# Pre-Standard Validation Framework of Sustainable Materials for Sterile Barrier Systems.

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Addressing the absence of regulatory pathways for biomaterial-based packaging systems.

Created Date: 17th January 2026
Published Date: ---

***Abstract-*** Sustainable materials remain largely absent from sterile medical packaging, not solely because of performance limitations, but because there is no structured pathway guiding their progression into regulated validation systems. While ISO 11607-1 and ISO 11607-2 define requirements for sterile barrier systems, they do not provide a roadmap for early-stage material screening. This creates a disconnect between sustainable material innovation and regulatory acceptance.

This report proposes a staged Pre-ISO Validation Framework to bridge that gap. The framework operates through five progressive stages: (1) structural and morphological screening, (2) stabilisation through controlled conditioning, (3) functional proxy testing aligned to microbial barrier requirements, (4) performance validation under simulated transport and handling conditions, and (5) readiness assessment for formal ISO validation. Each stage contains pass, conditional-pass, or feedback loops to earlier stages, reducing escalation risk.

Using bacterial cellulose as a case study, the framework demonstrates how structured, evidence-based screening can lower financial risk, improve environmental efficiency, and create a credible pathway toward ISO-compliant sustainable sterile packaging.

## I. Introduction to Sterility

Sterility is a fundamental requirement in both medical device and pharmaceutical industries. In this context, sterility will be defined as the absence of all viable microorganisms, including bacteria, fungi, and viruses[1]. While sterilization processes are responsible for achieving sterility, packaging systems are responsible for maintaining it throughout; handling, storage, transport etc. Sterile packaging therefore functions as a critical control boundary between product and environment. The performance of this boundary depends on factors like physical, mechanical, and cleanliness characteristics of the materials used to form the barrier.

Sterile packaging materials are commonly manufactured and handled within controlled cleanroom environments that are governed by "ISO" cleanroom standards. The International Organization for Standardization (ISO) is an independent, non-governmental body that develops widely accepted international standards to promote consistency and quality across industries[2]. ISO cleanroom standards (specifically the ISO 14644 series) define cleanrooms and associated controlled environments by the concentration of airborne particles present and classify environments accordingly[3]. These environments impose strict limits on airborne particulate contamination and require materials to exhibit predictable handling behaviour and minimal particulate shedding. ***Figure 1*** illustrates the ISO 14644-1 cleanroom classification system, showing the range of cleanroom classes (ISO 1–ISO 9) and the maximum permitted particle concentrations for different particle sizes.

ISO 14644-1 Cleanroom Standards

| | Class | Maximum Particles/m³ | | | | | | FED STD 209E equivalent |
|---|---|---|---|---|---|---|---|---|
| | | >=0.1 µm | >=0.2 µm | >=0.3 µm | >=0.5 µm | >=1 µm | >=5 µm | |
| LEAST STRINGENT | ISO 1 | 10 | 2 | | | | | |
| | ISO 2 | 100 | 24 | 10 | 4 | | | |
| | ISO 3 | 1,000 | 237 | 102 | 35 | 8 | | Class 1 |
| | ISO 4 | 10,000 | 2,370 | 1,020 | 352 | 83 | | Class 10 |
| | ISO 5 | 100,000 | 23,700 | 10,200 | 3,520 | 832 | 29 | Class 100 |
| | ISO 6 | 1,000,000 | 237,000 | 102,000 | 35,200 | 8,320 | 293 | Class 1,000 |
| | ISO 7 | | | | 352,000 | 83,200 | 2,930 | Class 10,000 |
| | ISO 8 | | | | 3,520,000 | 832,000 | 29,300 | Class 100,000 |
| MOST STRINGENT | ISO 9 | | | | 35,200,000 | 8,320,000 | 293,000 | Room Air |

***Figure 1.*** *ISO 14644-1 cleanroom classification system showing maximum allowable airborne particle concentrations by particle size for ISO Classes 1–9. Adapted from ISO 14644-1.[3]*

To give an example, ISO-5 cleanrooms are required to have approximately 300–480 air changes per hour of HEPA-filtered air and impose extremely low particle limits, including fewer than 29 particles per cubic meter ≥ 5 µm, alongside additional limits for ≥ 0.5 µm and ≥ 1 µm particles [2]. By comparison, a conditioned non-cleanroom office environment may contain more than 10,000 times the particulate concentration of an ISO 5 space[4]. These requirements therefore significantly constrain the types of materials that can be processed for sterile packaging operations.

## II. ISO 11607: Packaging for Terminally Sterilized Medical Devices

The primary international standard governing sterile medical packaging is ISO 11607, *Packaging for Terminally Sterilized Medical Devices*[3]. ISO 11607 defines the requirements for materials, sterile barrier systems (SBS), and packaging systems intended to maintain sterility until the point of use. Crucially, ISO 11607 adopts a performance-based approach. It does not prescribe specific materials, but requires that materials demonstrate adequate properties and integrity.

In addition to its core clauses, ISO 11607 includes several annexes that provide guidance relevant to material evaluation and testing that are relevant to understand the scope of this project:

- **Annex A:** provides informative guidance on the intent and rationale of the standard, clarifying how sterile barrier performance should be interpreted and assessed.
- **Annex B:** outlines environmental conditioning requirements for materials prior to testing. These conditioning protocols account for the influence of temperature, humidity, and atmospheric exposure on material performance and are particularly relevant for hygroscopic or moisture-sensitive materials[5].
- **Annex C:** describes methods for determining whether a material should be classified as porous or non-porous, including reference to air permeance testing (e.g. ISO 5636-5). This classification is critical because porous materials are subject to different microbial barrier test methods than non-porous films[5].

Taken together, this standard establishes a demanding regulatory landscape that any alternative material must ultimately satisfy. However, it also highlights that material performance must be interpreted through the lens of both technical requirements and contextual conditions that influence real-world functionality. This balance between rigorous performance criteria and environmental factors naturally lead to questions about the resource footprint of existing sterile packaging systems and the sustainability implications of alternative materials. We will discuss this over the next couple chapters.

## III. Sustainability in Sterile Packaging

While ISO 11607 establishes what constitutes acceptable sterile packaging performance, it remains largely agnostic to environmental sustainability considerations. The standard specifies how sterility must be maintained, but it does not address the packaging material's life cycle. This distinction is significant as growing environmental pressures increasingly demand that material performance should be considered alongside life-cycle impacts and resource intensity.

A useful and new framework for understanding sustainability in materials selection is Sustainable Materials Management (SMM). SMM examines materials across their entire life cycle and aims to decouple material from economic value creation through two primary mechanisms: dematerialization and detoxification[6]. Dematerialization focuses on delivering the same function with less material or energy input, while detoxification seeks to reduce hazardous substances and associated environmental harm. Together, these principles provide a structured rationale for reassessing current sterile packaging options, which are predominantly derived from fossil-based polymers.

This perspective is particularly relevant to this project because it provides a macro-level justification for exploring bio-based sterile barrier alternatives. Bio-derived materials such as bacterial cellulose (BP) may function as dematerializing substitutes for petrochemical-based packaging by reducing reliance on non-renewable resources and lowering embedded environmental burdens, while still aiming to satisfy performance requirements. The broader materials science community increasingly recognizes the urgency of transitioning toward renewable and biologically inspired materials to mitigate environmental degradation and resource depletion[7].

Other recent research into sustainable materials further reinforces the relevance of these cellulose-based systems. Cellulose and other biopolymer materials are widely identified as promising candidates for sustainable packaging applications due to their abundance and renewability[8]. Comprehensive reviews of cellulose-based materials highlight their potential to deliver competitive mechanical and barrier performance while supporting lower-impact life cycles compared to conventional polymer systems[9]. Although much of this research is still focused on food packaging, the underlying material sustainability arguments are transferable to sterile packaging contexts when regulatory and performance constraints are to be appropriately addressed.

In parallel, lifecycle-oriented models such as the Value Hill framework provide a conceptual lens for examining how value and environmental impact evolve across a product's lifespan. As illustrated in ***Figure 2***, the Value Hill depicts how materials gain economic and functional value during extraction, processing, and manufacturing, reaching a peak during the use phase; before experiencing a rapid decline at end-of-life in conventional linear systems. Circular approaches aim to slow or reverse this decline by retaining or recovering value through strategies such as reuse, recycling, or alternative recovery pathways[10]. When applied to sterile packaging, the framework therefore encourages the addition of only essential "value" (energy), recognizing that excessive value addition can amplify environmental impacts at end-of-life.

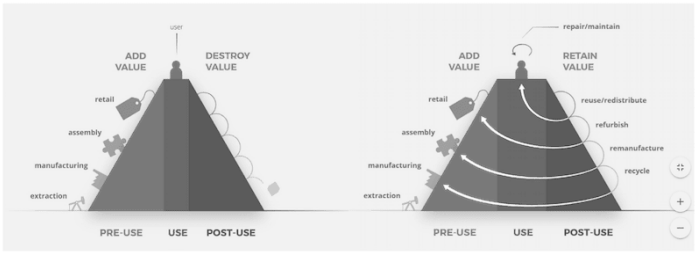



***Figure 2.*** *The Value Hill model illustrating the accumulation of material value during production and use, followed by value loss at end-of-life in linear systems, and the potential for value retention through circular strategies such as reuse, recycling, and recovery. Adapted from Achterberg et al.[10]*

Taken together, these frameworks suggest that sustainability in sterile packaging cannot be addressed through material substitution alone. Instead, it requires an integrated consideration of material origin, lifecycle impacts, and system-level value retention. The following sections build on this foundation by examining why biomaterials (taking BP as the main example) warrant investigation within the highly constrained context of sterile barrier systems.

## IV. Initial Investigation: Biomimicry as a Materials Inquiry

The initial direction of this project emerged from an interest in whether material strategies (biomimicry) observed in nature could inform more sustainable approaches to sterile packaging. Rather than treating biomimicry as a purely aesthetic or formal inspiration. This investigation was framed around a practical question: *could naturally occurring materials or biological processes offer functional properties relevant to sterile barrier performance while reducing environmental impact?*

Biological systems are amazing. They routinely achieve complex functionality such as protection, filtration, and containment while using minimal material input and ambient processing conditions [11]. This contrasts sharply with many conventional materials, which rely on energy-intensive polymer synthesis, multi-layer lamination, and tightly controlled manufacturing environments. Therefore, biomimicry offered a unique early conceptual lens through which material efficiency and environmental burden could be considered simultaneously.

A property that initially drew this investigation toward natural examples with protective or barrier-like functions was for instance;

- The wings of cicadas possess nanoscale pillar structures that confer both super hydrophobicity and physical antimicrobial activity. This means the bacteria that contacts the nanopatterned surface can be mechanically ruptured without chemical agents, a property that has inspired biomimetic surface fabrication in engineering research [12],[13].

- Natural composite materials such as beetle exoskeletons provide examples of structural efficiency. The flower beetle's shell combines layered nano-structures that integrate mechanical strength with structural coloration, demonstrating how hierarchical biomaterials balance protection, stiffness, and damage resistance through optimized micro-architectures[14],[15].

- Fungal mycelium and other materials derived from mushrooms have gained attention as sustainable biomaterials due to their lightweight, biodegradable composites and ability to be grown from low-value agricultural residues with relatively low energy input[16]. Mycelium materials have demonstrated potential across diverse applications, from acoustic absorption panels to construction and packaging, indicating that fungal networks can be tailored for functional performance while aligning with sustainability objectives[17].

- Investigating shark skin was the most compelling biological example of surface-mediated barrier and antimicrobial functionality. The outermost layer of shark skin is covered with microscopic placoid scales, known as dermal denticles, which form a highly ordered, ribbed surface structure ***(Figure 3).*** While these denticles serve multiple and different functions, what we need draw out here is their surface topography has also been shown to inhibit bacterial adhesion and colonisation[18],[19].

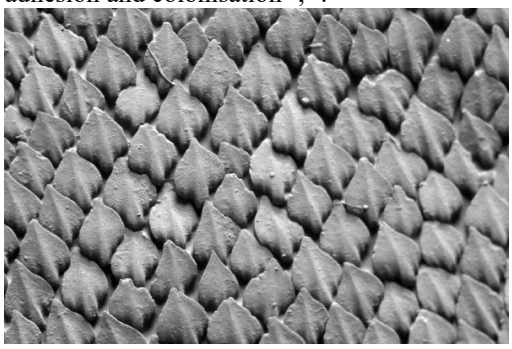


***Figure 3.*** *Micro-structured surface of shark skin showing overlapping placoid scales (dermal denticles).*

This antimicrobial effect arises not from chemical agents, but from the physical micro-patterning of the surface, which disrupts bacterial settlement. Biomimetic translation of this principle has led to engineered surfaces such as Sharklet AF, a micropatterned texture designed to reduce bacterial attachment in medical and industrial environments[20],[21].

These biological examples grounded the early stages of the project in a broad biomimetic inquiry, rather than superficial analogy, and provided tangible target properties against which candidate materials could be evaluated.

## V. Exploratory Concepts: Biomimetic Surface Behavior and Grown Materials

Following the initial biomimetic investigation, the project entered a more speculative phase, exploring whether non-traditional material behaviors could be leveraged to address contamination control while reducing environmental impact. Rather than proposing direct material substitutions, this stage examined *how* a surface behaved under properties like mechanical stress, moisture exposure, or microbial contact and what could be reimagined through biological analogies.

### 5.1 Behavioural Analogies: From Blood Clotting to Shear-Responsive Barriers

The first conceptual direction considered whether sterile barrier materials could respond dynamically to contamination, rather than acting as passive membranes. Biological systems such as blood clotting offer an instructive analogy where the material's properties change rapidly in response to external threats, limiting damage without overengineering the entire system[22].

Translating this logic to sterile packaging led to speculative ideas such as shear-thickening or self-sealing barrier architectures, inspired by non-Newtonian fluids (e.g. oobleck) and self-healing coatings used in other engineering contexts[23]. In theory, such materials could stiffen contamination when exposed to

mechanical disturbance or airborne particulates. However, while these ideas are conceptually compelling, no existing literature demonstrates their feasibility within the constraints of sterile barrier validation, nor their compatibility with ISO 11607 performance requirements[3]. This highlighted an early limitation: behavioural novelty alone is insufficient if it cannot be reconciled with standardised testing and predictable material performance within an adequate time frame.

### 5.2 Patterned Wettability: Beetle-Inspired Hydrophilic–Hydrophobic Surfaces

Another concept was a more materially grounded avenue that explored patterned surface wettability, inspired by desert beetles that collect water from fog using alternating hydrophilic and hydrophobic regions on their exoskeletons. Such biological strategies have been widely studied in engineered systems for water harvesting, anti-fouling, and microfluidic control[24].

Recent studies show that beetle-inspired surfaces with hydrophilic protrusions on superhydrophobic backgrounds can precisely control droplet nucleation, pinning, and directional transport ***(Figure 4)***[25].

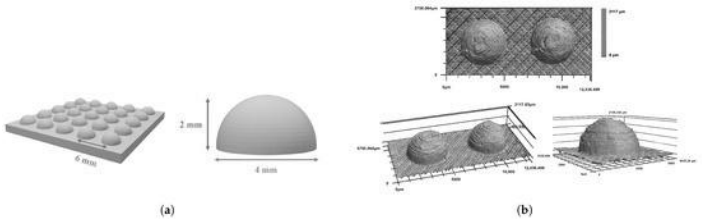



***Figure 4.*** *(**a**) The designed pattern of the beetle-inspired bumpy structure. The diameter of bumps is 4 mm, the center-to-center spacing of bumps is 6 mm, and the height of bumps is 2 mm. (**b**) Laser confocal images of beetle-inspired bumpy structures*

In optimised configurations, these surfaces achieve water collection rates exceeding 360 g/m²h, significantly outperforming homogeneous surfaces[26]. Translated in sterile packaging language, this research prompted the speculative concept of a hydrophobic sterile barrier incorporating microscale hydrophilic "sacrificial zones." In such a system, airborne moisture droplets (which often carry microbial contamination) would condense on hydrophilic regions, while the surrounding surface would resist adhesion. Despite the conceptual appeal, there is currently no evidence that patterned wettability alone can meet microbial ingress resistance, aging stability, or sterilisation compatibility requirements defined in ISO 11607[3].

### 5.3 Grown Materials: Mycelium-Based Composites

For a slight change, this project also examined mycelium-based composites (MBCs) as potential sustainable materials for barrier applications. MBCs are formed by binding lignocellulosic substrates with fungal mycelium, producing lightweight and biodegradable composites from low-value agricultural residues[27].

From a sustainability standpoint, these materials align strongly with circular economy principles due to their low embodied energy. However, the literature emphasises that MBCs must be manufactured under strictly sterile conditions to ensure uniform colonisation and reproducible properties[28]. Incomplete sterilisation can lead to less material performance, undermining reliability. Although certain fungal species form dense dimitic or trimitic hyphal networks that contribute to mechanical strength, these structures alone do not constitute microbial barrier performance.

So while post-processing methods can render mycelium inert and non-viable, there is currently no evidence that MBCs meet the controlled porosity or microbial barrier validation required for sterile packaging systems[28].

### 5.4 Convergence Toward Bacterial Cellulose

Through this exploratory phase, a distinction emerged between conceptual inspiration and material readiness. While patterned wettability and mycelium-based systems offered valuable insights into surface behaviour and sustainable fabrication, they lacked direct alignment with sterile barrier performance requirements.

By contrast, bacterial cellulose (BC) has demonstrated barrier-adjacent performance in packaging contexts. BC is synthesised by bacteria such as *Komagataeibacter xylinus*, forming an interconnected nanofibrillar network with high mechanical strength, chemical stability, and tunable porosity[29]. Composite BC films have demonstrated high oxygen barrier performance and antimicrobial efficacy exceeding 99% against *E. coli* and *Staphylococcus aureus* in food packaging applications[30].

Despite this promise, BC has not been evaluated under ISO 11607 sterile barrier validation. Which includes: microbial ingress testing, accelerated aging, transit simulation, or compatibility with medical sterilisation methods such as gamma irradiation or ethylene oxide.

This absence finally revealed a broader structural gap**: the lack of a defined pathway for emerging sustainable materials to be assessed against sterile packaging standards.**

It was this identified gap, (rather than the absence of promising materials) that ultimately motivated the development of a pre-standard evaluation framework, which is introduced in the following section.

## VI. Development of a Pre-ISO Validation Framework for Sustainable Sterile Packaging Materials

Despite the growing urgency for sustainable material alternatives in almost every field, bio-derived rarely progress into regulated sterile packaging applications. This limitation is not necessarily due to an absence of promising material properties, but rather the lack of a clear and structured pathway for introducing novel materials into existing validation systems[31].

Crucially, this project does not propose materials such as bacterial cellulose as a sterile barrier material in its current form. Instead, it identifies a systemic gap within the validation pipeline: sustainable biomaterials struggle to enter sterile packaging systems because there is no intermediate framework that translates exploratory material science into the specific performance language required by ISO standards.

The standard avoids prescribing how materials should be developed or prepared to meet its requirements. In practice, this results in a binary outcome for researchers working with novel materials: either proceed directly to full ISO validation; incurring substantial cost and risk of failure—or abandon the material altogether. This project argues that such an intermediate stage is essential.

A central principle of the proposed framework is that established material science tests can be meaningfully mapped onto recognised sterile packaging validation methods. Parameters such as pore size distribution, porosity, and air permeance which are commonly measured using SEM image analysis, liquid displacement techniques, and Gurley air resistance testing etc.are directly linked to microbial barrier behaviour in porous materials[32].

The idea is to connect laboratory-scale material characterisation to regulatory-relevant performance tests, and then the framework translates abstract material properties into criteria that align with existing standards. This translation is particularly critical for bio-derived materials, where conventional assumptions regarding polymer morphology, moisture response, and mechanical behaviour may not apply[33].

### 6.1 Framework Scope and Intent

The framework proposed in this project is not a certification tool and does not replace ISO 11607 validation. Instead, it functions as a preparatory roadmap intended to support researchers, material developers, and packaging engineers in making informed decisions before committing to formal regulatory testing.

Specifically, the framework:

- Defines low-cost screening tests to assess whether a material exhibits fundamental barrier-relevant behaviour.
- Identifies conditioning and modification strategies—drawn from bacterial cellulose and sustainable materials literature—that may stabilise performance under humidity, sterilization exposure, and mechanical stress[34].
- Introduces a decision-gate logic, ensuring that only materials demonstrating minimum viability progress to full ISO validation.
- Establishes a transparent and repeatable process applicable to bacterial cellulose as well as other emerging sustainable materials.

Importantly, this approach aligns with Sustainable Materials Management principles by reducing unnecessary testing, minimising resource expenditure, and improving the efficiency of early-stage material development[35].

Bacterial cellulose was selected as a reference material for this framework not because it is already compliant with sterile packaging standards, but because it occupies a plausible middle ground between experimental biomaterials and conventional barrier substrates.

### 6.2 Framework Walkthrough: From First Material Encounter to ISO Readiness

The pre-ISO validation framework proposed in this project is intended to function as both a technical decision tool and a practical guide for researchers working with novel sustainable materials. Unlike conventional validation standards, which assume the prior existence of a mature packaging substrate, this framework begins at the earliest point of material engagement: when a researcher first encounters or fabricates a new material and must decide whether it is even plausible to continue.

To support this, the framework is presented in two complementary formats:

(1) a tabulated checklist, and
(2) a narrative, stage-by-stage walkthrough.

The tabulated format defines each stage in explicit, decision-oriented terms, outlining objectives, key considerations, indicative tests, and minimum criteria required to progress. This structure mirrors the logic of regulated validation systems, enabling transparent Go/No-Go decisions and reducing ambiguity in early-stage material screening.

In parallel, the narrative format describes each stage as a material development journey, guiding the reader through the mindset and reasoning required at each step. This storytelling approach reflects the reality of early material research, where decisions are often made with limited data, basic tools, and iterative understanding rather than formal test reports.

#### 6.3.1 Stage 1 — Pre-Screening Material Characterization (Table)

Stage 1 represents the earliest point of engagement with a novel sustainable material. At this stage, the material is not evaluated as a sterile barrier, nor is it judged against ISO performance thresholds. Instead, the objective is to determine whether the material possesses the minimum structural and physical characteristics required to justify further investigation within a sterile packaging context.

The Stage 1 table ***(Figure 5.)*** is structured as a pre-screening checklist. Each row corresponds to a fundamental question that must be addressed before proceeding, with associated objectives, key material considerations, indicative low-cost test methods, and explicit Go/No-Go criteria. The tests referenced in this table

are material science characterisation methods, not formal packaging validation tests.

Failure at this stage indicates that the material is either fundamentally incompatible with sterile barrier applications or requires substantial reformulation before re-entry into the framework.

The table is intended to be used sequentially. Progression through Stage 1 is conditional: if a material fails any Go/No-Go criterion, the process stops or loops back to material modification, thereby preventing unnecessary progression to costly downstream testing.

| Stage 1 Question | Objective (What you are really checking) | Key Things to Consider | How "Approximate" Is Defined | Indicative Tests / Tools | Minimum Requirement to Pass Stage 1 |
|---|---|---|---|---|---|
| **Q1. Does the material physically exist as a barrier?** | Confirm the material can function as a continuous physical separator | Continuity, cohesion, self-support, absence of visible defects | Macroscopic: naked eye + gentle handling | Visual inspection, manual handling, optical microscopy | Continuous sheet/film; no visible holes or delamination; does not crumble or flow |
| **Q2. What type of barrier material is this (porous vs non-porous)?** | Classify the material without judging performance | Presence of voids, connectivity of pores, overall morphology | Qualitative + structural, not numerical | Optical microscopy, SEM (low magnification) | Clear classification as porous or non-porous based on structure |
| **Q3. Does the microstructure plausibly support microbial exclusion (proxy logic)?** | Use structure as a predictor before microbial testing | Pore size, pore connectivity, thickness, fibre packing density | Order-of-magnitude estimates (e.g. sub-µm vs multi-µm) | SEM image analysis, literature comparison | Median pore size plausibly < ~1 µm OR dense non-porous morphology |
| **Q4. Is the material dimensionally and structurally stable in ambient conditions?** | Eliminate materials that fail under normal handling or humidity | Warping, swelling, cracking, shrinkage | Qualitative before/after comparison | Ambient exposure, basic humidity conditioning | Maintains shape and integrity after exposure to ambient RH |
| **Q5. Can the material be produced with basic repeatability?** | Ensure results are not one-off artefacts | Thickness variation, surface uniformity, consistency between samples | Visual + simple measurement | Calipers, mass/area comparison, visual inspection | Multiple samples show comparable thickness and structure |
| **Q6. Is the material compatible with further testing workflows?** | Confirm it can physically survive downstream tests | Cut-ability, handling strength, mounting ability | Practical handling judgement | Sample preparation trial | Can be cut, mounted, and handled without tearing or shedding |

***Figure 5.*** *The Stage 1 — Pre-Screening Material Characterization Table.*

### 6.3.2 Stage 1 — Pre-Screening Material Characterization (Storyboard)

While the table ***(Figure 5.)*** provides clarity and repeatability, it does not fully capture the reasoning process that underpins early material assessment. To address this, the following section presents Stage 1 as a narrative walkthrough

- Question 1 — "Does this material even exist as a barrier?"

At this stage, the user is not measuring performance but they are confirming existence. The material must form a continuous, self-supporting structure that separates one side from another. This assessment requires minimal tools: visual inspection and gentle handling. If the material contains visible holes, delaminates when lifted, or lacks cohesion at the molecular or fibrillar level, it cannot progress further.

- Question 2 — "What kind of barrier am I dealing with?"

Here, the user must shift mindset: this is classification, not judgement. The goal is to understand whether the material behaves structurally as a porous or non-porous substrate. Using minimal tools: optical microscopy or low-magnification SEM the user must examine the material for voids, pore connectivity, and internal structure. No numerical thresholds are required at this stage. A clear qualitative classification is sufficient.

- Question 3 — "Does the structure make sense for microbial exclusion?"

At this point, the user applies proxy logic.
Rather than testing microbes directly, the user evaluates whether the material's microstructure exists within a plausible regime for microbial barrier performance. This involves approximate pore sizing, thickness observation, and assessment of fibre packing density. *(Approximation here means order-of-magnitude understanding, not precision.)* For example: Sub-micron vs multi-micron pores or Dense networks vs open channels SEM image analysis or comparison to published literature is sufficient. If the structure clearly allows free microbial passage, the material should not proceed further in its current form.

- Question 4 — "Does the material survive normal environmental exposure?"

Sterile barrier materials must tolerate real environments, not ideal lab conditions.
The user exposes the material to ambient humidity and temperature and observes changes in shape, integrity, or surface condition. This step filters out materials that swell, warp, crack, or lose cohesion under everyday conditions. No specialised equipment is required but only before-and-after comparison. Materials that cannot maintain dimensional stability under these conditions will be unlikely to succeed.

- Question 5 — "Can this material be made more than once?"

Here, the user assesses basic repeatability by comparing multiple samples. Thickness, density, and surface structure should be broadly consistent. Extreme variability signals that further material development is required before proceeding.

- Question 6 — "Can this material physically move forward in the pipeline?"

The material must be cut, mounted, and handled without tearing, shedding particles, or losing integrity. If it cannot survive basic preparation, it will not survive microbial, mechanical, or sealing tests later.
Passing this step means the material is physically ready to enter conditioning and screening stages.

Stage 1 functions as an intentionally permissive classification and risk-reduction gate. Its purpose is to establish whether a material can be meaningfully described. As such, a wide range of

materials are expected to pass this stage, including medical-grade papers, nonwoven cellulose substrates, bacterial cellulose films, coated fibre networks, selected mycelium-based sheets, and porous polymer membranes.

### 6.4.1 Stage 2 — Conditioning and Material Stabilization (Table)

Where Stage 1 establishes whether a material can *enter* the sterile packaging conversation, Stage 2 addresses whether it can be *prepared* to survive within it. At this stage, the material is no longer treated as a static specimen but as a system that will experience environmental stress, processing steps, and handling prior to validation. This stage asks whether known conditioning and modification strategies can reduce variability, manage environmental sensitivity, and produce a repeatable material state suitable for meaningful barrier screening.

The Stage 2 table ***(Figure 6.)*** is structured as a conditioning map rather than a pass/fail checklist. Each row defines a known source of instability (e.g., moisture sensitivity, surface fragility, mechanical weakness), alongside potential stabilisation strategies drawn from existing biomaterials literature.

Unlike Stage 1, **failure at this stage does not necessarily eliminate a material from the framework**. Instead, it indicates that additional conditioning iterations or process control are required before progression. The table is therefore intended to be used iteratively, allowing materials to loop within Stage 2 until a stable baseline is achieved or until further development is deemed impractical.

| Stage 2 Question | Objective | Key Variables to Control | Indicative Conditioning Methods | Typical Ranges (Guidance) | Evidence to Record | Go / No-Go Criteria |
|---|---|---|---|---|---|---|
| **Q7. What environmental factors destabilise the material?** | Identify dominant sensitivity (not optimise) | Humidity, temperature, drying history | Ambient exposure; controlled chamber exposure | RH: 30–90% Temp: 20–40 °C | Visual change, warping, swelling, surface tackiness | **Go** if dominant sensitivities are identifiable and consistent |
| **Q8. Can instability be reduced through controlled drying?** | Reduce moisture-driven variability | Drying rate, final moisture content | Oven drying; air drying; freeze drying | Oven: 40–60 °C Freeze-dry: −40 °C → RT | Dimensional change; handling behaviour | **Go** if post-dry samples retain shape and cohesion |
| **Q9. Can surface behaviour be stabilised without redefining the material?** | Improve handling & durability | Surface chemistry, hydrophilicity | Thin coatings (e.g. PVA, PEG), mild crosslinking | Coating thickness: sub-10 µm | Visual integrity; absence of flaking | **Go** if coating remains intact and does not delaminate |
| **Q10. Does conditioning improve repeatability?** | Reduce sample-to-sample variation | Thickness, density, surface texture | Replicate conditioned batches | Minimum n = 3–5 samples | Thickness spread; visual consistency | **Go** if variability is reduced vs unconditioned state |
| **Q11. Does the conditioned state survive environmental challenge?** | Confirm stability under realistic conditions | RH cycling, temperature exposure | Conditioning per ISO atmospheres | RH: 23 ± 2% → 50–75% Temp: 23 ± 2 °C | Pre/post comparison | **Go** if no gross deformation or loss of integrity |
| **Q12. Is the material now test-ready?** | Confirm readiness for barrier screening | Cutability, mounting, handling | Manual cutting & mounting | N/A | Handling notes; particulate observation | **Go** if samples survive preparation without failure |

***Figure 6.*** *The Stage 1 — Pre-Screening Material Characterization Table.*

The environmental conditioning ranges used in this stage were selected to reflect realistic handling and storage conditions referenced within ISO. ISO 11607-1 requires evaluation of the influence of temperature and humidity on packaging materials (§5.1.4) but defers to standard conditioning atmospheres commonly used for paper- and fibre-based materials (e.g. ISO 187; ASTM D4332) ([5],[36]). Relative humidity levels between approximately 23–75% RH and temperatures of 20–40 °C are widely used in early material evaluation to reveal moisture sensitivity and surface degradation without inducing non-representative failure modes.

Sample sizes of three to five specimens were used to balance evidence generation with the exploratory intent of the pre-ISO framework. At this stage, the objective is not statistical validation but identification of gross variability and repeatability following conditioning. Small sample sets are commonly employed in early materials research to assess process sensitivity before committing to resource-intensive testing[37].

### 6.4.2 Stage 2 — Conditioning and Material Stabilization (Storyboard)

While the Stage 2 table (Figure 6.) defines conditioning steps and decision gates, the underlying logic of this stage is best understood as a transition from classification to preparation. Stage 1 asked whether the material *could* exist within a sterile packaging context; Stage 2 asks whether it can be *stabilised* enough to survive meaningful testing.

- Question 1 — "What actually causes this material to fail?"

The user begins by observing, not fixing. The goal is to identify which environmental factors like humidity, temperature, or drying history most strongly influence the material's behaviour. The material is exposed to everyday conditions rather than extremes. Swelling, curling, surface tackiness, or loss of rigidity are recorded. At this point, failure is informative, not disqualifying.

- Question 2 — "Can I reduce instability without changing what the material is?"

Here, the user introduces controlled drying as a first stabilisation step. Different drying routes: air-drying, low-temperature oven drying, or freeze drying are explored not to optimise performance, but to reduce variability. The material must retain cohesion and basic dimensional stability. Drying is used as the first measure because moisture is the most dominant, reversible, and non-destructive source of instability in bio-derived materials.

- Question 3 — "Does the surface need help?"

The user considers whether surface behaviour limits further testing. Thin coatings or mild crosslinking strategies are introduced as *enablers*, not performance enhancers. The question is not whether the coating improves barrier properties, but whether it prevents sticking, flaking, or surface damage during handling and conditioning. Any modification must remain physically integrated with the substrate.

- Question 4 — "Is this behaviour repeatable?"

Stabilisation is only meaningful if it can be reproduced. At least 3–5 samples prepared using the same drying route (e.g. air-dried at 23 °C, 50 % RH or oven-dried ≤40 °C) are compared for thickness (±10 %), visual uniformity, and handling behaviour. Large variation between samples indicates that the conditioning

process—not the material—remains unstable. Consistency across the batch signals readiness to proceed.

- Question 5 — "Does the conditioned material survive real environments?"

Conditioned samples are re-exposed to defined environments (23 °C / 50 % RH baseline; 30–35 °C / 75–85 % RH challenge) for a fixed period (e.g. 24–72 h). Pre- and post-exposure states are compared, focusing on dimensional change, warping, swelling, cracking, or loss of cohesion. Materials that fail to retain basic integrity under these conditions should not progress further.

- •Question 6 — "Is this material now test-ready?"

Finally, the material must physically survive the pipeline ahead. It must be cut, mounted, and handled without tearing or shedding particles. Passing this step does not imply ISO readiness—but it confirms that the material is sufficiently stabilised to justify barrier screening in Stage 3.

A material that passes this stage is not validated, optimized, or compliant, however it is no longer speculative. It has demonstrated that its weaknesses are manageable, its behavior is repeatable, and its preparation can be controlled. Only at this point does it become rational to invest in microbial barrier screening and packaging-specific tests.

### 6.5.1 Stage 3 — Functional Proxy Screening (Table)

Stage 3 marks the transition from structural stability to functional relevance. At this point, the material has demonstrated that it can exist as a coherent substrate (Stage 1) and that its behaviour can be stabilised through basic conditioning (Stage 2). The objective of Stage 3 is not to prove sterile barrier compliance, but to determine whether the conditioned material exhibits proxy behaviours that plausibly align with sterile barrier requirements.

Failure at this stage does not indicate that a material is unsuitable in principle, but that it lacks sufficient functional alignment in its current form to justify further progression within a sterile packaging context.

The table ***(Figure 7)*** is intended to be used sequentially. Materials that fail any Go/No-Go criterion should either be modified and re-enter Stage 2 or be redirected toward non-sterile applications.

| Proxy Question | Objective | Key Properties Considered | Indicative Tests | Go / No-Go Criteria |
|---|---|---|---|---|
| **Q13. Does the material resist particle passage?** | Assess proxy barrier behaviour without microbes | Pore size regime, pore connectivity, thickness | SEM image analysis, liquid penetration, air permeance (Gurley) | No rapid through-flow; resistance consistent with porous barrier substrates |
| **Q14. Does the material allow controlled gas exchange?** | Evaluate breathability vs barrier balance | Air permeability, tortuosity | Gurley air resistance, pressure decay | Measurable resistance (not impermeable, not free-flowing) |
| **Q15. Does the material maintain integrity under light stress?** | Screen mechanical robustness | Tensile strength, tear initiation | Manual tensile handling, low-load tensile test | No tearing or delamination under low loads |
| **Q16. Does moisture exposure remain reversible?** | Identify moisture-driven failure modes | Swelling, recovery, cohesion | Humidity cycling (50 % ↔ 85 % RH) | Material returns to near-original dimensions |
| **Q17. Does the surface remain intact?** | Screen cleanliness and particle risk | Fibre shedding, surface cohesion | Tape lift, visual inspection | No visible fibre release or surface breakdown |

***Figure 7.*** *The Stage 3 — Functional Proxy Screening Table*

### 6.5.2 Stage 3 — Functional Proxy Screening (Storyboard)

While the table formalises Stage 3 as a checklist, the logic of this stage is best understood as a shift in questioning. The user is no longer asking *what the material is*, but *what the material does*.

- Question 1 — "Does this material slow things down?"

Sterile barriers do not need to be impermeable; they need to resist passage. At this step, the user evaluates whether air, liquid, or fine particles encounter resistance when interacting with the material. This is not a microbial test. Instead, the user observes flow behaviour: does penetration occur instantly, gradually, or not at all? Materials that behave like open meshes are filtered out here.

- Question 2 — "Is there a balance between breathing and blocking?"

Here, the user looks for controlled permeability. Completely sealed materials raise condensation and sterilisation risks, while overly open materials fail barrier logic. Using simple air resistance tests, the user assesses whether the material occupies a plausible middle ground already familiar in medical papers and porous polymer membranes.

- Question 3 — "Does the material fall apart when lightly challenged?"

The user now introduces gentle mechanical stress. The goal is not to quantify strength, but to observe failure modes. If the material tears, delaminates, or sheds fibres under basic handling, it is unlikely to survive sealing, transport, or sterilisation later. Passing this step indicates basic functional robustness.

- Question 4 — "Is moisture response predictable rather than catastrophic?"

Because sterile packaging routinely encounters humidity during sterilisation and storage, the user exposes the material to controlled moisture cycling. The focus is on reversibility: swelling is acceptable, permanent distortion is not. Materials that cannot recover shape or cohesion are filtered out at this point.

- Question 5 — "Does the surface stay where it belongs?"

Finally, the user assesses surface integrity. Fibre release, dusting, or surface breakdown introduce contamination risks incompatible

with sterile environments. A material that appears structurally sound but sheds under light contact is stopped here.

Stage 3 functions as a credibility gate. Materials that pass are not sterile barriers… but they now behave like materials that could become sterile barriers. At this point, the material has earned progression into ISO-aligned conditioning, sealing interaction, and sterilisation compatibility screening.

### 6.6.1 Stage 4 — Pre-ISO Go / No-Go Gate (Table)

Stage 4 consolidates all data generated in Stages 1–3 into a formal decision checkpoint. Unlike earlier stages, no new experiments are introduced. Instead, this stage evaluates whether the material has demonstrated sufficient structural stability, proxy barrier behaviour, environmental robustness, and mechanical viability to justify progression into regulated ISO 11607 validation testing.

| Decision Domain | What Is Being Confirmed | Evidence Required (From Previous Stages) | Minimum Go Threshold | ISO Alignment |
|---|---|---|---|---|
| **Q18. Structural Plausibility** | Pore regime consistent with microbial exclusion | SEM (post-conditioning), pore size distribution | Median pore size < ~1 µm OR literature-supported microbial exclusion regime | ISO 11607-1 §5.1.6 |
| **Q19. Porous Classification Stability** | Material consistently behaves as porous | Air permeance (pre & post conditioning) | Classification unchanged after humidity conditioning | ISO 11607-1 Annex C |
| **Q20. Environmental Robustness** | No gross deformation under defined humidity | 23°C / 50% RH and 38°C / 85% RH exposure | No delamination, swelling distortion, or pore collapse | ISO 11607-1 §5.1.4 |
| **Q21. Functional Proxy Barrier** | Evidence of microbial exclusion potential | MBP % OR surrogate particle penetration | ≥95% MBP (defined condition) OR low 1 µm penetration | ASTM F2638 / F1608 pathway |
| **Q22. Mechanical Handling Viability** | Can survive packaging manipulation | Basic tensile / burst screening | No tearing under manual handling; strength within literature range for porous substrates | ISO 11607-1 §5.1.7(e) |
| **Q23. Cleanliness Risk** | No obvious particulate shedding | Visual inspection / tape lift pre-screen | No visible linting or loose fibres | ISO 11607-1 §5.1.7(d) |
| **Q24. Repeatability** | Small batch consistency | ≥3–5 samples within ±10–15% thickness variance | Variability controlled | ISO 11607-1 §5.1.5 |

***Figure 8.*** *The Stage 4 — Pre-ISO Go / No-Go Gate (Table)*

The Stage 4 table ***(Figure 8)*** functions as a final pre-submission checklist. Each criterion directly maps to an ISO 11607-1 requirement or associated ASTM barrier pathway. Progression beyond this point commits financial, laboratory, and regulatory resources. Therefore, failure at this stage halts advancement and returns the material to modification. This gate exists to prevent premature or speculative ISO testing.

### 6.6.2 Stage 4 — Pre-ISO Go / No-Go Gate (Storyboard)

Stage 4 is not about discovery but it is about discipline. By this point, the user has generated data. The material has been observed, dried, conditioned, stressed, and screened. Now the question changes:
"Is this material worth submitting to the regulatory system?"
• **First**, they confirm structure has not degraded. The pore regime measured earlier must still exist after conditioning. If the SEM now shows enlarged voids or collapsed networks, the microbial plausibility assumption collapses with it.
• **Second**, they confirm classification stability. If air permeance changed so drastically that the material no longer behaves consistently as porous, it cannot move into the ASTM porous-material barrier pathway.
• **Third**, they revisit environmental robustness. A sterile barrier must survive storage and transport conditions. If exposure to 38°C and 85% RH caused warping, swelling, or microstructural instability, the material is not ready.
• **Fourth**, they ask the most uncomfortable question: Did the proxy barrier evidence actually show meaningful exclusion? If the MBP test or surrogate particle test did not demonstrate high exclusion efficiency, ISO microbial testing would almost certainly fail.
• **Fifth**, they assess handling reality. Can this sheet be cut, sealed, and moved without tearing? If not, there is no point progressing to seal validation.
• **Finally**, they check repeatability. If sample-to-sample variation is uncontrolled, the issue lies in process development@ not validation. This is the moment where the material graduates from "interesting biomaterial" to "candidate sterile substrate."
If it passes, the next stage is no longer exploratory. It enters formal validation:

- ASTM F2638 (aerosol surrogate)
- ASTM F1608 (microbial ranking)
- Seal strength (F88)
- Aging (F1980)
- Distribution (D4169)
- Sterilization compatibility (ISO 11135 / 11137)

If it fails it must return to Stage 2 for modification.

### 6.6 Stage 5 — Transition to ISO 11607 Validation

Stage 5 is the formal handover to regulated testing. If a material passes Stages 1–4, it has shown structural stability, functional plausibility, and repeatable behaviour. It is now ready to enter recognised sterile packaging validation under ISO 11607-1 and ISO 11607-2.At this stage, accredited laboratories perform the required tests, including:

- Microbial barrier testing (e.g., ASTM F1608, ASTM F2638)
- Seal strength and integrity (e.g., ASTM F88, ASTM F1929)
- Aging studies (ASTM F1980)
- Distribution simulation (ASTM D4169 or ISTA)
- Sterilization compatibility testing
-

Stage 5 is not part of the experimental framework developed in this project. It is the point at which regulatory compliance begins. The purpose of the framework presented in Section 6 is therefore simple: to ensure that only materials with credible technical readiness reach this stage, reducing unnecessary cost, time, and material waste while creating a structured entry pathway for sustainable biomaterials into sterile packaging validation. Please see ***Appendix 1.*** for the vertical process map of each stage.

## VII. Implementation Feasibility and Resource Implications of the Pre-ISO Framework

### 7.1 Estimated Time and Cost per Stage

*Disclaimer: The following cost and time estimates are based on typical academic laboratory rates, published testing laboratory price lists, and industry-reported sterile packaging validation costs. Values represent indicative ranges rather than fixed quotations, and are intended to demonstrate relative escalation across stages rather than exact financial forecasting.*

The staged structure of the proposed framework is not only methodological but economic. One of its primary justifications lies in the progressive escalation of cost and time associated with sterile barrier validation. Published sterile packaging guidance and laboratory price schedules demonstrate that early material characterisation can be conducted at relatively low cost, whereas ISO-aligned microbial and integrity testing rapidly increases financial exposure[38–42]. By structuring development into gated stages, the framework seeks to minimise the risk of advancing unsuitable materials into high-cost regulatory testing.

Stage 1 (Pre-Screening Material Characterisation) primarily involves internal laboratory analysis, including optical microscopy, scanning electron microscopy (SEM), thickness measurement, and basic tensile screening. University or shared laboratory SEM facilities typically charge between €50 and €150 per hour, with a standard imaging session requiring two to four hours[42]. When combined with basic consumables and internal laboratory time, Stage 1 screening can typically be completed within approximately one week at an estimated cost below €1,000, assuming access to institutional facilities. At this stage, the economic barrier to entry is intentionally low, supporting exploratory material classification before any regulatory alignment is attempted.

Stage 2 (Stabilisation and Conditioning) introduces environmental exposure and repeatability testing. Controlled humidity chambers and low-temperature drying equipment are common laboratory tools, but external chamber rental may cost several hundred euros per week depending on facility access[43]. Conditioning cycles under standard laboratory environments (e.g., 23 °C ± 2 °C and 50 % ± 5 % RH) typically require several days to stabilise porous or hydrophilic materials[44]. Including repeat sampling and controlled drying trials, Stage 2 may extend over two to three weeks, with indicative costs ranging from several hundred to a few thousand euros depending on equipment access. Importantly, these costs remain modest relative to downstream sterile packaging tests.

Stage 3 (Functional Proxy Screening) marks a transition toward performance-linked testing. Air permeance (e.g., ISO 5636 or Gurley methods), tensile strength (ISO 527 or ISO 1924), and moisture analysis require calibrated mechanical and permeability equipment. External laboratory testing for individual material performance tests typically ranges from several hundred to approximately one thousand euros per method[45]. When multiple properties are assessed concurrently, overall costs may rise into the low thousands, with a duration of approximately three to four weeks including laboratory scheduling and reporting. At this stage, the framework begins to approximate sterile barrier functionality while still avoiding microbial exposure studies.

Stage 4 (Pre-ISO Gate Testing) represents the first high-cost escalation point. Microbial ingress testing (ASTM F1608) and aerosol penetration testing (ASTM F2638) are recognised routes for demonstrating microbial barrier performance under ISO 11607-1 requirements[38–46]. Commercial sterile packaging laboratories report that microbial barrier and integrity test packages typically range from several thousand to over ten thousand euros depending on sample size and protocol scope[47–48]. Booking, execution, and reporting commonly require six to eight weeks. Without earlier screening stages, unsuitable materials entering this level of testing represent a significant financial risk.

Stage 5 (Full ISO 11607 Validation) involves complete sterile barrier system validation, including sealing validation (ASTM F88), burst testing (ASTM F1140), distribution simulation (ASTM D4169), sterilisation compatibility, and stability assessment[38,49]. Industry guidance and medical packaging case studies suggest that full packaging validation programmes frequently exceed €30,000 and may surpass €100,000 depending on device complexity and regulatory pathway[47,50]. Real-time stability studies may extend timelines to six to twelve months.
The economic gradient across these stages demonstrates the structural rationale of the framework. Early screening stages can typically be executed within weeks at relatively low cost, while later regulatory stages require months and substantial financial investment. By filtering materials progressively, the framework reduces the likelihood of advancing fundamentally unsuitable sustainable materials into costly ISO-level validation.

### 7.2 Risk Exposure and Financial Escalation Points

Financial risk in sterile packaging development escalates non-linearly. The most significant cost inflection occurs when transitioning from internal material characterisation to regulated packaging validation. For example; Microbial ingress testing under ASTM F1608 requires controlled aerosolization systems and microbiological containment facilities, increasing both cost and procedural rigidity[51].

Failure at this late stage often necessitates material reformulation and full re-testing, compounding financial loss. By contrast, failure at Stage 1 or Stage 2 results primarily in laboratory time expenditure rather than regulatory testing fees. The framework therefore functions as a financial risk-reduction mechanism. Each stage acts as a containment boundary, limiting sunk costs until sufficient evidence of material plausibility is established.

### 7.3 Infrastructure and Expertise Requirements

Execution of the framework assumes access to:

- Materials characterisation facilities (SEM, mechanical testing, conditioning chambers)
- Basic microbiology laboratory capability (for CFU-based proxy testing)
- Packaging test laboratories (for ASTM F2638 or later validation stages)

ISO 11607 itself does not prescribe laboratory infrastructure but requires demonstrable evidence of performance under defined environmental and sterilisation conditions[52]. In industrial settings, such testing is commonly outsourced to accredited laboratories. In academic settings, core facilities may provide partial capability, though regulatory-grade validation typically requires certified testing environments.

The framework is therefore most immediately applicable to research groups or SMEs collaborating with testing laboratories, rather than individual inventors without institutional access.

### 7.4 Scalability and Industrial Applicability

The staged logic of the framework is material-agnostic. While bacterial cellulose is used as a case reference, the process applies to any porous or semi-porous substrate proposed for sterile barrier use. Because early stages rely on widely recognised material science methods, the framework scales across different material classes without modification of regulatory logic.

From an industrial perspective, the gating structure mirrors established stage-gate product development models, improving compatibility with existing quality management systems[53]. By reducing unnecessary entry into formal ISO validation, the framework aligns with lean development principles and reduces iteration waste. However, scalability depends on reproducibility of material production. Materials exhibiting high batch-to-batch variability may require significant upstream process stabilisation before effective application of this framework.

### 7.5 Environmental Resource Efficiency

Medical packaging represents a significant and growing fraction of healthcare waste. Single-use sterile barrier systems are predominantly composed of multilayer fossil-derived polymers (e.g., polyethylene, polypropylene, PET) and spunbonded polyolefins such as Tyvek®, which are rarely recycled due to contamination and material complexity[54],[55]. The World Health Organization estimates that healthcare activities generate millions of tonnes of waste annually, with plastics forming a major proportion of non-hazardous medical waste streams[54]. In parallel, life cycle assessments of sterile packaging systems indicate that polymer production typically contributes 40–70% of total cradle-to-grave greenhouse gas emissions, while sterilisation processes (e.g., ethylene oxide or gamma irradiation) can account for an additional 10–30% depending on cycle configuration and energy source. End-of-life incineration further contributes fossil $CO_2$ emissions and resource depletion, particularly for multilayer polyolefin systems that are not recyclable [55–58].

The environmental story behind this framework begins upstream of disposal. Traditionally, sustainability discussions in medical packaging focus on end-of-life management. However, Sustainable Materials Management (SMM) principles argue that the greatest environmental leverage occurs earlier in the life cycle—during material selection, development, and validation[57]. Every failed validation cycle carries embedded energy and material costs: sample fabrication, conditioning, sterilisation exposure, transport to certified laboratories, microbiological media preparation, and disposal of test materials after contamination exposure. These impacts accumulate even when a material ultimately proves unsuitable.

The staged framework addresses this hidden environmental burden by shifting failure detection earlier. For example, sterilisation processes such as ethylene oxide treatment require controlled humidity, gas exposure cycles, and aeration phases that consume energy and infrastructure resources[58]. Gamma sterilisation similarly involves high-energy radiation facilities with significant operational footprints[59]. If a material fails after undergoing these processes, the environmental cost of that sterilisation cycle is irrecoverable. By contrast, early-stage screening (e.g., SEM imaging, thickness measurement, humidity conditioning at laboratory scale) requires comparatively modest energy inputs and generates minimal waste.
The framework therefore embeds environmental efficiency not by eliminating testing, but by sequencing it intelligently. It recognises that development waste is still waste. By reducing unnecessary sterilisation cycles, repeated laboratory transport, and disposal of failed packaging configurations, the framework aligns with circular economy principles that prioritise prevention over remediation[57].

Importantly, this does not claim that sustainable biomaterials automatically reduce impact. Bio-derived substrates can also carry energy-intensive processing burdens. Instead, the framework ensures that only materials with structural plausibility advance toward full validation, thereby reducing cumulative development waste regardless of material origin.

## VIII. CONCLUSION

This project identified a structural gap between sustainable biomaterial research and regulated sterile barrier validation. While materials such as bacterial cellulose demonstrate promising structural and environmental characteristics, existing standards—particularly ISO 11607—are designed to verify mature packaging systems rather than support early-stage material development. As a result, sustainable materials lack a defined pathway into regulated medical packaging applications.

In response, this work developed a staged, ISO-aligned pre-validation framework that bridges material science characterisation and formal sterile barrier testing. By introducing structured screening, conditioning, proxy barrier assessment, and decision-gate logic prior to ISO validation, the framework reduces technical uncertainty, financial risk and unnecessary environmental burden. It does not replace regulatory standards; rather, it clarifies how materials can be systematically prepared to meet them.

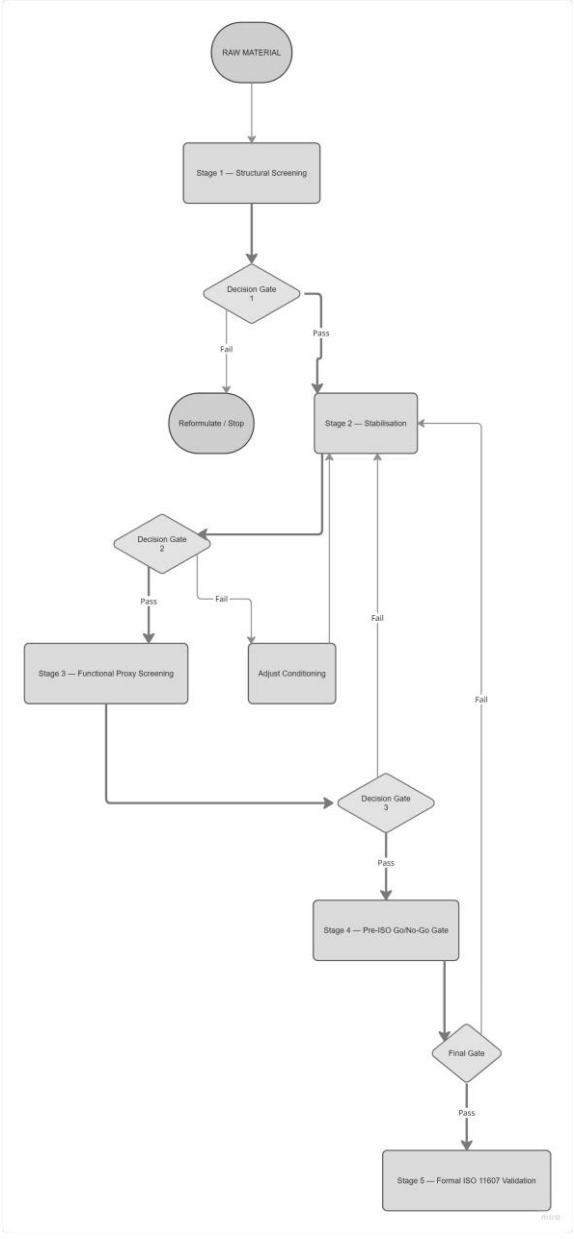
The framework also demonstrates that the primary barrier to sustainable sterile packaging innovation is not necessarily material capability, but the absence of translation mechanisms

between exploratory research and regulatory compliance. By formalising this translation, the project provides a practical tool for researchers and developers seeking to evaluate bio-derived materials within a medical packaging context.

Future work should experimentally validate the proposed screening thresholds, refine cost modelling under industrial conditions, and expand applicability to a broader range of sustainable substrates. Nevertheless, the structure presented here establishes a defensible starting point for integrating sustainability considerations into sterile barrier material development without compromising regulatory integrity.

## APPENDIX

***Appendix 1.***

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