters are strictly established with temperature maintained at 20±5°C, humidity between 30-70%, and a minimum differential pressure of 10 Pascals between rooms of different classifications (9,15). Unlike conventional industrial units, Mesosystem utilises the Akivision system, a continuous monitoring software

that integrates with air handling units. This system records data minute-by-minute and triggers immediate alarms in the event of any deviation, allowing for real-time corrective action (9,15).

The physical structure is designed to prevent the accumulation of particles and microorganisms, featuring smooth surfaces with minimal recesses and suitable materials for frequent sanitisation. The air system is unidirectional and maintained through positive differential pressure, ensuring that air always flows outward from the cleanest zones to the adjacent environments (9,15). Physical access to these controlled sectors (cleanrooms) is strictly mediated via specialized antechamber systems known as airlocks, which serve as physical barriers and designated transition zones for personal gowning or material transfer. These airlocks feature electromagnetic interlocking doors that can never be opened simultaneously, effectively protecting the operational pressure differentials and safeguarding the cleanroom's environmental integrity (9,15).

The human element is governed by strict hygiene rules and GMP training. The number of personnel inside cleanrooms is kept to a functional minimum, and high standards of personal hygiene are mandatory, including regular hand disinfection and the prohibition of nail polish or physical risks such as watches and jewellery (4,9). Gowning protocols are strictly adapted to the classification of each room to maintain environmental integrity. In non-classified areas and ISO 8 (Class D) zones, which typically include corridors, warehouses, and secondary packaging areas where there is no direct contact with the product, personnel are required to wear lab coats, caps, shoe covers, gloves, and masks, including beard or moustache covers where applicable. In contrast, higher-standard environments such as ISO 7 (Class C) and ISO 5 (Class B) demand a much higher level of protection to ensure total isolation, requiring the use of full sterile suits, caps, and masks (4,9,14).

To optimize these controls, the industrial facility is divided into two main specialized production sectors. The Medical Devices Area faces higher asepsis requirements, featuring ISO 7 cleanrooms for compounding reactors, filling machines, primary packaging machinery, and component washing. For the highest-risk operations, such as the open handling or weighing of raw materials and in some filling machines (syringe and vials filling machines), ISO 5 (Grade B) local conditions are provided via laminar flow personal protection equipment (4). In contrast, the Cosmetics Area predominantly operates in ISO 8 (Grade D) environments, which are fully suitable for the manufacture and primary filling of advanced liquid and solid cosmetic formulations (16). To contextualize these assignments, Table 3 synthesizes the operational definitions, ISO class correlations, and core airflow requirements that dictate manufacturing (9,14).

Table 3 - Structural and operational comparison of European Union GMP cleanroom classifications.

Grade (GMP)	Definition and Critical Operations	ISO Equivalent (At Rest / In Operation)	Technology / Airflow Requirements
Grade A	Critical Zone: High-risk operations (e.g., filling, stopper bowls, open primary packaging, aseptic connections under "first air").	ISO 4.8 / ISO 4.8	Unidirectional airflow (LAF), RABS, or Isolators. Minimized direct intervention.
Grade B	Background Environment: Support zone for Grade A (when an isolator is not used). Essential for aseptic preparation and filling.	ISO 5 / ISO 7	Continuous monitoring of differential pressure.
Grade C	Clean Zones: Less critical stages in aseptic manufacture or background for isolators. Preparation of products for terminal sterilisation.	ISO 7 / ISO 8	HEPA-filtered ventilation with controlled airflow rates.
Grade D	Clean Zones: Lower criticality stages or initial preparation of components for terminally sterilised products.	ISO 8 / Not Defined*	Less stringent particle and microbiological requirements.

Note: (*) Limits for Grade D in operation are established by the manufacturer based on a comprehensive risk assessment and historical environmental monitoring data. **LAF**: Laminar Air Flow; **RABS**: Restricted Access Barrier Systems; HEPA: High-Efficiency Particulate Air.

The industrial deployment of these grades requires distinct engineering philosophies depending on the product's sterilization path. In processing lines requiring strict aseptic manipulation, Grade A environments are mandatory to ensure that the "first air", defined as the primary, ultra-pure air stream exiting the High-Efficiency Particulate Air (HEPA) filters, reaches the open product without encountering any upstream obstacles or operators. To achieve this, direct human intervention is minimized by deploying advanced barrier containment, such as Restricted Access Barrier Systems (RABS) or hermetic Isolator systems fitted with glove-port technology (4). Conversely, for formulations undergoing terminal sterilization, the product is sealed within its primary container under less critical conditions (typically Grade C or D) and subsequently subjected to a validated physical sterilization process (such as autoclaving), allowing for an optimized, risk-balanced approach to cleanroom technology (4,17).

To maintain these standards, cleaning and disinfection protocols are rigorous and include the periodic rotation of disinfectants to prevent microbial resistance. Effectiveness is confirmed through frequent microbiological surface controls (4,18). The equipment is operated solely by qualified personnel and subject to strict preventive and corrective maintenance. Each room maintains a comprehensive documentary portfolio detailing hygiene, cleaning, and equipment

operation procedures, alongside mandatory log sheets that record every activity to ensure full batch traceability (16).

2.2.3. Gowning Routines and Airlock Management

The prevention of particulate and microbiological cross-contamination at the boundaries of the classified environments is maintained through a structured gowning routine executed within the dedicated changing areas (9). At Mesosystem, the entry protocol is designed to ensure a systematic transition from civilian state to controlled manufacturing conditions. Upon entering the changing zone, operators must first store all personal belongings, clothing, and accessories inside designated individual lockers, minimizing the introduction of external fibres and potential physical contaminants into the production perimeter (19).

Once personal items are secured, the personnel must immediately don the cleanroom attire, which comprises a specific industrial uniform, a protective hair cap to contain hair shedding, and specialized shoe covers (16). This gowning sequence ensures that the basic vectors of human contamination are physically contained prior to accessing the classified sectors, such as the ISO 8 (Grade D) and ISO 7 (Grade C) operational zones (19). This standardized discipline ensures that the micro-environmental baseline conditions of the plant are safeguarded during daily manufacturing routines (9).

2.3. Normative Framework

Quality at Mesosystem is interpreted not as a static state, but as strict compliance with technical and legal requirements. Following the precepts of the Quality Management pioneer Philip Crosby, the organisation assumes that the foundation of the quality system is prevention and the performance standard should strive for "zero defects" (7). To materialise this vision, the company maintains a Quality Management system certified in three fundamental international standards (20).

2.3.1. ISO 9001:2015 – Quality Management System

This standard constitutes the backbone of Quality Management. This international standard focuses on process optimization and customer satisfaction through seven fundamental principles: customer focus, proactive leadership, engagement of people, process approach, continuous improvement, evidence-based decision-making, and relationship management (7). Its practical implementation is directly reflected in the reduction of operational waste and thorough process standardization, heavily utilizing the Plan-Do-Check-Act cycle to ensure that customer feedback, corrective actions, and internal audit results are systematically converted into effective, documented improvements (7).

A defining paradigm shift introduced by the 2015 revision is the institutionalization of risk-based thinking across all organizational layers. This methodological approach effectively replaces the traditional, reactive concept of preventive actions with a proactive, continuous evaluation of operational risks and strategic opportunities (7). By embedding risk management directly into the process architecture, the organization can anticipate potential failures in production or supply chain stability, deploying mitigation strategies before any non-conformity (NC) impacts the final product. Also, the standard relies on a comprehensive assessment of the context of the organization, demanding a structured analysis of both internal and external influential factors, alongside the dynamic needs and expectations of all relevant interested parties (7).

Crucially, ISO 9001:2015 is built upon the Annex L, a standardized core text and common terminology framework shared across modern ISO management system standards (7). In an advanced manufacturing environment, this structural alignment serves as a critical strategic enabler. The horizontal compatibility provided by the Annex allows the company to seamlessly integrate its baseline Quality Management system with sector-specific regulatory frameworks, such as the ISO 22716 guidelines for cosmetic GMP (4) and the ISO 13485 standard for medical devices (9,21). Consequently, this unified approach eliminates operational redundancies, harmonizes internal documentation structures, and fosters a holistic corporate culture driven by data integrity, operational excellence, and sustainable continuous improvement.

2.3.2. ISO 13485:2016 – Medical Devices

Given the critical and highly sensitive nature of a portion of Mesosystem’s product portfolio, this standard constitutes the definitive pillars that govern safety, risk mitigation, and efficacy. While historically sharing structural roots with the baseline ISO 9001 quality framework, this sector-specific standard intentionally decouples from a focus on customer satisfaction and corporate performance, placing its entire emphasis on regulatory compliance, comprehensive documentation, and absolute traceability throughout the product's entire life cycle, stretching from initial design and development to final distribution and post-market surveillance (8). For Mesosystem, continuous compliance with this stringent framework acts as a critical strategic enabler, granting the organization authorized access to highly regulated global healthcare markets and providing the strict technical baseline required for the successful attainment and maintenance of the CE (European Conformity) marking under the current Medical Device Regulation (MDR) (8).

Under the operational lens of ISO 13485:2016, the organization also integrates risk management framework governed by the ISO 14971:2019 standard. This mandates that risk assessments are not treated as isolated, static events, but rather as continuous iterative

workflows applied to every manufacturing batch (8,22). Potential hazards linked to raw material biocompatibility, chemical stability, and cross-contamination are systematically quantified, ensuring that engineering controls are embedded into the process architecture to minimize any risks. Because these advanced formulations are intended for intradermal application, the standard imposes severe infrastructural constraints regarding environmental cleanliness and biocontamination control (21,22). Production steps must be executed within strictly controlled environments, such as classified cleanrooms, where airborne particulate levels, relative humidity, pressure differentials, and microbiological bioburden are continuously monitored to safeguard product sterility (14,21,22).

Lastly, a fundamental cornerstone of this medical-grade quality system is the rigorous execution of formal process validation protocols. In accordance with regulatory expectations, any production sequence whose final output cannot be fully or non-destructively verified through subsequent testing, such as sterile filtration, aseptic filling, and primary packaging sealing, must undergo comprehensive prospective validation. This operational discipline is achieved through structured installation, operational and performance qualification cycles (17,23). By establishing empirical evidence that the industrial machinery, automated parameters, and operator interventions consistently operate within strict validated boundaries, the QA department guarantees that every single batch reliably complies with its critical quality attributes. This robust documentary shield ensures that potential system drifts are caught pre-emptively, protecting the integrity of the medical device portfolio and cementing a proactive culture of technical rigor (20).

2.3.3. ISO 22716:2007 – Good Manufacturing Practices (GMP) for Cosmetic Industry

This standard provides the essential regulatory guidelines for GMP within the cosmetic sector, primarily focusing on the absolute minimization of biological, physical, and chemical contamination risks throughout the industrial lifecycle (4,24). At Mesosystem, compliance with these international standards is integrated into a cohesive, high-performance operational framework structured around five fundamental axes. It begins with organization and management, which ensures that all processing phases are meticulously documented via Standard Operating Procedures and executed by qualified, continuously trained personnel (4). The infrastructure and equipment axis imposes strict layout constraints, requiring a strict unidirectional material and personnel flow design within the production plant to systematically prevent cross-contamination and mix-ups (4,5). Furthermore, this axis demands rigorous facility sanitation regimes, restricted access to compounding zones, and the precise metrological calibration of all critical process instruments and compounding vessels (4,5).

To maintain product integrity, the materials management axis provides continuous oversight of the entire manufacturing stream. This covers every stage from the initial intake and quarantine of raw materials and packaging components to the analytical release of the final formulation batch (4). Under this standard, the engineering of the production equipment must satisfy specific hygienic design criteria; processing equipment, piping, and filling machinery are typically constructed from high-grade, non-reactive materials to withstand successive cleaning cycles without undergoing pitting or chemical leaching (4). Additionally, a crucial sub-requirement of this material flow control is the systematic management of retention samples. The quality department must harvest and securely archive reference samples from both raw material lots and bulk cosmetic batches, preserving them under controlled environmental conditions for an extended period past the product's official shelf-life to ensure a bulletproof physical backup for retrospective laboratory investigations (4).

The company employs a robust deviation management architecture, featuring highly responsive, pre-validated procedures for investigating out-of-specification (OOS) results, processing customer complaints, and executing immediate product recalls if safety thresholds are breached (4,24). This reactive loop is balanced by a deep commitment to systemic innovation and evolutionary continuous improvement. By integrating internal quality audit findings, equipment efficiency metrics, and the latest scientific developments into the annual product quality review, the organization successfully transitions its manufacturing practices from a state of static compliance to a dynamic, quality-driven operational environment that guarantees the continuous performance and consumer safety of its advanced cosmetic formulations (4,24).

To provide a concise overview of the company's integrated regulatory framework, Table 4 synthesizes and contrasts the primary focus, technical drivers, and operational targets of the three main certifications.

Table 4 - Operational Comparison of the Integrated Management Standards.

Standard	Primary Focus	Core Technical Driver	Application Target
ISO 9001:2015	Corporate Quality	Process approach & business risk management	Customer satisfaction & continuous improvement
ISO 13485:2016	Clinical Safety	Strict process validation (IQ/OQ/PQ) & cleanrooms	Medical devices
ISO 22716:2007	Plant Hygiene	Unidirectional flow & CIP/SIP sanitization	Cosmetic formulations

Note: IQ: Installation Qualification; OQ: Operatorial Qualification; PQ: Performance Qualification; CIP: Clean-in-Place; SIP: Sterilize-in-Place.

3. The Production Cycle: From Formulation to Finished Product

The manufacturing process at Mesosystem is an integrated system that combines pharmaceutical rigour with medical cosmetic innovation. This chapter describes a product's trajectory, analysing the critical variables that ensure its integrity and compliance with European legislation.

Legally, a cosmetic is defined as any substance or mixture intended to come into contact with the external parts of the human body (epidermis, hair system, nails, lips, and external genital organs) or with the teeth and the mucous membranes of the oral cavity (3). The primary functions of these products are strictly regulated and include cleaning, perfuming, changing the appearance, protecting, keeping in good condition, or correcting body odours (3,25).

At Mesosystem, this concept is elevated to the level of medical cosmetics, where the development and commercialisation of every formula are subject to the strict supervision and regulatory oversight. This oversight ensures that even common products, such as moisturisers or serums, meet the highest safety and quality standards before reaching the consumer (24).

Also, it is important to understand the distinction between cosmetics and medical devices, as it dictates the regulatory pathway and manufacturing requirements (25). Unlike cosmetics, medical devices often have a physical or mechanical mode of action and may be used for the diagnosis, prevention, monitoring, treatment, or alleviation of disease, without pharmacological action (26). This includes higher-risk products such as Class III (injectables) (26,27). Table 5 presents different classes of these medical devices. These require a much more stringent regulatory framework, governed by ISO 13485:2016, and must demonstrate safety and efficacy through rigorous technical documentation (20,26).

Table 5 - Classification of Medical Devices according to Regulation (EU 2017/745).

Class	Risk Level	Description	Examples
Class I	Low	Non-invasive devices with no direct internal contact	Bandages, surgical masks, or handheld instruments
Class IIa	Low-Medium	Short-term invasive devices (e.g., used for less than 30 days)	Hypodermic needles, surgical gloves, digital thermometers, and hearing aids
Class IIb	Medium-High	Long-term invasive devices or those with higher potential risk	X-ray machines, insulin infusion pumps and lung ventilators
Class III	High	Devices that contact the heart, central nervous system, or are injected	Dermal fillers (hyaluronic acid), injectable solutions, pacemakers, and heart stents

While medical cosmetics may contain high concentrations of active ingredients, they remain classified as cosmetics as long as their primary function and application align with the legal definition (3,25). However, products intended for injection or those that cross the dermal barrier to treat a medical condition are classified and manufactured under the stricter medical device protocols (26,27).

3.1. Different Physical Forms and Formulations

The extensive diversity of Mesosystem's portfolio necessitates a profound mastery of various galenic forms, as each physical state is engineered to ensure optimal delivery of active ingredients while addressing specific stability and quality control challenges.

Liquid systems represent a fundamental pillar of the company's manufacturing, requiring precise control over molecular distribution and phase stability across different types of formulations. Within these systems, solutions function as homogeneous monophasic mixtures where solutes are entirely dissolved, demanding constant monitoring to prevent precipitation under fluctuating temperatures (28,29). Emulsions, which are complex biphasic systems of water and oil, are stabilized by specific surfactants, such as polysorbates for oil-in-water emulsions or sorbitan esters for water-in-oil systems (28,30). From a QC perspective, the presence of these surfactants, particularly highly foaming anionic or amphoteric agents, requires delicate handling during analytical testing (31). For instance, during density determinations with a graduated syringe, the entrapment of air bubbles must be strictly avoided, as it can significantly distort the mass-to-volume ratio and lead to inaccurate results. Suspensions involve solid particles dispersed in a liquid medium, a process that necessitates strict control over sedimentation rates to ensure that active ingredients remain uniformly distributed for consistent dosing (28).

Semi-solid formulations provide the necessary viscosity for controlled release and skin adherence, categories which include creams, gels, ointments, and pastes (29). Creams and gels, characterized as colloidal dispersions, rely on specific excipients like cellulose derivatives or colloidal silica to maintain their structured network (28,32). Because these formulations typically exhibit non-Newtonian behaviour, their QC evaluation demands rigorous standardization (32). Viscosity measurements with a rotational viscometer require precise spindle (needle) selection and rotational speed control, as the shear rate directly affects the fluid's structural network during the five-minute reading (32,33). Ointments and pastes are distinguished by a higher lipid content or solid load; in the case of pastes, the high percentage of insoluble solids requires meticulous attention to the homogeneity of the mixture. This focus on uniform dispersion is critical to avoid gritty textures and to ensure that active ingredients are delivered effectively (28,29).

Solid systems are strategically employed to protect highly sensitive compounds from environmental degradation, specifically targeting ingredients susceptible to oxidation or hydrolysis. A prime example in the professional line is the production of lyophilised powders, which incorporate cryoprotectants like sucrose or mannitol (used by Mesosystem) to shield the active ingredients from physical stress during the freezing phase (27). For these systems, QC focuses not only on the physical integrity of the compacted powder but also on the reconstitution process, ensuring that the final osmolality meets clinical standards once the professional adds the saline solution (34).

By mastering these diverse physical forms, Mesosystem ensures that every formulation, from simple solutions to complex solid matrices, meets the highest standards of pharmaceutical and cosmetic excellence. To consolidate this operational diversity, Table 6 provides an overview of the primary galenic systems, summarising their distinct physical forms alongside their specific technical descriptions.

Table 6 - Overview of the primary galenic systems.

System Category	Physical Form	Technical Description
Liquid Systems	Solutions	Homogeneous mixtures with dissolved ingredients
	Emulsions	Mixtures of water and oil using surfactants
	Suspensions	Solid particles dispersed in a liquid
Semi-solid Systems	Creams	Mixtures of oil and water using surfactants
	Gels	Structured networks (colloidal dispersions)
	Ointments & Pastes	High lipid content or insoluble solid load
Solid Systems	Powders	Loose or compacted solid particles

3.2. Strategic Segmentation: Professional and Homecare Lines

Mesosystem operates within a logic of duality, strategically dividing its portfolio to address both clinical excellence and home-care continuity. This segmentation allows the company to offer a comprehensive range of cosmetic solutions, categorised into professional and homecare lines, each tailored to specific intervention levels and safety requirements (6).

The professional line comprises high-performance products with mesotherapy constituting one of the core areas of activity, encompassing interventions for facial, body, and capillary indications (6,35). These formulations are typically presented as liquid preparations, such as solutions in ampoules or vials, enabling precise and controlled administration (6,28,35). The scope of these products is broad, including anti-ageing interventions, reduction of wrinkles, acne scarring and hyperpigmentation, enhancement of skin firmness and radiance, protection against oxidative stress, and the management of localised adiposity, cellulite, and hair loss (6,35).

The professional portfolio also includes chemical peels available in solution or gel form. These products exert revitalising, rejuvenating, and exfoliating effects, promoting deep skin cleansing and renewal (6,28). Their versatility allows application across a wide range of skin types, including mature, sensitive, dry, oily, acne-prone, and hyperpigmented skin (6,28,29). Frequently, these regimens are commercialised as integrated systems or packs that include all necessary components for a complete protocol, such as active solutions or cocktails, peeling agents, masks, and moisturising creams, thereby standardising procedures and optimising outcomes (6,29). Due to their high biological activity and potential for systemic impact, these products require strict application protocols and a controlled environment to ensure safety and efficacy (3,6,24).

Another relevant category within this line comprises lyophilised formulations, which consist of solid powders obtained through the removal of water from solutions or suspensions (sublimation). This process enhances the stability and preservation of active ingredients, ensuring high efficacy upon reconstitution prior to use (27,36).

Additionally, the portfolio includes a wide range of semi-solid preparations, such as pastes, ointments, and creams, tailored to both facial and body applications (6,28). Facial formulations are typically indicated for conditions such as dryness, sensitivity, irritation, reactivity, and sunburn, while body products are primarily oriented towards firming treatments and the reduction of cellulite and skin laxity (6,28,29). Complementing these are specific creams with targeted functions, including thermogenic formulations designed to promote toxin elimination and reduce fluid retention, regenerating creams, post-peeling care products, and sunscreens, all of which play a crucial role in supporting and enhancing treatment outcomes (6,28,29).

The Homecare Line consists of complementary formulations designed for the final consumer to continue treatment outside the aesthetic clinic. These products feature a significantly broader safety margin, focusing on maintaining and enhancing results through daily use without the necessity for direct professional supervision (3,6,29). The range includes face and body care products such as cleansing gels and serums, hydrating masks, and moisturising creams, often tailored to the specific treatments previously performed in a clinical context (6,29,31). Additionally, the homecare portfolio encompasses hair care products, including shampoos, exfoliating treatments, and sprays, which are developed to improve scalp microcirculation, regulate sebum production, revitalise hair follicles, and enhance the overall health and appearance of the hair (6,28,31).

By maintaining this distinction, Mesosystem ensures that high-potency formulations remain in expert hands while providing accessible, safe, and effective solutions for long-term skin maintenance.

3.3. Industrial Workflow Stages (Production Process)

The production flow is a sequence of interdependent stages, where QC acts as the gateway between each phase, ensuring that every formulation adheres to the highest safety and efficacy standards (4). This industrial workflow is not merely a mechanical progression but a strictly regulated process that begins with the meticulous selection of raw materials and concludes with the release of the final product into the market (4,24).

Each stage is designed to mitigate risks of cross-contamination and ensure batch-to-batch consistency (4,8,9). In an environment where the portfolio ranges from sterile mesotherapy solutions to complex semi-solid systems, the synchronisation between the production team and the quality laboratory is essential (4). This integrated approach ensures that the chemical integrity of the active ingredients is preserved throughout the transformation process, ultimately delivering a product that meets both regulatory requirements and professional expectations (9,24).

3.3.1. Validation and Pre-Manufacturing Approval

Before commencing large-scale production of a cosmetic product, every formulation must undergo a rigorous validation process to ensure its safety, efficacy, and consistency. A primary requirement is the preparation of the PIF (Product Information File), a mandatory technical dossier required for every cosmetic product placed on the EU market. The PIF must contain proof of GMP compliance, detailed safety data, and the Cosmetic Product Safety Report (CPSR). The CPSR specifically includes detailed toxicological profiles and exposure analyses, ensuring full compliance with Regulation (EC) No 1223/2009 (3,37). Additionally, before

commercialization, it is legally compulsory to register the product in the Cosmetic Products Notification Portal (CPNP). This centralized notification ensures that competent authorities and poison centres have immediate access to critical product information for market surveillance and safety purposes. This pre-manufacturing phase is critical to ensure that the transition from a laboratory-scale prototype to industrial output does not compromise the product's quality or consumer safety (3,37).

Central to this validation is the implementation of physicochemical and microbiological controls and establish the technical datasheet of the product with all physicochemical and microbiological parameters and acceptable criteria. These involve comprehensive testing of both raw materials and the final formulation, measuring parameters such as pH, viscosity, osmolarity, texture, colour, and odour (32,38). To guarantee the microbiological safety of the formulation over its intended shelf life, a Preservative Efficacy Test, commonly known as a challenge test, is strictly mandatory (18,39). This assay deliberately inoculates the product with a standardized spectrum of bacteria and fungi to empirically validate the robustness of the preservative system against potential consumer contamination (18,39).

Also, the product is subjected to accelerated stability tests, where it is placed in climate chambers under extreme conditions, typically 40°C and 60% humidity. These tests allow the technical team to predict the product’s shelf life and stability without awaiting real-time results, confirming that the active ingredients remain effective without physical or chemical degradation (38,40). Before market release, the formulation must undergo rigorous claim substantiation. In the context of medical cosmetics, any marketed benefits, such as 'anti-ageing', 'regenerative', or 'depigmenting' properties, must be scientifically validated through *in vitro*, *ex vivo*, or *in vivo* clinical studies (25,37). This includes dermatological testing on human volunteers to formally confirm skin compatibility, mucosal acceptability, and overall clinical efficacy, ensuring strict adherence to European regulatory expectations (37,38).

3.3.2. Bulk Preparation and Quarantine

The transition to the industrial stage begins with Bulk Production, a process governed by strict adherence to the master formula and the specific Manufacturing Order (MO). The sequence initiates with the Weighing phase, where raw materials that have been previously inspected and approved are measured individually (4). This procedure is conducted within a laminar flow chamber (ISO 5) to prevent contamination and utilises calibrated scales to ensure absolute precision (4,9). This accuracy is paramount to guaranteeing batch-to-batch consistency and the chemical integrity of the final formulation. Following this step, any unused raw material is immediately sealed in its original packaging, properly re-identified, and returned to the controlled warehouse to prevent degradation or cross-contamination (4,5).

Following weighing, the process moves to Mixing and Storage. The ingredients are transferred to industrial reactors or agitators (33). Once the bulk intermediate product is obtained, it is stored in closed tanks, which are meticulously identified with labels detailing the product name, internal code, MO number, batch number, quantity, expiry date, and any special storage conditions required (4,7).

The batch does not proceed immediately to the filling machines; instead, it is placed in Quarantine and Control (4). During this mandatory phase, the bulk remains held in a designated area while a QC technician performs a comprehensive battery of physicochemical and microbiological tests. These assays verify critical parameters including pH, density, viscosity, osmolarity, colour, appearance, and odour (32,34,38). Simultaneously, a representative sample is collected for microbiological assessment, this aliquot is immediately stored under controlled refrigeration to preserve its original microbial profile and prevent proliferation until the moment of analysis (5,41). This stage acts as a definitive safeguard to ensure the product base meets all pre-established specifications.

The final stage of this phase is Approval or Rejection. If the bulk complies with all quality standards, according to the specific technical datasheet, it receives a green label and is authorised to advance to the filling stage (4,7). Conversely, if any NCs are detected, the batch remains blocked, and the quality department must intervene to decide whether the material will be rejected or reprocessed (reworked). This rigorous gateway ensures that only compliant products reach the final primary packaging phase (4,7).

3.3.3. Primary Packaging in a Controlled Environment

The next stage of the manufacturing process begins with Primary Packaging, where the bulk product is transferred into its immediate container, such as ampoules, vials, syringes, or tubes. Prior to the filling operation, the primary containers, which are often pre-serigraphed or labelled with mandatory regulatory information, must undergo a strict verification process (3,42). The QC department is responsible for approving the artwork and labelling compliance to ensure all legal requirements are met before the packaging materials are released to the production line (3,42). This operation is carried out within cleanrooms (Classified Rooms), specifically ISO 8 environments, which are strictly monitored to control air quality, pressure, and temperature. The use of these classified areas is essential to mitigate the risk of cross-contamination and to ensure that products maintain their required microbiological purity (9,14,23).

The Filling Conditions are managed through the use of specialised machinery tailored to the specific galenic form, including dedicated equipment for vials, ampoules, and syringes, as well as general filling systems for creams and liquids. Each piece of equipment is assigned a unique numerical identification tag to ensure full traceability (7). To prevent cross-contamination

between different batches, a strict 'Line Clearance' protocol is enforced, requiring documented cleaning, disinfection, and QC verification after each use (4). Throughout this stage, several in-process controls are strictly enforced to maintain product integrity, beginning with a visual inspection where the operator performs a sensory evaluation to confirm the colour, texture, and homogeneity of the bulk product prior to filling (32). To ensure the nominal quantity meets regulatory limits, volume control checks are conducted at the start of the run and at regular intervals throughout the process, providing a constant verification of dosage accuracy (as detailed in Section 4.4.1) (4,7). To illustrate the precision and scale of this automated stage, Figure 2 displays the specialized machinery utilized for the filling of vials and tubes within the classified environment.

Figure 2 - Automated primary packaging equipment in an ISO 8 cleanroom: (left) Liquids filling machine; (right) Vials filling machine;

During the sealing and maintenance phase, containers are secured using validated sealing methods following the fill to ensure a hermetic closure, which is essential for preventing oxidation or microbial ingress and preserving the formula's stability until use (43). A visual representation of this critical step is provided in Figure 3, demonstrating the transition of a cosmetic tube from its open state post-filling to a fully secured and hermetically sealed primary container.

Figure 3 - Primary packaging integrity: Visual comparison of a cosmetic tube before (open) and after the hermetic sealing process.

To guarantee the continued integrity of this classified environment, the equipment undergoes regular maintenance and rigorous cleaning protocols (9,23). Also, weekly microbiological controls are performed on the machinery and the environment to ensure that the high safety standards required for medical cosmetics are consistently upheld.

3.3.4. Lyophilisation: Preservation of High-Performance Actives

For high-performance active ingredients that are unstable in aqueous solutions, such as specific enzymes and vitamins, Mesosystem utilises lyophilisation, or freeze-drying, to significantly enhance stability and extend shelf life (34,44). This sophisticated cryodesiccation process typically spans approximately 48 hours, during which water is removed through vacuum sublimation (14). The procedure is divided into three critical stages: freezing, where the temperature drops to -40°C to turn water into ice crystals; primary drying, where a vacuum facilitates the transition of ice directly to vapour as temperatures rise to 7°C; and secondary drying, which eliminates residual moisture by increasing the temperature to 20°C (14). To ensure the operational reliability of these stages, the lyophilisation equipment is subjected to strict preventive maintenance, including routine vacuum leak tests to definitively verify the chamber's hermetic integrity (4,36).

To protect the active ingredients from physical stress during the freezing phase, cryoprotectant mannitol is incorporated into the formulation (20). Prior to loading the vials into the freeze-dryer, all associated materials, particularly the product trays, undergo rigorous visual inspection and preparation (4). This methodology results in a stable, compacted powder, as illustrated in Figure 4, which effectively preserves the compound’s bioactivity by eliminating the risks of hydrolysis and oxidative degradation (29). In strict compliance with GMP, all critical

process parameters, namely the continuous temperature and pressure curves, are meticulously monitored and formally documented in the master batch record to guarantee full traceability and cycle reproducibility (4,36). Maintained in this stabilised solid state, the product requires reconstitution by a qualified professional, typically through the addition of a sterile saline solution, immediately prior to clinical application (20). This precise, point-of-use preparation ensures that the lyophilised ingredients are delivered at their peak potency, mitigating risks of premature degradation and ensuring maximum bioavailability during the procedure (34,44).

Figure 4 - Lyophilisation process of advanced cosmetic formulations: Vials arranged on freeze-dryer trays prior to the cryodesiccation cycle.

3.3.5. Moist Heat Sterilisation: Safety and Microbiological Control

For products that demand the total absence of microbial load, such as injectables and specific mesotherapy solutions presented in ampoules or vials, Mesosystem employs moist heat sterilisation (45,46). The primary objective of this stage is the absolute elimination of all forms of microorganisms, including bacteria, fungi, viruses, and highly resilient spores (12,47). This is achieved using an autoclave, where products are subjected to saturated steam under pressure, typically reaching temperature of 121°C for 15 minutes (12,26). Each sterilisation cycle is specifically validated for the formulation, guaranteeing that the required lethality is achieved without inducing any physicochemical degradation to the sensitive active ingredients (12,45).

The success of this process relies on the rigorous monitoring of critical parameters, such as temperature, pressure, time, effective air removal, and homogeneous steam distribution, ensuring that the thermal treatment is repeatable and does not compromise the product's physical or chemical integrity (26). To guarantee transparency and traceability, the equipment generates a cycle report and graph for each batch, providing immediate parametric evidence

and formally declaring a 'Valid Process' (17,46). An example of this parametric release documentation is presented in Figure 5. Following the cycle, a final inspection is performed to confirm that the primary packaging remains intact and that the hermetic seal has been maintained, providing a definitive barrier against external contamination (9,20,26).

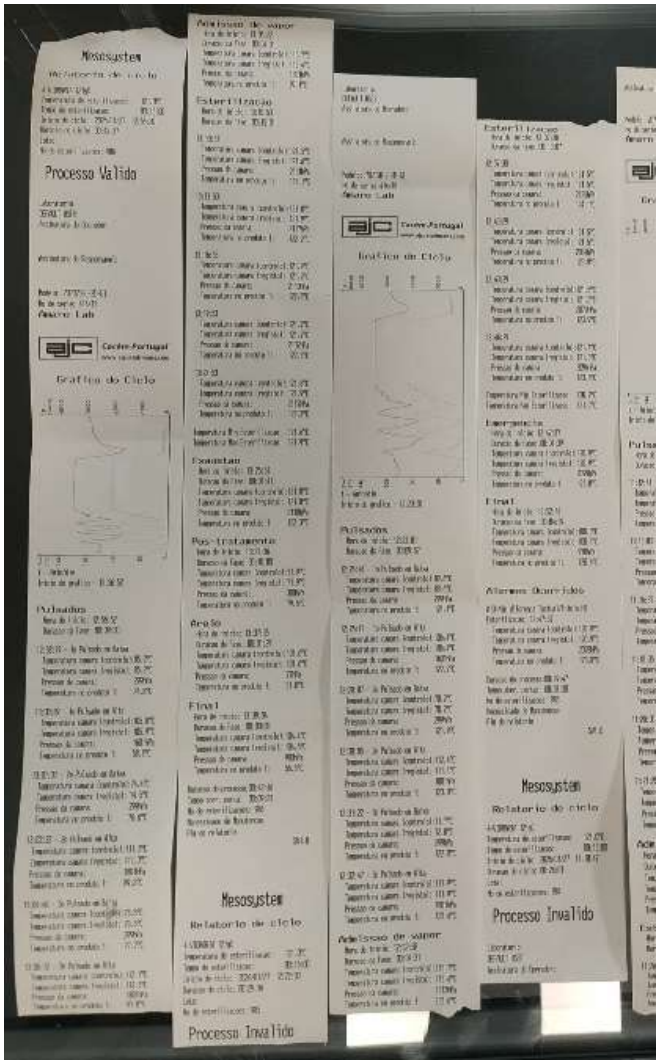

Figure 5 - Parametric release documentation: Autoclave physical printout detailing the critical temperature and pressure curves of a validated moist heat sterilisation cycle.

3.3.6. Secondary Packaging and Final Assembly

Following the successful completion of the primary packaging and any necessary sterilisation or lyophilisation processes, the products advance to the Secondary Packaging stage. This phase serves as the final physical barrier, where primary containers such as ampoules, vials, or tubes are carefully integrated into their commercial packaging. Although this stage typically occurs outside the strictly classified cleanrooms, it is conducted under rigorous hygiene and environmental conditions to ensure that the integrity of the finished product is never compromised (43). The primary objective of this process is to provide mechanical protection

against impact, light exposure, and temperature fluctuations during subsequent transport and storage (40,43).

For primary containers that are not pre-serigraphed, such as anonymous glass vials or ampoules, this stage begins with the precise application of adhesive labels. These labels must display critical traceability data, including the internal batch number, expiry date, product identification, and brand (3,42). The Secondary Packaging process is a meticulous assembly that includes the insertion of the Instructions for use, when necessary, an essential regulatory component that provides specialists and consumers with comprehensive instructions for use, contraindications, and storage requirements (3,42). Concurrently, the boxes are equipped with tamper-evident seals and protective inserts (such as blisters or custom holders) to secure the primary containers. The secondary packaging itself must strictly display all elements mandated by the EU Cosmetics Regulation, including the company name and country of origin, responsible person, nominal quantity, period after opening, International Nomenclature of Cosmetic Ingredients (INCI), barcode, and specific conservation instructions (25,42).

Before the batch is palletised, a final Quality Verification is performed on the packaging line to ensure the structural integrity of the boxes and the presence of all mandatory components (Figure 6) (7). This inspection rigorously checks for physical defects, such as tears, deformations, or dirt, and validates the exact quantity of units per box, as well as the total number of boxes produced against the master production record (7,48).

Figure 6 - Secondary packaging assembly. Internal view of the final commercial presentation demonstrating the secure integration of primary containers within custom protective inserts.

Once this final assembly is complete, the products are moved to a warehouse for storage. Products intended for promotional sets or multi-product packs are often stored as individual units and assembled on demand upon order receipt. This marks the end of the industrial transformation flow and the beginning of the final release cycle for global distribution (42,48).

3.3.7. Storage and Traceability

Traceability represents a critical layer of the production workflow, serving as a comprehensive system that links every stage of the manufacturing process to the finished unit (4,49). This system ensures that Mesosystem can meticulously track the journey of a product, from the reception of raw materials to the final delivery to the consumer (5,49). Each batch is assigned a unique alphanumeric identification number upon the initiation of bulk production. This number is cross-referenced within the MO and the Product Guide, which comprehensively detail the specific equipment used, the environmental conditions recorded in the cleanrooms, the individual technicians involved, and the precise lots of raw materials and packaging components utilised (an example of this labelling, from the bulk intermediate to the final product, is illustrated in Figure 7) (4,5,20).

Figure 7 - Comprehensive batch traceability: Internal bulk identification label cross-referenced with the alphanumeric coding printed on the final commercial packaging.

To ensure unambiguous identification and mitigate human error, Mesosystem employs a standardized batch numbering system. This code consists of a letter designating the year of manufacture (e.g., 'C' for 2026) followed by a two-digit sequential number corresponding to the production run, alongside the expiry date (2,42). In strict adherence to packaging coding guidelines designed to prevent visual misinterpretation, easily confused letters, such as I, O, Q, and U, are intentionally excluded from the batch nomenclature (2,42).

The effectiveness of this system relies on the reconciliation of data between the primary and secondary packaging. By ensuring that the batch numbers and expiry dates are consistently mirrored across all levels of packaging, the company facilitates a transparent and rapid response mechanism for market surveillance (24,49). The formal release of the lot is ultimately authorized via the signature of the responsible person on the MO. Furthermore, in compliance with the EU Cosmetics Regulation (EC) No 1223/2009 and GMP standards, all batch records and quality documentation are securely archived for a minimum period of 10 years (3,4,20).

In the event of a quality inquiry, NC, or a regulatory audit, this robust traceability framework allows for the immediate identification and isolation of specific batches, ensuring consumer safety and maintaining the integrity of the global supply chain (24,25). This documented accountability acts as a guarantee of quality, proving that every product has been manufactured and handled in strict accordance with GMP and international cosmetic regulations (24,25).

4. Quality Control: Operational Workflow

The QC department at Mesosystem operates as the definitive technical authority, ensuring that no product is released to the market without robust, objective evidence of compliance. Its mandate is vital for guaranteeing the safety, efficacy, and regulatory alignment of every manufactured lot (4,21). The scope of the QC department is inherently transversal, exerting rigorous surveillance over the entire production lifecycle, from the qualification of raw materials and packaging components to the continuous monitoring of the manufacturing environment and the final validation of the finished product (4,21).

4.1. Raw Materials and Packaging Reception Control

4.1.1. Raw Materials

The integrity of Mesosystem’s formulations is directly contingent upon a rigorous qualification and reception protocol for all incoming raw materials (50). This process initiates with a stringent supplier selection phase, where partners are evaluated based on their ability to consistently provide raw materials that meet the company's predefined chemical and safety criteria(51).

Every delivery must be accompanied by two mandatory documents: the Certificate of Analysis (CoA), which certifies that the specific lot meets predefined chemical specifications, and the Safety Data Sheet, which provides essential data regarding handling risks, environmental impact, and emergency safety measures (52). Upon arrival, materials are immediately placed in a designated quarantine area. The QC department performs a strict visual inspection of the delivery containers to verify their physical integrity and ensure no damage or contamination

occurred during transit. The technician then performs a comprehensive cross-reference between the supplier’s documentation, the quantities received, and internal standards (51). Raw materials are approved by comparing the CoA with the specifications defined by Mesosystem for that raw material.

Once compliance is verified, the material is identified with a green approval label, containing the batch number, expiry date, and authorized signature, and transferred to the temperature-controlled warehouse, organized alphabetically for full traceability (52). In contrast, if any NC is detected, whether due to documentation discrepancies, compromised packaging, or analytical failure, the material is immediately flagged with a red label and segregated in a restricted area for non-conforming products (53). A formal NC report is then opened, initiating a supplier complaint and a return process in direct collaboration with the Purchasing Department. As a final safeguard, the production manager performs a point-of-use visual inspection before the compliant material is introduced into the industrial reactors, ensuring no alterations occurred during storage (50).

4.1.2. Packaging Control

As part of a recent continuous improvement initiative to ensure strict compliance with ISO 9001:2015 and GMP requirements, the incoming logistics and verification of all packaging materials follow a recent structured, multidisciplinary workflow formalized through standard work instructions and individual specification sheets that are cross-referenced with the suppliers' technical data sheets and registered within the company's enterprise resource planning platform, called “NAV”, defining the exact acceptance criteria for each packaging type (4,8).

Upon delivery at the warehouse, the components (both primary and secondary packaging) are immediately placed into a locked status within a restricted quarantine area, preventing premature cross-contamination or unauthorized use in the production lines, while automatically notifying the QC department (50). The QC technician initiates the primary inspection phase by conducting a detailed visual and artwork audit on a representative sample of the lot (54). For printed packaging materials, this stage requires close cross-functional coordination with the Marketing department, which provides the original procurement documents and authorized reference samples. This collaboration allows the technician to rigorously evaluate the serigraphy, physical integrity, cleanliness, and labelling content against the active product specifications, ensuring that the INCI listings, nominal quantities, and warning symbols are fully accurate and legible (55).

Following the analytical and physical assessments, the definitive disposition decision is overseen by the QA department, which validates the entire technical package. If approved, a green compliance label containing the internal batch number, inspector signature, and release date is issued, officially clearing the material for production storage. Conversely, a failure triggers an immediate rejection, leading to the isolation of the lot with a red label in a segregated area and the issuance of a formal NC report for supplier claim management (4,8).

For the evaluation of structural components during the physical inspection, specialized dimensional and gravimetric analyses are conducted. Gravimetric control determines the material's grammage (expressed in g/m^2), particularly for secondary cardboard packaging (56). This is executed by evaluating one representative unit per lot using an analytical balance and precision cutting templates of 5x5 cm or 2x2 cm. Concurrently, dimensional inspections are performed on three units per lot, utilizing callipers and calibrated rulers to ensure that diameters, heights, and thicknesses remain within a standard tolerance of ±2.0 mm relative to the technical drawings (4,8).

To ensure statistical reliability and eliminate sampling bias, the inspection process is governed by the ISO 2859-1 standard for inspection by attributes (57). This system employs defined Acceptance and Rejection numbers based on the lot size to determine the disposition of the entire delivery (57). By anchoring this updated workflow to standardized data-recording sheets, the organization guarantees complete end-to-end traceability, providing a robust documentary shield that satisfies both internal process reliability and external regulatory expectations (8,50).

4.2. Physicochemical and Sensory Testing

Upon the completion of the bulk intermediate manufacturing phase, the QC technician initiates a comprehensive analytical protocol (54). This operational sequence is systematically governed and recorded within a dedicated product specification sheet, which details all the standardized acceptance criteria and analytical thresholds required for a multi-parametric evaluation of the batch. The methodological framework for this testing, categorized by formulation rheology, is visually systematized in Figure 8. This stage is critical to ensure batch-to-batch reproducibility and to verify that the formulation meets the predefined specifications before it is committed to primary packaging (58).

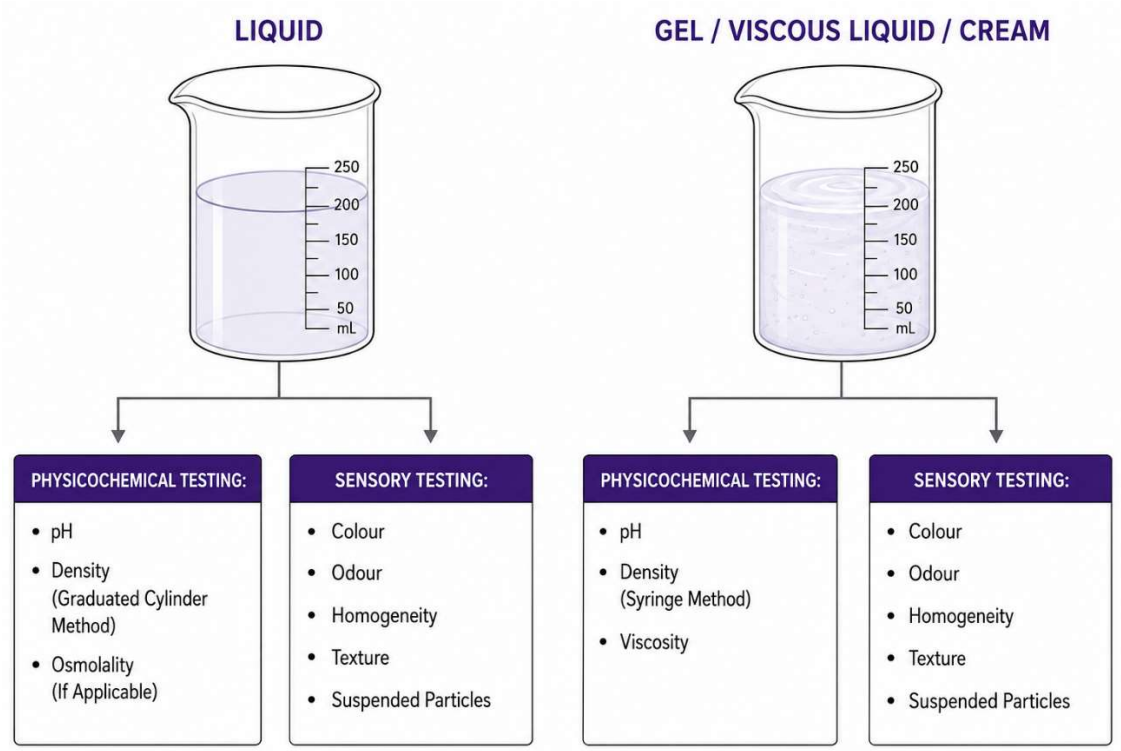

Figure 8 - Methodological framework for physicochemical and sensory testing, tailored to formulation rheology.

Osmolality testing is applied on a case-by-case basis depending on specific product monographs and formulation requirements (e.g., sterile mesotherapy solutions or mucosal applications), rather than being an absolute routine release parameter for every cosmetic batch.

4.2.1. Sensory and Organoleptic Evaluation

The first line of quality assessment involves organoleptic analysis, which utilizes human sensory perception to evaluate the product's physical identity and aesthetic compliance (58). At Mesosystem, this evaluation is performed through objective visual, olfactory, and tactile inspections, comparing the current batch against an established reference standard or a previously approved lot. This comparison is vital to ensure consistency across production cycles and to meet the consumer's expectations regarding the product's sensory profile (32,54,59).

Visual inspection focuses primarily on colour and homogeneity. The product is observed under standardized lighting conditions to detect any anomalies such as spotting, gradients, or pigment oxidation, which could indicate chemical instability or improper mixing (54). Additionally, the macroscopic evaluation screens for undispersed solid particles or agglomerates, which act as primary indicators of inadequate blending or raw material incompatibility (30,60). For liquid formulations, the absence of turbidity, precipitates, or

supernatants is verified, while for emulsions and gels, the focus is on phase separation and the exclusion of persistent air bubbles. In the specific case of lyophilised products, the morphology is examined to ensure it remains a compact solid without fractures or loose particles (30,60).

The olfactory evaluation is conducted in a neutral environment to confirm the intensity of the formulation's characteristic scent or the total absence of odour, particularly in sterile solutions (54). Lastly, tactile analysis is employed to assess texture-related attributes such as spreadability, consistency, and absorption rate, alongside specific functional sensations such as cooling or thermoactive effects frequently formulated in body massage creams (32,58). This comprehensive sensory screening acts as a critical safeguard, any aesthetic deviation, even if the physicochemical parameters are within range, can trigger a deeper investigation into the batch's physical stability or raw material integrity (54,58).

Following sensory approval, the bulk undergoes quantitative physicochemical testing to validate its chemical integrity and rheological behaviour.

4.2.2. Determination of pH

The determination of pH is a pivotal parameter for ensuring both physiological compatibility with the skin barrier and the long-term chemical stability of the formulations (31,38). All products are strictly monitored to ensure they remain within the narrow pH range defined during the development phase; any significant drift could compromise the efficacy of the preservative system or the potency of specific active ingredients, such as depigmenting or regenerative agents (30,36).

At Mesosystem, pH is measured potentiometrically using a combined glass electrode, which integrates both a reference system (Ag/AgCl) and an indicator sensor within a single body (61,62). This method relies on the potential difference generated across a hydrated glass membrane due to ion exchange, a signal that the instrument subsequently converts into pH units according to the Nernst equation (62). The structural configuration of this electrode and the standard laboratory setup are illustrated in Figure 9.

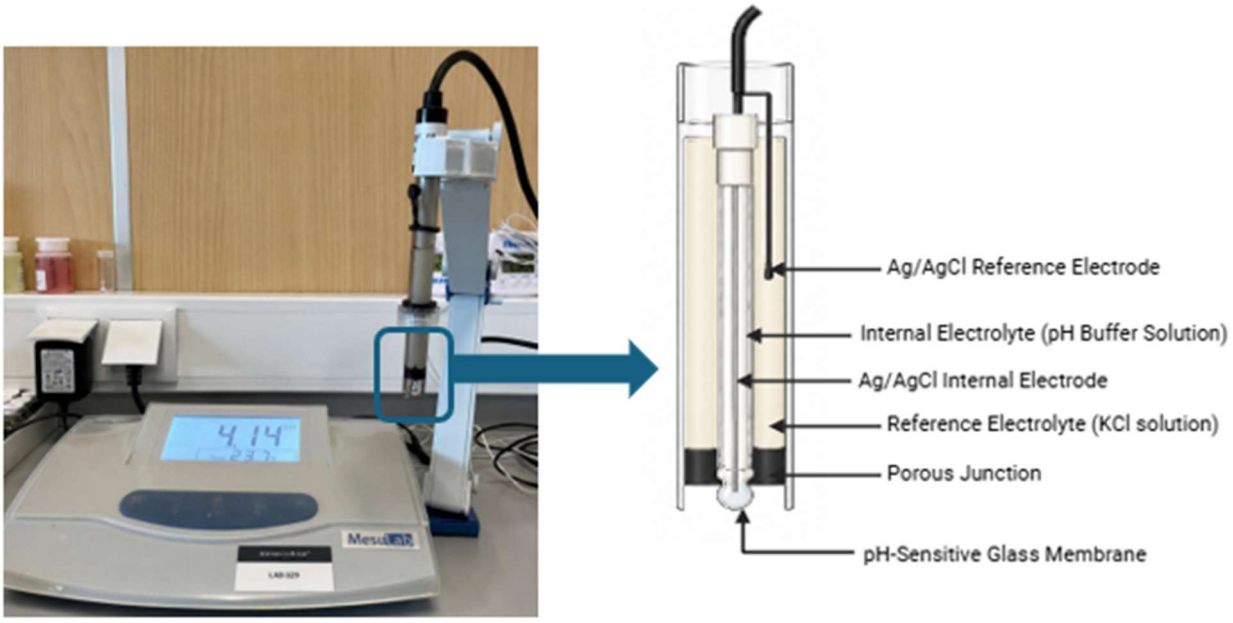

Figure 9 - Analytical setup for physicochemical pH assessment: (left) Operational digital pH meter; (right) Structural layout of the combination glass electrode illustrating the internal reference and sensing membrane.

To maintain the highest standards of analytical reliability, the equipment undergoes a standardised calibration protocol every 48 hours, utilizing buffer solutions of pH 4.01 and 7.00 (61,63). In strict adherence to Good Laboratory Practices (GLP), these reference buffer solutions are systematically replaced every 30 days and clearly labelled with their batch number, expiration date, and exact date of opening to prevent standard degradation. This internal verification complements periodic external calibrations and is meticulously recorded on dedicated log sheets to ensure full traceability (1,4). Also, strict maintenance of the electrode, including thorough rinsing with deionized water between samples and storage in a potassium chloride (KCl) electrolyte solution, ensures the sensitivity and reproducibility of the measurements (62). By adhering to this rigorous maintenance and calibration schedule, the QC department guarantees that the analytical data remains a definitive safeguard for product safety and batch-to-batch consistency (2,21).

4.2.3. Viscosity and Rheological Characterisation

Viscosity measures a fluid's resistance to flow and is a key indicator of batch-to-batch consistency and structural uniformity. In the cosmetic industry, rheology is essential not only for ensuring the stability of formulations but also for guaranteeing a superior sensory experience, as it directly influences how a product is spread and absorbed by the skin (32,53). Also, maintaining a consistent viscosity is critical for operational efficiency, it prevents dosing inaccuracies in filling machinery and minimizes mechanical stress during the primary packaging phase (4,54,64).

Most cosmetic formulations exhibit non-Newtonian behaviour, meaning their viscosity fluctuates depending on the shear rate applied. Specifically, they often display shear-thinning or viscoelastic profiles (29,65). To accurately characterize these complex fluids, Mesosystem utilizes a rotational viscometer (specifically, the IKA Rotavisc lo-vi model, shown in Figure 10). While absolute viscometers (such as cone-and-plate systems) are used for definitive rheological profiling, this relative needle viscometer is the ideal instrument for routine QC to ensure that each batch strictly adheres to its predefined internal specifications (2,66).

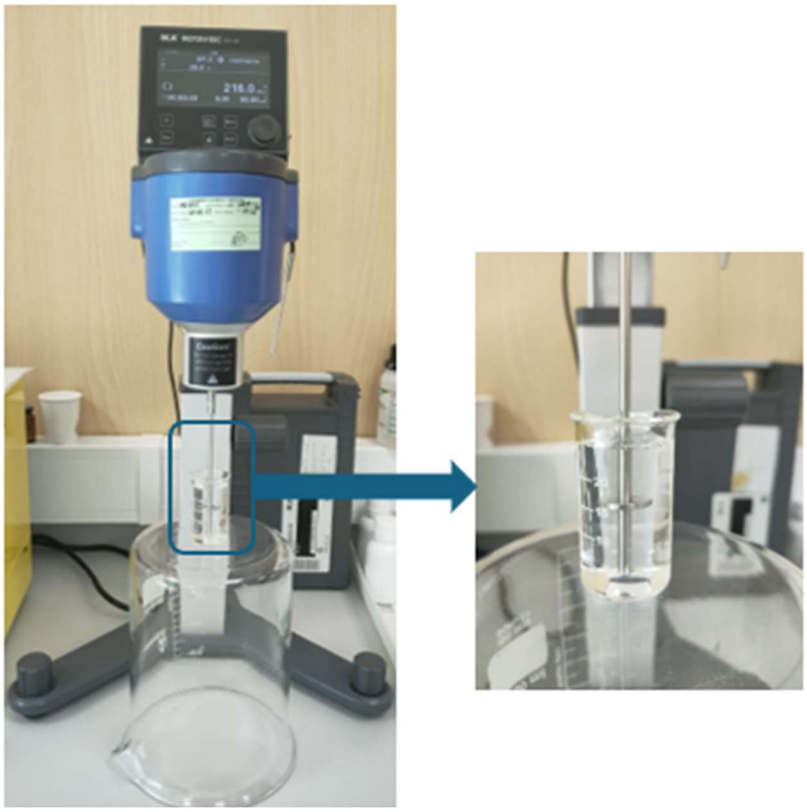

Figure 10 - Rheological quality control: IKA Rotavisc lo-vi relative needle viscometer employed for the routine viscosity assessment of semi-solid cosmetic batches.

The analytical procedure is strictly standardized to ensure reproducibility. Before each measurement, the equipment's levelling is verified. The specific spindle (needle) and rotational speed, expressed in Revolutions per Minute (RPM), are not selected arbitrarily; they are predefined in each product's specification sheet, having been established through successive optimization readings during the R&D and formulation phases (21,66). The chosen spindle is submerged into the sample exactly up to the designated immersion mark located on its shaft, and the test is conducted for a stabilized period of five minutes. The final viscosity is expressed in millipascal-seconds (mPa.s). By maintaining these rigorous conditions, constant temperature, specific spindle geometry, and fixed RPM, the QC department ensures that the rheological profile of the product remains stable, preserving both its functional efficacy and its commercial appeal (21,66,67).

4.2.4. Density Determination

The determination of density, expressed in grams per millilitre (g/mL), constitutes a fundamental physical assay for the quality control of bulk formulations, including creams, gels, and liquid solutions (38). Significant deviations in this parameter often serve as primary indicators of physical instability, such as phase separation, sedimentation, loss of volatile compounds, or the unwanted incorporation of air during the industrial mixing phase. Such drifts are critical because they directly impact both the aesthetic uniformity of the product and the precision of the final filling volume during the packaging stage (32,54,68).

While direct instrumental techniques such as digital density meters or hydrometers are available, Mesosystem determines density through a rigorous and versatile indirect gravimetric method based on the relationship between a precisely measured mass and a defined volume (69). To maintain high analytical accuracy across various galenic forms, the QC department differentiates the procedure according to the product's viscosity. For low-viscosity formulations and liquid solutions, the technician utilizes a calibrated graduated cylinder, recording the mass of the sample at three increasing volumes, typically 20, 30, and 50 mL, using a high-precision analytical balance. This sequential weighing allows for a more robust data set than a single measurement (64).

In contrast, for high-viscosity formulations such as dense creams or gels, the procedure is adapted to account for the material's flow resistance. In these cases, a graduated syringe is employed to measure specific volumes of 2, 4, and 5 mL before transferring each aliquot to a beaker for weighing. The use of a syringe is essential in this context as it allows for the effective elimination of air pockets that could otherwise distort the volumetric reading and lead to inaccurate results (68). For both liquid and viscous products, the final density is calculated as the arithmetic mean of the three consecutive measurements, utilizing the standard formula (“d=m/V”, where “d” represents density, “m” the net mass, and “V” the volume). To ensure full GMP traceability, the final calculated value is formally registered in the batch's dedicated analytical log sheet (4).

This triple-check approach effectively minimizes experimental error and ensures that the bulk product adheres to the strict technical specifications before advancing to the primary packaging phase (2,64).

4.2.5. Osmolality Determination

Osmolality is defined as the total concentration of osmotically active particles in a solution, expressed as the number of osmoles of solute per kilogram of solvent (Osm/kg). In the case of specialized dermatological solutions, particularly those intended for advanced aesthetic and mesotherapy procedures, osmolality is a strictly controlled parameter (70). This assay ensures that the product maintains osmotic equilibrium with the biological environment, minimizing the risk of cellular stress, discomfort, or irritation upon application. Also, precise osmolality control is vital for optimizing the bioavailability of active compounds, ensuring they are delivered effectively without compromising the integrity of the cutaneous tissue (34,71).

At Mesosystem, this measurement is performed using a cryoscopic osmometer, specifically the Löser type 7 model (Figure 11). The equipment operates based on the principle of freezing point depression, a colligative property where the freezing point of a liquid is lowered in direct proportion to the concentration of dissolved particles (solutes) (70). Compared to alternative techniques such as vapour pressure osmometry, the cryoscopic method is highly valued in QC for its independence from ambient gas interferences and temperature fluctuations, rapid results, and the requirement of only small sample volumes, which do not interfere with the analytical accuracy (34,72).

Figure 11 - Cryoscopic osmolality determination: Löser type 7 osmometer utilized for the precise tonicity assessment of sterile mesotherapy and mucosal formulations.

The analytical procedure begins with a mandatory internal calibration to ensure the equipment's reliability. This is achieved using standard reference solutions (typically 0, 300, or 900 mOsm/kg), depending on the expected range of the sample (1). Once calibrated, the product sample is placed into a specific measuring tube and inserted into the thermistor head of the osmometer. The sample is then subjected to a controlled cooling process until freezing

is induced by the automated insertion of the crystallization needle (1,34,70). The instrument detects the precise temperature at which the solid-liquid equilibrium is reached and automatically converts this thermal data into concentration units, expressed in milliosmoles per kilogram (mOsm/kg). By adhering to this rigorous testing protocol, the QC department guarantees that every batch of advanced aesthetic solutions meets the exact tonicity requirements necessary for safe clinical use (1,34,70).

Should any analytical parameter deviate from the established acceptance criteria, a formal investigation is initiated. Depending on the severity of the deviation, the batch may undergo a validated rework protocol or be officially rejected, as detailed in Section 4.6 (Management of Non-Conformities) (2,4).

4.3. Microbiological Control and Environmental Monitoring

4.3.1. Microbiological Control: Bioburden Assessment

The determination of the microbial load, or bioburden, is a critical procedure performed to ensure that the product's contamination levels remain within strictly defined limits and evaluate the efficacy of preservatives (5). This process is conducted under rigorous aseptic conditions within a Class ISO 5 laminar vertical airflow workstation to prevent any exogenous contamination of the samples (14). While routinely performed once per non-sterile batch, this bioburden assessment is also triggered as an extraordinary measure if anomalies are detected in the cleanroom's air handling units, or if environmental and personnel monitoring results exceed established action limits (23).

The methodology involves extracting a 10 µL sample using a calibrated sterile inoculation loop to carefully extract the product. The sample is then applied to the surface of specific culture media using the cross-hatching streaking technique (14,73). This procedure consists of spreading the inoculum in a continuous zigzag pattern across the entire agar surface, followed by a second streak performed at a 90º angle to the first one, as illustrated in Figure 12 (14,73).

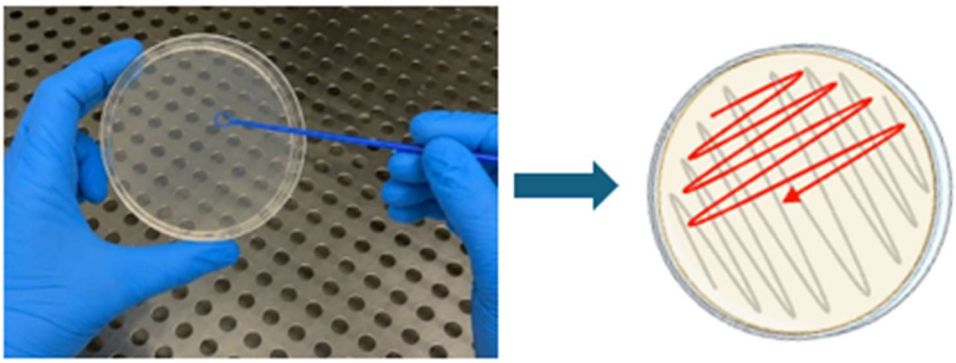

Figure 12 - Microbiological inoculation methodology: Execution of the cross-hatching streaking technique on solid agar media to ensure uniform sample distribution and accurate bioburden quantification.

This technique is the most adequate for bioburden assessment because, unlike quadrant streaking intended for strain isolation, the cross-hatching pattern ensures a maximum and uniform distribution of the product across the total available area (74). By utilizing the entire plate, it effectively prevents colony confluency and facilitates the accurate counting of Colony Forming Units (CFUs), which is essential for verifying compliance with the strict limits defined by ISO 17516:2014 (75). In cases where high microbial loads are suspected, successive dilutions may be performed prior to inoculation to ensure that the resulting growth remains within the measurable range of the plates (52,75).

Two primary media are utilised for the assessment of microbial contamination: Tryptic Soy Agar (TSA) and Sabouraud Dextrose Agar with Chloramphenicol (CAF). To ensure absolute standardisation and mitigate internal preparation risks, these culture media are not formulated in-house; they are acquired as pre-poured, ready-to-use plates from a certified external supplier.(75) TSA is a versatile, non-selective medium that supports the growth of a wide range of aerobic mesophilic bacteria by providing essential nitrogen and carbon sources through casein and soybean meal digests (76). In contrast, Sabouraud CAF is a selective medium, specifically formulated for the isolation of yeasts and fungi. This media has acidic pH and the inclusion of CAF, a broad-spectrum antibiotic, is vital as it suppresses bacterial overgrowth, allowing for the selective recovery of opportunistic fungi (18,77).

The incubation process is strictly controlled to provide the optimal conditions for the proliferation of different microbial groups. Following inoculation, TSA plates are incubated at 30-35ºC for a period of 3 to 5 days for the detection of Total Aerobic Microbial Count (TAMC) (41,78). Simultaneously, Sabouraud CAF plates are transferred to a separate incubator maintained at 20-25ºC for 5 to 7 days to determine the Total Combined Yeasts and Moulds Count (TYMC) (14,73). These specific temperature ranges and incubation periods ensure that even slow-growing strains are detected, providing a comprehensive profile of the product's bioburden (74).

Final readings are conducted to count the CFU, ensuring that the results adhere to the strict microbiological limits defined for both cosmetic and medical device formulations. Results are expressed in CFU/mL or CFU/g. According to ISO 17516:2014, general cosmetics must maintain a TAMC ≤1000 CFU/g and TYMC ≤100 CFU/g. However, for high-risk products, limits are stricter: TAMC ≤100 CFU/g and TYMC ≤10 CFU/g (Table 7).

Table 7 - Microbiological limits for cosmetic products according to ISO 17516:2014.

Target Application	Risk Level	TAMC (Bacteria)	TYMC (Yeast and Fungi)	Specified Pathogens*
Group A (Babies less than 3 years old, Ocular area, Mucous membranes)	High	100 CFU/g	10 CFU/g	Absence in 1g or 1mL
Group B (General cosmetic products)	Standard	1000 CFU/g	100 CFU/g	Absence in 1g or 1mL

Note: * *S. aureus*, *P. aeruginosa*, *E. coli* and *C. albicans.*

While the routine monitoring at Mesosystem focuses on the quantification of total viable counts (TAMC and TYMC), the identification of specific pathogens, such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Candida albicans*, is not performed as a release requirement for every batch (76). These specific microorganisms are categorized under ISO standard and must be strictly absent in 1 g or 1 mL of the finished product due to their potential to cause severe infections in consumers (5,79).

The decision to not perform these specific screenings internally on a routine basis is justified by a risk assessment approach (77). If the raw materials are of high purity, the manufacturing process includes validated sterilization steps (such as moist heat sterilization), and the environmental monitoring (ISO 5) is consistently compliant, the probability of pathogen presence is considered negligible (14,77).

The identification of specific pathogens becomes mandatory in several critical scenarios, starting with OOS investigations where total counts of bacteria or fungi exceed safety limits (4). In the event of such a NC, a standardized protocol is triggered, beginning with a repetition of the assay to rule out potential analytical errors. If the contamination is confirmed, precise identification of the pathogen is required to assess the severity of the risk to public health and to launch a comprehensive root-cause investigation. This investigative process evaluates critical factors such as environmental air quality, operator hygiene, raw materials, and equipment integrity (4,23).

Also, during the validation of new products or stability testing, this identification is essential to confirm that the preservative system is effective against a standardized spectrum of microorganisms (18,39). This rigorous screening is also triggered by any suspicion of raw material contamination, particularly if a specific supplier or batch shows signs of compromised integrity. Regulatory compliance for high-risk medical devices often necessitates more

stringent specific testing as requested by international pharmacopoeias or notified bodies to ensure maximum safety (18,39).

Depending on the investigation's findings and the nature of the microorganisms identified, the affected batch may be reworked, subjected to further sterilization, or permanently rejected. The detailed procedural flow and Quality Management actions triggered by these events are further discussed in Chapter 4.6 (Management of Non-Conformities) (4,21,78). It should be noted that when these specific screenings or complex microbial identifications are required, regarding Mesosystem protocols, the process is conducted through a contract with a specialised external entity, as these assays often demand specific selective media and biochemical characterization beyond the scope of routine internal monitoring (21,78).

4.3.2. Microbiological Control: Water System Control

Water is a critical raw material in the manufacturing of cosmetics and medical devices, acting as a primary ingredient and a potential source of microbial contamination (11). To ensure the quality of the purified water system, microbiological monitoring is performed using the membrane filtration technique, which allows for the processing of large volumes of water to detect even low levels of microbial presence (12,80). To guarantee the statistical representativeness and accuracy of the analytical results, the water collection process follows a rigorous aseptic and stabilization protocol. This methodology is designed to eliminate external variables that could distort the chemical or microbiological profile of the water system, focusing primarily on the removal of stagnant water and the prevention of cross-contamination during the sampling phase (10,81).

The procedure begins with the removal of any tap attachments and the thorough disinfection of the tap’s interior and exterior with alcohol. Following this, a systematic purging of the sampling lines is conducted. Prior to collection at each designated tap or valve, the water is allowed to flow for a minimum average period of one minute (12,82). This stabilization phase is essential to eliminate stagnant water within the piping and to ensure that the sample reflects the quality of the water circulating in the main distribution loop rather than the localized environment of the tap (12,82).

Following the stabilization of the flow, the conditioning of the sample is conducted using specific 500 ml flasks, where glass bottles are autoclaved at 121ºC for 15 minutes prior to use to ensure absolute sterility, or sterile plastic options are selected depending on the specific analytical requirements of the subsequent tests (17,82). To further minimize the risk of contamination from potential residues within the containers, a double-rinsing protocol is implemented. Each flask is rinsed twice with water from the source itself immediately before the final filling with a

minimum volume of 300 mL (73). During this stage, the technician must adhere to strict aseptic techniques, ensuring that the interior of the container and its cap remain protected from environmental exposure (82). This meticulous approach to sampling ensures that the internal water quality monitoring system is based on reliable, high-integrity data, which is vital for the safety of the pharmaceutical and cosmetic manufacturing processes (10,73).

Once transferred to the laboratory's laminar airflow workstation, a sterile filtration funnel is placed onto a vacuum pump manifold, and a sterile 0.45 µm Mixed Cellulose Esters (MCE) gridded membrane is carefully positioned at its base (80). This specific pore size is designed to retain bacteria while the grid serves as a critical visual reference for systematic counting. A precise volume of 100 mL of water sample is then drawn through the membrane using a vacuum pump, after which the membrane is aseptically transferred using sterile flat-ended forceps to a Petri dish containing Reasoner's 2 (R2) agar, ensuring that no air bubbles are trapped between the membrane and the medium to guarantee optimal adhesion (Figure 13) (73,80). This low-nutrient medium is specifically selected for water monitoring as it facilitates the recovery of stressed or slow-growing oligotrophic bacteria, preventing the metabolic shock often associated with highly enriched media such as TSA (12,83). To guarantee full recovery of these slow-growing colonies, the plates are incubated within a temperature range of 30°C to 35°C for an extended period of 5 to 7 days before performing the final CFU quantification (12,83). The microbiological analytical data and traceability details are systematically recorded in a dedicated internal testing report (see Annex A).

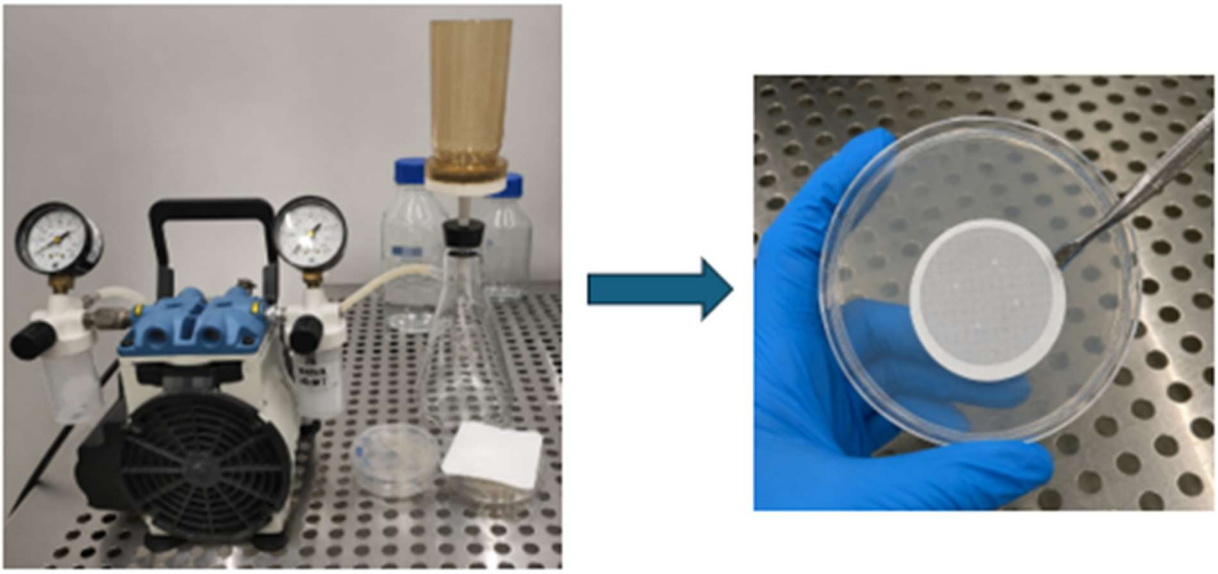

Figure 13 - Water system microbiological monitoring: (left) Aseptic vacuum filtration setup utilized for processing water samples under a laminar airflow workstation; (right) Careful transfer of the 0.45 µm MCE membrane onto R2 agar using sterile flat-ended forceps, ensuring complete surface adhesion.

Following this incubation window, the quantitative results are expressed in CFU/100 mL. In accordance with internal quality standards and pharmacopoeia guidelines for purified water, the action limits are highly stringent, establishing a preventive internal threshold of less than $1x10^2$ CFU/100 mL to confirm that the treatment system is functioning correctly, as detailed in Table 8 (11,83,84).

Table 8 - Microbiological acceptance limits for Potable Water, Purified Water (PW), and Water for Injections (WFI).

Water Grade	Total Viable Aerobic Count	Specified Pathogens*
Potable Water	At 22ºC: ≤100 CFU/ml At 37ºC: ≤ 20 CFU/ml	Absence in 100mL
Purified Water (PW)	≤100 CFU/ml	Absence in 100mL
Water for Injections (WFI)	≤10 CFU/ml	Absence in 100mL

Note: * *S. aureus*, *P. aeruginosa*, *E. coli* and *C. albicans.*

This monitoring is performed as a standard weekly procedure to verify the continuous efficacy of the softening, RO, and UV treatment stages, and to ensure the absence of biofilms within the distribution piping (10). Ensuring the absence of biofilms is critical because these complex microbial communities, once established on the inner surfaces of the distribution piping, are extremely difficult to eradicate. Biofilms consist of microorganisms embedded within a self-produced matrix of extracellular polymeric substances, which acts as a protective shield against chemical sanitization and UV treatment (81). If left uncontrolled, the biofilm can periodically release planktonic bacteria into the water flow, leading to persistent and unpredictable contamination of the finished products (81). Furthermore, biofilms can be a source of endotoxins, which are particularly hazardous in medical devices and sensitive formulations, as they can trigger inflammatory responses even if the live bacteria have been neutralized (11,12).

4.3.3. Environmental Monitoring of Classified Zones

Beyond product testing, Mesosystem implements a comprehensive environmental monitoring programme to validate the efficacy of sanitization protocols and the maintenance of the qualified state of the cleanrooms. This surveillance is divided into the assessment of air quality, surface hygiene, and personnel aseptic behaviour (23,85).

Air sampling is conducted using specialized active air samplers, represented in Figure 14. This equipment is calibrated to operate at a flow rate of 100 L/min, aspirating a total volume of 1000

L of air over a 10-minute period. The sampled air directly impacts any airborne viable particles onto the surface of TSA and Sabouraud CAF agar plates (15,86). This active method is superior to passive sedimentation, where settle plates are merely exposed to the environment for approximately 4 hours, as it allows for a precise quantitative assessment of the microbial quality of the air within the Grade A and B zones, ensuring that the HEPA filtration systems are operating at peak efficiency (15,86). The alert and action levels, alongside the acceptance limits for these air quality parameters, are detailed in Table 9 (9).

Figure 14 - Environmental biocontamination control: Active air samplers utilized for the quantitative microbiological assessment of airborne viable particles within classified cleanroom environments.

Table 9 - Environmental and Personnel Microbiological Monitoring: Alert levels, action levels, and acceptance limits across cleanroom grades based on EU GMP Annex 1.

Cleanroom Grade	Sampling Method	Alert Level	Action Level	Acceptance Limit
ISO 5 (Grade B)	Active*	3 CFU/m3	5 CFU/m3	10 CFU/m3
	Passive**	1 CFU/4h	2 CFU/4h	5 CFU/4h
ISO 7 (Grade C)	Active*	30 CFU/m3	50 CFU/m3	100 CFU/m3
	Passive**	15 CFU/4h	25 CFU/4h	50 CFU/4h
ISO 8 (Grade D)	Active*	50 CFU/m3	80 CFU/m3	200 CFU/m3
	Passive**	25 CFU/4h	40 CFU/4h	100 CFU/4h

Note: *Air samplers; **Settle plates.

The monitoring of facility surfaces employs either contact plates (RODAC - Replicate Organism Detection and Counting) or a swab-sampling technique. For flat surfaces, sterile agar contact plates are pressed directly against the testing area for at least 10 seconds, applying uniform pressure. For irregular surfaces or equipment interiors, a sterile swab is pre-moistened in a neutralizing solution (such as Ringer's solution or phosphate buffer), designed to counteract any residual disinfectants (23,87). The swab is systematically passed over the target surface and then carefully streaked onto the culture media plates. This procedure is essential for validating the success of the chemical disinfection of the product-contact surfaces (87).

Equally critical to environmental control is the monitoring of operators, as personnel constitute the primary vector for cleanroom contamination (16,88). Utilizing the swab technique, samples are collected from high-risk contact points on the operators' cleanroom attire, specifically targeting the protective cap, frontal chest zone, and armpits. Concurrently, the operators' gloves are monitored by swabbing the fingertips, nails, and interdigital spaces (9,19,89). This procedure is essential for validating the aseptic behaviour of the staff and ensuring that proper gowning protocols are strictly maintained during processing. The respective microbiological limits for both facility surfaces and operators' attire are defined in Table 10 (9).

Table 10 - Surface and Personnel Microbiological Monitoring: Alert, action, and acceptance limits for facility surfaces and operator hygiene based on EU GMP Annex 1.

Parameters	Cleanroom Grade	Alert Level	Action Level	Acceptance Limit
Surfaces	ISO 5 (Grade B)	-	-	5 CFU
	ISO 7 (Grade C)	15 CFU	20 CFU	25 CFU
	ISO 8 (Grade D)	30 CFU	40 CFU	50 CFU
Personnel (Gowns and Hands)	ISO 5 (Grade B)	-	-	5 CFU
	ISO 7 (Grade C) and ISO 8 (Grade D)	50 CFU	80 CFU	100 CFU

The QC department implements a risk-based schedule for environmental and personnel monitoring. For manufacturing areas in constant operation, microbiological controls are conducted on a strict weekly basis, whereas rooms that are not under continuous use are subjected to monthly verifications to guarantee they remain within their established environmental specifications (23,87). Concurrently, personnel monitoring is executed weekly by rotating the evaluation of two operators per week. This target sampling approach allows the department to maintain a holistic overview of the facility's hygiene while continuously verifying

that staff members are maintaining proper aseptic techniques and workplace hygiene standards during processing (9,85).

4.4. Post-Production and Final Production Verification

The final stage of the QC workflow at Mesosystem involves a series of critical assessments designed to verify the physical and functional integrity of the finished product. These procedures ensure that the manufacturing and sterilization processes have not compromised the formulation or its primary packaging (9,90).

4.4.1. Lyophilisation

For products subjected to freeze-drying process, a specialized inspection of the lyophilization is performed. QC technicians evaluate the physical integrity and morphology of the compact powder, ensuring it exhibits a uniform, porous structure and presents as a compact solid without any fractures, loose particulates, or structural irregularities. Specifically, the inspection screens for critical defects such as "collapse," "melt-back," or cracking, which indicate deviations in the critical temperature and vacuum profiles during the primary or secondary drying phases (27).

A consistent and uniform morphology is not only an indicator of a successful lyophilisation cycle but is also essential for ensuring rapid and complete reconstitution of the product at the time of use (91). A highly porous and intact structure guarantees that the active ingredients dissolve instantly and clearly when the clinical professional introduces the specified diluent (e.g., sterile saline solution) (44). Any deviation in the appearance may suggest residual moisture or stability issues, triggering a more detailed analytical review, as these issues could lead to the degradation of the active ingredients or the formation of insoluble aggregates upon reconstitution (90,92). An example of a compliant and a rejected lyophilisation is represented in Figure 15.

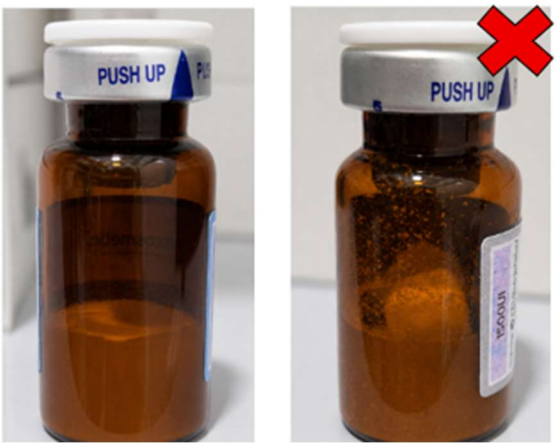

Figure 15 - Macroscopic evaluation of lyophilised morphology: Comparison between a fully compliant, intact, and porous (left) and a rejected unit exhibiting structural collapse and melt-back (right).

4.4.2. Container Closure Integrity Testing (CCIT)

To guarantee the maintenance of the sterile barrier, all ampoules and vials undergo Container Closure Integrity Testing (CCIT) following the autoclaving process. This is achieved through a destructive dye ingress test under vacuum, which is critical for detecting micro-leaks at the vial-stopper interface or glass defects that could lead to microbial ingress or product oxidation (9,50). Because this is a destructive assay, it is typically performed on a reduced, representative sampling size of 8 samples per lot; however, if any NCs are detected, the inspection scope is immediately expanded (93).

In this procedure, the sterile containers to be analysed, alongside a positive control (a container with an intentionally induced defect to validate dye penetration) and a negative control (a definitively sealed container), are fully submerged in a challenge solution containing 0.01% Patent Blue V (E-131) dye supplemented with a surfactant, which is essential to lower the liquid's surface tension and allow the dye to penetrate even the smallest micro-capillaries or structural defects (45,93). The immersion vessel is then placed inside a vacuum chamber, where a negative pressure of 0.05 MPa is applied and sustained for a 15-minute hold period to force any air trapped inside a compromised container to escape. After this initial phase, the vacuum pressure is released to return the chamber to atmospheric conditions, but the containers are left submerged in the dye solution for an additional 30-minute period to create a reverse pressure gradient that forces the external blue solution into any defective units (45). An example of the procedure is shown in Figure 16.

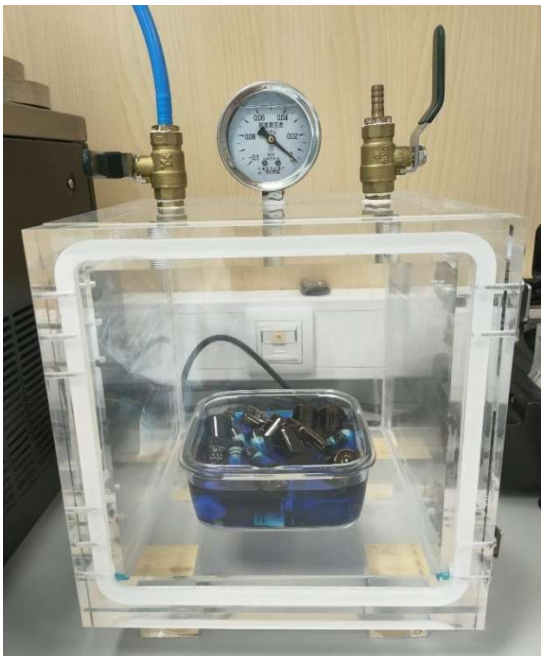

Figure 16 - Container Closure Integrity Testing (CCIT): Vacuum-assisted dye ingress assay utilizing Patent Blue V to evaluate the hermetic seal of sterile vials, demonstrating the detection of micro-leaks through internal dye penetration.

Finally, the containers are removed from the chamber, thoroughly washed externally to remove superficial residue, and individually inspected against a bright background, where any visible blue coloration inside the sterilized product indicates a NC and results in the immediate rejection of the unit (17,43). By subjecting the containers to this procedure, and validating it against the controls, it is ensured that the primary packaging remains hermetically sealed, confirming that the sterilization phase has successfully secured the product without damaging the vial-stopper interface or the glass integrity (17,43).

4.4.3. Final Inspection and Release

The concluding phase of the QC process is a comprehensive check of the finished goods, executed by a quality technician before the batch is officially authorized for market distribution. This operational phase involves a rigorous physical and documentary verification focused on absolute traceability and compliance (4,7). The technician meticulously reviews the labelling content, ensuring that all regulatory information, variable data, and batch numbering perfectly match the master production records, specifically the MO and the Product Guide (42,94).

The physical integrity of the finished goods is evaluated through a multi-tiered inspection that encompasses the product itself, the primary packaging, and the secondary protective box (8). This assessment is conducted on a randomized, statistically representative sample whose size is pre-defined based on the total batch volume (48). The inspection rigorously screens for critical defects such as tears, structural deformations, inadequate sealing, or the presence of external dirt that could compromise the product's commercial presentation. For sterile and parenteral products, this visual inspection is even more stringent, requiring the evaluation of containers against a standardized defect library to detect extraneous contamination (9,54). For promotional sets or specific commercial configurations (packs), a final verification of multi-product packs is performed to ensure correct assortment and structural integrity. Should any NC be detected during this evaluation, the sampling scope is immediately expanded, potentially leading to a 100% inspection of the lot to segregate defective units (7,48).

This phase also includes a strict quantitative reconciliation, where the final counts of finished units, as well as the exact number of units per box and total boxes produced, are cross-checked against production yields to detect any discrepancies. Finally, all analytical data, including raw material certificates, in-process controls, microbiological clearances, and post-production test results, are consolidated (54). Only when this holistic review confirms full compliance with the established specifications does the QA department authorize the final release, guaranteeing that only products meeting the highest safety, regulatory, and quality standards reach the market (8,26).

4.5. Stability Testing and Retention Sample Repository

Mesosystem’s commitment to quality extends far beyond the immediate manufacturing date, encompassing a robust post-market surveillance and long-term stability programme (24). This proactive approach ensures that the products remain safe, effective, and chemically stable throughout their entire shelf-life (43).

4.5.1. Stability Studies and Shelf-Life Validation

To confirm the long-term chemical, physical, and microbiological functionality of the formulations, the QC department conducts systematic stability studies (40). These strict evaluations are split into two parallel operational protocols designed to simulate and predict the product's entire lifecycle: accelerated stability testing and real-time (long-term) stability monitoring (49).

In accelerated stability studies, batch representative samples are placed inside calibrated climatic chambers and subjected to controlled thermal and environmental stress conditions, typically maintained at 40°C with a relative humidity of 60% RH (33,40). This protocol artificially accelerates chemical degradation and physical alterations, allowing the QC department to predict the product's degradation profile, evaluate phase separation risks, and validate the continuous efficacy of the preservative system over a compressed timeframe (43,94).

Concurrently, real-time stability studies are maintained under standard ambient storage conditions, typically at 25°C, providing definitive, empirical data on the product's officially established shelf-life (40,49). Throughout both stability protocols, a strict pull-schedule is established to sample the products at predetermined intervals, such as 1, 3, and 6 months. At each interval, the formulations undergo a comprehensive multi-parametric re-evaluation to detect subtle, cumulative changes (94). This includes monitoring organoleptic properties for deviations in colour, odour, and appearance, alongside the precise tracking of physical-chemical parameters such as pH drifts, shifts in viscosity or rheological behaviour, and centrifugation testing to assess emulsion stability (33,54). Additionally, microbiological integrity is evaluated through periodic bioburden screenings to confirm that the preservative system remains robust against microbial contamination over time (5,36).

This exhaustive screening process guarantees that the formulation maintains its original dermatological properties, safety, and aesthetic appeal from the manufacturing date until its expiration point, ensuring absolute consumer safety (40,94). Once the official shelf-life has been completely exceeded, these retention samples are subjected to one final round of testing to gather conclusive empirical data regarding the maximum durability and ultimate degradation point of the cosmetic formulation (40,94).

4.5.2. Retention Sample Repository (*Amostroteca*)

A fundamental component of the organization's QA strategy is the maintenance of a dedicated Retention Sample Library, internally referred to as the *Amostroteca*. This specialized facility serves as a secure physical archive where representative units of every single manufactured batch are preserved under continuously monitored environmental conditions that replicate standard commercial storage (4,49).

In compliance with GMP and regulatory guidelines, these samples are retained for a designated timeframe that strictly exceeds the product's official expiry date, typically covering an additional one to two years (4). To maintain the highest level of security and prevent tampering or unauthorized handling, physical access to this repository is strictly restricted and exclusively controlled by the QC department. Additionally, the exact spatial location and status of every retained unit are meticulously mapped and tracked through a dedicated digital registry, ensuring immediate retrieval (4,7).

The volume of samples collected per batch is meticulously calculated to ensure it is sufficient to perform at least two full analytical and microbiological re-evaluations if required (4,24). These retention units are indispensable for the company's traceability and defensive quality protocols. In the event of a market complaint, adverse reaction report, or suspected quality deviation, the repository allows the QC department to execute immediate comparative testing between the pristine retained units and the specific samples returned from the market (8,24). This operational capability is vital for conducting thorough internal investigations, establishing definitive root-cause analyses, and distinguishing between genuine systematic manufacturing defects and post-distribution external factors, such as improper handling or inadequate transport conditions (4,49).

This storage undergoes strict life-cycle management, where samples are systematically audited and subjected to controlled disposal protocols once their legal retention period lapses, ensuring optimal space utilization and compliance with waste management standards (4,7).

4.5.3. Data Integrity and Audit Readiness

A crucial pillar of the organization's modern quality governance is the strict adherence to data integrity principles, ensuring that all analytical results, environmental monitoring trends, and operational deviations are meticulously documented.

To achieve full compliance with international regulatory expectations, such as those defined by BSI and SGS, the quality departments enforce lifecycle data management aligned with the ALCOA+ framework (1,10). This conceptual standard guarantees that all recorded quality data

remains completely Attributable, Legible, Contemporaneous, Original, and Accurate, ensuring its integrity throughout its entire retention window. Operationally, this is achieved by transitioning from manual logs to a centralized, validated digital database equipped with rigorous access controls and automated audit trail capabilities (1,10).

The implementation of these audit trails ensures that any modification, entry, or deletion of quality records is permanently time-stamped and mapped to a specific authorized user, eliminating the risk of data omission or retrospective manipulation (4,20). This digitized infrastructure guarantees permanent audit readiness by enabling the rapid, secure retrieval of complete batch histories and analytical clearances during unannounced or routine regulatory inspections. Beyond serving as a defensive compliance tool, this historical repository undergoes systematic evaluation through statistical trend analysis and periodic quality reviews (9,20).

By actively analysing long-term microbiological and physical-chemical baselines, the engineering team can detect subtle drift patterns within the cleanrooms or the purified water system before they cross official action thresholds (10,21). Integrating these data trends into a continuous improvement cycle allows the company to proactively optimize its manufacturing processes, minimize OOS incidents, and dynamically validate its strict quality standards (1,4).

4.6. Management of Non-Conformities

In strict alignment with ISO standards and GMP principles, any deviation from established specifications, validated processes, or internal procedures is formally documented as a NC (4,7). through the immediate issuance of a formal NC Report. At Mesosystem, the management of these deviations is a cornerstone of the Quality Management system, serving not only to safeguard product safety but also to identify systemic opportunities for process optimization, risk mitigation, and continuous reliability (4,24).

4.6.1. Out-of-Specification (OOS) Investigations

Whenever an analytical result, such as pH, viscosity, density, or microbiological counts, fails to meet the predefined acceptance criteria, it is categorized as an OOS result (4,5). This event initiates a multi-phase, cross-functional investigation to identify the definitive root cause. The process starts with a Phase I laboratory investigation, which focuses exclusively on ruling out a laboratory error. During this phase, the quality technician evaluates whether the failure is linked to analytical equipment malfunction, uncalibrated instruments, calculation mistakes, or human oversight during sample preparation (2,21).

If the laboratory environment and testing methodology are validated as completely correct, the investigation escalates to a Phase II stage, triggering a formal manufacturing deviation. At this juncture, it is necessary to deploy structured problem-solving methodologies, such as the Cause-and-Effect Diagram (also called Fishbone Diagram), represented in Figure 17 (7,95). This approach allows the team to dissect the compounding, thermal processing, or filling phases to pinpoint the true root cause, whether it stems from a raw material lot variation, a temperature fluctuation during emulsification, or a mechanical misalignment on the filling line (24,95).

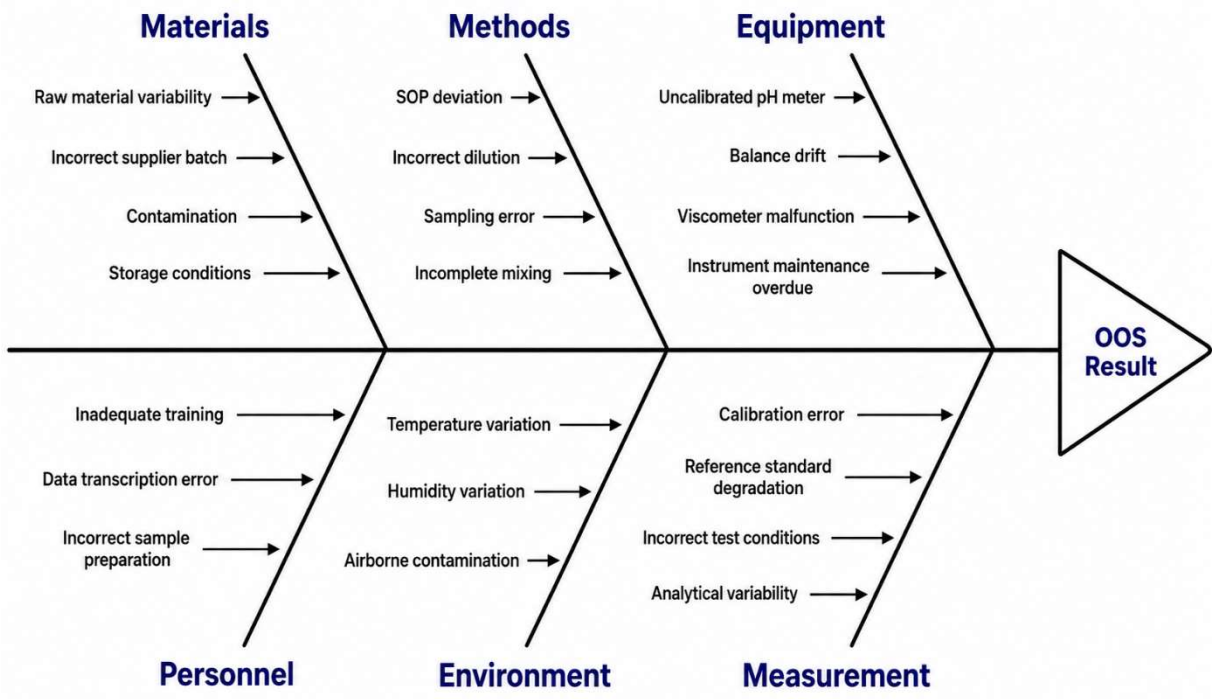

Figure 17 - Root-cause analysis methodology: Cause-and-Effect (Fishbone) Diagram adapted for an Out-Of-Specification (OOS) investigation within the cosmetic manufacturing flow.

Additionally, the department tracks out-of-trend results, which represent data that, while still within official specification limits, deviates significantly from the historical statistical baseline, allowing for preventive intervention before a true OOS occurs (2,21).

4.6.2. Rework and Disposition

When a batch is identified as non-compliant during the bulk analysis phase, the possibility of product recovery is evaluated through a formal, pre-validated Rework Protocol. This operational intervention is only considered if the specific deviation can be technically corrected without compromising the critical quality attributes, stability, or long-term safety of the formulation (4,8). All rework procedures must undergo a strict risk assessment, requiring explicit review by the QC laboratory and final formal authorization from the QA department (4,7).

Following the corrective manufacturing intervention, the reworked batch is subjected to a comprehensive, mandatory round of re-testing based on a statistically significant sampling size, ensuring that the results are representative of the entire volume (48,57). Conversely, if a product fails to meet critical safety thresholds, particularly regarding microbiological purity or irreversible chemical degradation, the batch is officially rejected. A formal rejection triggers the immediate segregation of the batch, which is prominently identified with a red status label and moved to a secure quarantine area to undergo supervised disposal according to environmental regulations and industrial waste management standards, preventing any accidental mix-ups with compliant stock (4,8).

4.6.3. CAPA (Corrective and Preventive Actions)

The ultimate objective of documenting NCs, out-of-trend, and OOS results is the activation of the Corrective and Preventive Actions (CAPA) system, which closes the loop between error detection and systemic resolution (8,20). Once the root cause of a deviation is established through the Phase II investigation, specific, time-bound actions are designed and deployed to eliminate the source of the failure and prevent its recurrence (7,96). These actions typically encompass the physical recalibration or mechanical retrofitting of industrial machinery, the structural revision of standard operating procedures and the implementation of targeted technical training for the operators involved (7,96).

Crucially, the CAPA system does not end with the implementation of the change, but also an effectiveness check is scheduled after a predetermined operational period to provide documented evidence, within a strictly established deadline, that the implemented solution has successfully mitigated the risk without introducing new operational issues (7,8). By integrating these metrics, the quality department acts as a proactive driver of operational excellence and continuous improvement, shifting the corporate culture from a purely reactive verification body to a predictive, quality-driven environment (8,20,96).

5. Implementation of Internal Water Quality Monitoring

5.1. Background and Objectives of the Intervention

Prior to the implementation of the new internal protocol, the detailed physicochemical control of water at Mesosystem was provided by an external laboratory. However, as part of the organization's commitment to continuous improvement, the internalization of these tests was proposed as a strategic improvement opportunity. My role during the internship was to adapt and implement a comprehensive analytical protocol based on the ISO 22716:2007 and Ph. Eur., ensuring the company maintains immediate and absolute control over its most critical resource (4,83,97).

The absence of revision proposals for monograph 0008 (Water, Purified) in the most recent issues of Pharmeuropa (such as volume 38.1) demonstrates the consolidation and regulatory stability of these classic analytical methods. This confirms that the tests for nitrates, oxidisable substances, and conductivity established by the Ph. Eur. remain the immutable and reliable reference standard for the industry (11,83).

According to Section 6 of ISO 22716:2007, the water purification system must be continuously monitored to ensure a constant quality profile that matches the intended cosmetic application. Since the standard does not prescribe rigid quantitative boundaries, Mesosystem bridges this regulatory requirement by adopting the stringent chemical and microbiological specifications of the Ph. Eur. for Purified Water (4,10,83). This multi-layered quality framework ensures that both the structural requirements of the ISO standard (process consistency, sanitization protocols, and preventive maintenance) and the strict analytical thresholds of the pharmacopoeia are simultaneously fulfilled, minimizing operational risks during product compounding (4,10,83).

To establish a clear reference framework for the routine control internalised during this intervention, the critical chemical and microbiological specifications mandated by the Ph. Eur. for Purified Water (in bulk) are consolidated in Table 11.

Table 11 - Physicochemical and Microbiological Specifications for Bulk Purified Water (Ph. Eur. Monograph 0008).

Analytical Parameter	Pharmacopoeial Limits
Conductivity	≤ 1.1 µS.cm^{-1} at 20ºC (or 1.3 µS.cm^{-1} at 25ºC)
Oxidisable Substances	Pink Colour Persistence ≥ 5 minutes
Nitrates	≤ 0.2 ppm (Visual colorimetric comparison)
Total Aerobic Microbial Count (TAMC)	≤ 100 CFU/mL
Heavy Metals*	≤ 0.1 ppm
Aluminium*	≤ 10 ppb

*Note: Monitored via passive engineering mitigation and process validation (see Section 5.2.4).

Beyond cost optimization, this integration is of paramount importance as it enables real-time quality surveillance, allowing for the immediate detection of trends and the implementation of proactive corrective actions (12,98). This shift not only reinforces internal technical autonomy but also ensures that water quality remains consistently aligned with the most stringent safety standards, serving as a robust foundation for the manufacturing of advanced medical and cosmetic formulations (73,97).

5.2. Experimental Protocol and Parameters Analysed

To ensure maximum analytical consistency and a holistic characterization of the purified water system, the sampling strategy was optimized to synchronize microbiological and physical-chemical evaluations (10,63). Consequently, following the validated aseptic procedure detailed in Section 4.3.2 (Microbiological Control: Water System Control), additional water volumes were collected simultaneously from the same sampling points. By extracting these supplementary aliquots in a single sampling event, it guarantees the absolute correlation between the microbiological bioburden and the subsequent physical-chemical data (12,99). These additional samples were stored under strictly controlled conditions to preserve their chemical integrity, specifically for the determination of pH, conductivity, nitrates, and oxidisable substances (82,100).

This integrated sampling approach not only ensures that the data is representative of the system's state at a specific point in time but also minimizes the risk of external cross-contamination, providing a robust baseline for the implementation of the new monitoring parameters (10,99).

5.2.1. Organoleptic and Basic Physicochemical Evaluation

The first stage of the experimental protocol involves an immediate organoleptic assessment, where the appearance of the purified water is visually verified to ensure it remains completely clear, colourless, and entirely free from suspended sediment, particulate matter, or turbidity (83). Any alteration in these sensory characteristics would serve as a critical preliminary indicator of gross mechanical filtration failure, breakdown of the hydrophobic venting filters, or microbiological contamination within the storage tanks (10,99).

Following the visual inspection, the fundamental chemical integrity of the water is assessed through the determination of pH and electrical conductivity, which represent the primary tier of instrument-based monitoring (63). The pH measurement is conducted using a high-precision potentiometer equipped with a combined glass electrode. To ensure the absolute accuracy and reproducibility of the readings, the system is calibrated using a two-point automated routine with standardized buffer solutions, typically at pH 4.01 and 7.00, while verifying that the electrode slope remains within the acceptable efficiency range (62). Monitoring the pH is vital for the early detection of purification system imbalances, as unexpected deviations may indicate a loss of ion-exchange capacity in the deionization resin beds or a structural compromise in the integrity of the RO membranes (62,101). Also, because purified water lacks a strong buffering capacity, the samples must be collected with minimal atmospheric exposure and stored in hermetically sealed containers with minimal headspace to prevent contact with ambient air. This protection is critical to mitigate the rapid absorption of atmospheric carbon dioxide (CO_2), a phenomenon that leads to the formation of carbonic acid (H_2CO_3) and causes an artificial downward drift in pH readings (62,101).

Simultaneously, the electrical conductivity is measured directly using a calibrated conductivity meter with a platinum cell, which provides a conductometric assessment that serves as the primary quantitative indicator of the RO system's purification efficiency. This parameter directly reflects the concentration of residual dissolved ions and total dissolved solids remaining in the water stream (63). In strict compliance with the Ph. Eur. standards for Purified Water in bulk, the electrical conductivity must not exceed a strict threshold of 1.3 µS/cm at a reference temperature of 20°C (83). Since liquid temperature heavily influences ionic mobility and alters the baseline resistance, the instrument applies an automated temperature compensation algorithm to normalize all readings (83). A continuous low conductivity measurement successfully confirms that the multi-stage purification sequence is effectively stripping the feedwater of inorganic salts, heavy metals, and ionic contaminants, thereby establishing the high-purity vehicle required to ensure the chemical stability and long-term performance of complex cosmetic and dermatological formulations (10,101).

5.2.2. Oxidising Substances Test

The detection of oxidisable substances constitutes a critical wet-chemical procedure used to assess the cumulative presence of organic matter, reducing agents, and oxidisable inorganic impurities within the purified water system (83,101). This analytical method is based on a classic redox reaction executed under a highly acidic medium, where the water sample is challenged with potassium permanganate ($KMnO_4$). In this reaction environment, provided by the addition of dilute sulphuric acid (H_2SO_4), the permanganate ion (MnO_4^-) acts as a powerful oxidising agent (63,101). Its characteristic deep violet coloration is systematically reduced to a colourless manganese state (Mn^{2+}) if it reacts with any organic contaminants, structural biofilms debris, or reducing chemical compounds present in the collected aliquot (12,99).

Operationally, the experimental procedure requires a strict volumetric ratio, where a 100 mL sample of the purified water is mixed with 10 mL of dilute sulphuric acid and a precise volume of 0.1mL of 0.02 M potassium permanganate solution (83). This mixture is then subjected to a thermal phase and brought to a vigorous boil for a fixed period of exactly five minutes. This critical heating phase provides the activation energy necessary to accelerate the kinetic oxidation process, ensuring that even complex or trace organic chains are fully broken down and reacted (101). The resulting colorimetric endpoint for the determination of oxidisable substances are illustrated in Figure 18, which contrasts the initial sample preparation with the final analytical outcome.

Figure 18 - Determination of oxidisable substances in water samples: colorimetric evaluation based on the potassium permanganate redox reaction, contrasting the initial analytical setup (left) with the qualitative persistence of the pink hue (right) as evidence of compliance with strict pharmacopoeial purity specifications.

In strict alignment with the Ph. Eur. regulatory standards, compliance with water purity thresholds is determined through a qualitative visual endpoint defined by the persistence of a faint pink coloration at the end of the boiling timeframe (83). If this distinct pink hue remains

stable after five minutes of thermal stress, it empirically confirms that the concentration of oxidisable contaminants is below the maximum admissible regulatory limit, validating the water batch as safe for the compounding of dermatological and cosmetic formulations (4,83).

Conversely, any degree of decolouration suggests the presence of excessive organic impurities. In an industrial Quality Management context, such a negative outcome would trigger an immediate Phase II manufacturing investigation, focusing on the potential degradation of the activated carbon filters, a breach in the reverse osmosis membrane arrays, or the early development of an organic biofilm matrix inside the storage and distribution pipework (12,102).

5.2.3. Determination of Nitrates

The monitoring of nitrate levels constitutes a vital analytical component of the chemical quality protocol, as the presence of these nitrogenous compounds serves as a primary indicator of potential chemical or agricultural runoff contamination within the incoming source water, or a critical breakdown in the deionization infrastructure (99,103). To quantify these trace levels, a highly sensitive colorimetric and redox-based method is employed, leveraging the chemical reaction between nitrate ions (NO_3^-) and a specific reagent solution of diphenylamine dissolved in a concentrated sulphuric acid (H2SO4) medium (83). In this strongly acidic environment, the nitrate ions act as a selective oxidizing agent, converting the colourless diphenylamine into a highly conjugated quinoid structure, which exhibits a characteristic deep blue coloration (83).

The experimental procedure is characterized by strict temperature control and precise phase sequencing to ensure the stability and kinetic reproducibility of the redox reaction (83). The purified water sample is first pipetted into a glass test tube and fully immersed in an iced water bath maintained between 0°C and 10°C (83). This preliminary cooling phase is an essential safety and operational constraint before the controlled addition of the concentrated sulphuric acid reagent, effectively mitigating the localized heat generation and preventing premature, violent boiling or decomposition of the indicator. For comparative and calibration purposes, a standard reference solution containing exactly 0.2 ppm of nitrates is simultaneously prepared and subjected to the identical environmental constraints (83,97).

Following this initial cooling stage and reagent integration, the test tubes are transferred to a calibrated water bath and heated to a stable temperature of 50°C for an incubation period of exactly 15 minutes (83). This thermal incubation provides the uniform activation energy required for full colour development, where the intensity of the resulting purple coloration is directly proportional to the concentration of oxidized nitrogenous impurities (83). The process described is depicted in Figure 19.

Figure 19 - Methodological setup for the semi-quantitative detection of nitrates: (left) initial low-temperature stabilization phase, showcasing the test tubes arranged chronologically inside the partitioned grid within a controlled ice bath; (right) final reaction phase, where all sample tubes, including the characteristically purple-coloured nitrate reference standard, are consolidated inside a graduated beaker to provide structural support for subsequent immersion in a thermoregulated hot water bath.

The final interpretation of the results relies on a rigorous visual comparative analysis executed under uniform lighting conditions: the intensity of the blue coloration developed within the purified water sample must not exceed the blue hue of the 0.2 ppm nitrate reference standard (83). If the sample's colour remains visibly lighter or entirely colourless compared to the standard, it is officially documented as compliant with the strict purity specifications defined by the Ph. Eur. for bulk Purified Water (83,97,99). In an industrial quality framework, any out-of-specification failure in this parameter would point directly to the chemical exhaustion of the ion-exchange resin beds, signalling that the anionic resins have lost their binding capacity and require immediate regeneration or replacement to prevent the degradation of the final cosmetic and dermatological formulations (99).

5.2.4. Other Pharmacopoeial Parameters

While the Ph. Eur. monograph for Purified Water establishes a comprehensive matrix of chemical and microbiological specifications, Mesosystem operates under a dynamic, risk-based quality risk management framework (10,11). Consequently, the routine in-house analytical control strategy is strictly focused on a vital subset of parameters, namely pH, electrical conductivity, nitrates, oxidisable substances, and TAMC. This specific analytical envelope is technically and economically justified by the inherent capabilities of the production plant, the validation status of the system, and the specific risk profile of the product portfolio (10,83).

The continuous execution of pH and conductivity testing provides an instantaneous metrological assessment of the water's ionic purity and atmospheric carbon dioxide (CO_2) equilibrium (12,83). Concurrently, the routine evaluation of nitrates and oxidisable substances acts as a highly sensitive early-warning system; nitrates serve as the primary indicator for mechanical degradation or ion-slippage across the purification barriers, while the oxidisable substances test monitors for any volatile organic compounds or early biofilm formation within the storage and distribution piping network (12,83). For the microbiological monitoring, the utilization of R2 agar is strictly aligned with pharmacopoeia recommendations for oligotrophic water environments, allowing for the slow-growing heterotrophic bacteria common in purified water systems to be accurately quantified (12,83).

In contrast, advanced elemental parameters mandated by the Ph. Eur., specifically the determination of heavy metals and aluminium, are excluded from daily, routine internal testing based on a combined structural and economic rationale (83). The primary justification lies in the concept of passive engineering mitigation, as the internal water purification infrastructure at Mesosystem utilizes advanced, multi-stage RO membranes (12,83). These polymer matrices possess an intrinsic, highly robust rejection rate, typically exceeding 98% to 99%, for multivalent ions, including heavy metals such as lead or mercury, and trivalent aluminium (Al^{3+}) (12,83). Because the manufacturing process controls these contaminants passively and mechanically at the point of generation, the operational risk of elemental breakthrough into the purified water storage is considered negligible, shifting the focus of QA from finished product inspection to process capability control (10,11).

This operational choice is heavily reinforced by metrological and economic viability considerations within industrial management. The exact quantification of trace aluminium at the strict 10 ppb threshold, or heavy metals at the 0.1 ppm limit, requires highly complex and specialized laboratory instrumentation, such as Graphite Furnace Atomic Absorption Spectroscopy or Inductively Coupled Plasma Mass Spectrometry (83,100). The significant capital expenditure required to purchase these systems, combined with the continuous operational costs and the need for specialized human resources to execute and validate these advanced analytical loops, would result in a negative return on investment for the facility, representing a redundant and non-value-added control loop (100).

Therefore, by relying on the verified validation state of the purification plant and restricting daily testing to the most volatile chemical and biological variables, Mesosystem optimizes its laboratory throughput and manufacturing efficiency while maintaining total regulatory compliance and ensuring that the water remains a chemically inert, safe vehicle for its advanced aesthetics and cosmetic formulations (10,11).

5.3. Analysis of Results and Operational Impact

The transition to a systematic internal monitoring protocol has fundamentally transformed the organization's approach to water quality management, yielding significant operational, financial, and strategic benefits. Central to this success is the integration of all physical-chemical and microbiological analytical data into validated digital platforms (2,21). By shifting away from fragmented manual records, the QC department implemented robust statistical process control methodologies, utilizing automated spreadsheet systems (2,21). This advanced tracking allows for a precise, continuous longitudinal analysis of the results over time, enabling the establishment of historical baselines and standard deviation-based control limits as strictly recommended by regulatory guidelines for pharmaceutical water systems (10).

By internalizing these critical analyses, the organization has achieved a highly efficient allocation of human and material resources while simultaneously increasing the frequency of process controls without scaling up operating costs (98). Also, this internal capability has enhanced the organization's agility and velocity of response. The immediate, on-site identification of any analytical deviation, such as an early shift in electrical conductivity or a minor pH drift, acts as an early-warning trigger. This allows for proactive, targeted maintenance interventions on the RO membrane arrays or the ion-exchange resin beds before the water quality can degrade past official pharmacopoeia specification limits (12,98). This real-time agility shifts the industrial paradigm from reactive troubleshooting to a highly efficient predictive maintenance strategy, successfully minimizing the risk of unscheduled production downtime, protecting equipment lifecycles, and safeguarding the manufacturing schedule against costly bottlenecks (96,104).

The implementation of this comprehensive protocol has structurally reinforced the company's commitment to internal traceability, data integrity, and regulatory excellence (8). The creation of a dense, centralized historical database provides a robust foundation for both internal and external quality audits and external regulatory inspections, ensuring seamless compliance with both the ISO 22716:2007 standard for GMP in cosmetic products and the ISO 13485:2016 standard for medical devices (4,8,20,96). Through consistent trend monitoring and process capability analysis, the quality department transitions from a purely reactive verification body into a predictive driver of operational excellence, ensuring that the purified water consistently and reliably exceeds the rigorous quality standards required for advanced dermatological and aesthetic formulations (4,96).

6. Conclusion

The curricular internship at Mesosystem, SA provided a comprehensive immersion into the stringent quality control framework that governs the production of advanced cosmetics and medical devices. Operating under the demanding regulatory triad of ISO 9001:2015, ISO 13485:2016, and ISO 22716:2007, the experience empirically demonstrated that Quality Control is not merely an endpoint verification, but a dynamic, preventative gateway integrated into every critical phase of the manufacturing workflow.

The core achievement of this project was the successful internalization of the physicochemical and microbiological water quality monitoring protocol, strictly aligned with the European Pharmacopoeia specifications. By bringing critical assays, such as the evaluation of conductivity, pH, nitrates, and oxidisable substances, in-house, the reliance on external laboratories was minimized while the frequency of control was optimized without scaling up operational costs.

Embracing the Kaizen philosophy of continuous improvement, this intervention proved that modern quality management must be proactive rather than reactive. The new autonomy to detect subtle analytical drifts in real-time facilitated a critical transition from simple troubleshooting to a highly efficient predictive maintenance strategy. This shift not only safeguards critical purification infrastructure, such as the reverse osmosis membranes and ion-exchange resins, but also systematically prevents unscheduled production downtime.

This work highlights that the operational excellence of a manufacturing plant relies heavily on the technical autonomy and analytical rigor of its Quality Control department. The implemented internal water monitoring system successfully guarantees the chemical and microbiological integrity of the factory's most critical raw material, ensuring the maximum safety and efficacy of the final formulations, while solidifying the company's commitment to regulatory excellence and continuous innovation.

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8. Annexes

Annex A: Internal microbiological data report.

mesosystem® Controlo microbiológico da água **Boletim de Ensaio N.º _____**

CARACTERIZAÇÃO DA AMOSTRA:

Tipo de amostra	☐ água purificada ☐ água destilada (WFI)
Ponto de amostragem:	
Data de recolha: ___/___/____	**Data do ensaio : _____/____/____**
pH:	
Conservação da amostra em frigorifico: ☐Sim T.(ºC) _____ ☐Não	
Responsável pela recolha:	

RESULTADOS:

	UFC/100mL	**UFC/mL**	**Analise de conformidade**
N.º de colónias observadas			☐ Conforme ☐ Não Conforme
Rastreabilidade dos materiais	R2A – Lote: Placas de Petri –Lote:		
Controlos:	**Ar:** Fungos ☐ Positivo ☐ Negativo Bactérias ☐ Positivo ☐ Negativo		**Meio:** Teste de crescimento: ☐ Conforme ☐ Não Conforme
Observações:			

Especificação:
1.Água purificada - limite máximo de 100 UFC/ml
2.WFI - limite máximo de 10 UFC/ 100ml

TÉCNICO DO LABORATÓRIO: RESPONSÁVEL CONTROLO DE QUALIDADE :

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