Introduction

It stands to reason that manufacturers of Medical Devices should control the contamination of the products that they are manufacturing and this is particularly true for sterile products; the most responsible manufacturers take this subject very seriously.

Those new to the industry are sometimes perplexed by the paradox of controlling the pre-sterilization contamination on a product that will be terminally sterilized. This white paper explains the reasons, need and regulations surrounding contamination control before discussing control and monitoring methods concluding with a look at how to manage instances of out of specification (OOS) results.

Regulatory Requirements

Regulations fall under two broad umbrellas, the Quality Management System (QMS) requirements and the Regulatory requirements. It is not always easy to separate the requirements as one is often the function of the other. In practical terms separation is immaterial since contamination control should be approached holistically in any case, but for the purposes of this discussion they are mentioned separately.

QMS requirements mandate manufacturers to maintain control of the manufacturing environment to contamination. For USA this is mandated by 21 CFR 820.70(c) which states: “(c) Environmental control. “…the manufacturer shall establish and maintain procedures to adequately control these environmental conditions…” For Europe, Canada and other key world markets the requirements are covered by ISO 13485:2012 paragraph 6.4 which states: “6.4 Work Environment: The organisation shall determine, and manage the work environment needed to achieve conformity to product requirements.”

The Medical Devices Directives applicable in Europe, but also the basis for similar regulation in other key world markets, have specific requirements concerning microbial contamination. The main medical devices directive, 93/42/EEC as amended, under Annex I, the Essential Requirements, section 8 covers the requirements for “Infection and microbial contamination”. One of the sub-paragraphs, 8.5 states: “Devices intended to be sterilized must be manufactured in appropriately controlled (e. g. environmental) conditions.”

To address the earlier apparent paradox regarding contamination control of terminally sterilized products there are 3 main considerations:

- The first are the regulatory requirements introduced above; quite apart from the legal need to comply with regulations, manufacturers need to appreciate the
inactivation kinetics of sterilization technologies which work on a logarithmic reduction basis, so while sterility itself is an absolute, the state of sterility is expressed in terms of probability as the ‘Sterility Assurance Level’ (SAL). Because any sterilization process is finite and entirely dependent upon the microbial loading, the “bioburden”, without control of the bioburden the SAL cannot be accurately controlled.

- The second and third are the effects of non-viable contamination on the human body. Not all contamination is viable. Bacterial endotoxins are one of the most significant pyrogens associated with sterile medical devices. Pyrogens are substances that cause a heat rise in the body, increasing levels of pyrogens can cause a fever and ultimately death. Bacterial endotoxins are fragments of the cell wall of Gram negative bacteria, live Gram negative bacteria shed endotoxins, and dead Gram negative bacteria liberate significantly more endotoxins. So, when a device carries contamination of Gram negative bacteria the very act of sterilizing it liberates endotoxins.

- Finally, contamination also comprises non-viable contamination. Devices containing significant particulate and/or fibre contamination that come into contact with blood and/or cerebrospinal fluid (CSF) have the potential to cause blockages, thromboses or other adverse reactions.
Environmental Controls

Cleanrooms are the default choice for the control of the manufacturing area. Companies new to the industry can misunderstand what a cleanroom is. A cleanroom is not a magic box that mysteriously makes medical devices clean and contamination free. Packaging poorly sourced components in a badly maintained cleanroom with untrained staff into medical grade pouches achieves nothing, but this level of misunderstanding is surprisingly common. The best a cleanroom can achieve in itself is to ‘not add’ to the contamination of a medical device during its manufacture, assembly and packaging.

The definition of a cleanroom taken from ISO 14644-1:1999 is:

“A room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimise the introduction, generation and retention of particles inside the room and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary”

Cleanrooms are classified according to particle size using the relevant standard ISO 14644-1:1999. Typical classification is carried out at 0.5μm, and often at 5.0μm too.

For medical devices there are no hard and fast rules for which classification of cleanroom is required against any product type. Experience shows that medical device cleanrooms are commonly Class 7 or Class 8 with the lower the number being the cleaner specification used for implants and surgically invasive devices and class 8 cleanrooms used for less critical applications. Manufacturers would be well advised to determine their cleanliness requirements as a result of a formal risk analysis exercise since some Notified Bodies are beginning to require the rationale more formally.

Contamination Types

Contamination types falls into two broad categories: viable and non-viable. Significant sources of contamination inevitably are from cleanroom personnel who contribute to approximately 80% of all contamination that is found within the cleanroom. Real every-day examples of the non-viable types include:

Fibrous contamination:
• nasal hair
• eyelashes
• eyebrow hairs
• body hairs
• head hair
• clothing fibres

Particulate contamination:
• nasal discharge
• scabs
• dried blood
• finger nail dirt
• finger nails
• ear wax
• saliva
• tobacco smoke
• nail varnish
• lipstick
• foundation
• blusher
• other make-up
• skin grease
• moisturisers
• hair products

Sources of contamination
Apart from the contamination caused by people, the other sources of contamination are the products, raw materials and any automation used in the production process.

It is important to have good controls over raw materials that enter the cleanroom environment, not just in terms of good and effective transfer procedures but the very origin of the raw materials and their supply chain.

Low quality raw materials, with respect to contamination, have the ability to contaminate your cleanroom themselves. Where there is any doubt about the microbial quality of raw materials and/or their supply chain bioburden testing should be undertaken before their release for use.

In respect to maintaining sterility of a medical device the standard, ISO11137: 2006 + A1: 2013 “Sterilization of health care products -- Radiation -- Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices” clearly outlines the need for stable as well as low bioburden. It is therefore
important that the variation in bioburden is monitored as spikes can cause dose audit failures and potentially product recalls.

One of the most common reasons for dose audit failures seen is due to variation of raw materials from natural sources or that have been transported from another continent. Medical Device manufacturers need to specify the microbiological quality plus the transport route including timeliness for delivery as they are key for bioburden control but are often overlooked in purchasing agreements.”

Effects of Contamination
The effects of contamination include potential for infection, physical damage and metabolic/immunological responses.

A lack of control over contamination can lead to sterility failures which have the very real prospect of causing infection. Dependant on the infection site, the severity and type of infection this can lead to medicinal intervention, surgical intervention such as dissection or amputation, and potentially death.

Another effect is physical damage caused by fibre and particulate contamination. Again, varying degrees of damage can occur, depending on the site, the severity and type of contamination. This can be from low level problems such as minor blockage of arterioles to larger scale blockages of critical blood pathways, thromboses and ultimately death. Fibrous contamination has the ability to damage valves within the venous system which can be very painful in action and lead to oedema and similar consequences.

The potential for metabolic/immunological responses is virtually limitless as it is caused by whatever contamination may be present on the device. Soap residues due to poorly rinsed hands or contamination with paint-stripper residue following a weekend’s DIY are all potential contaminants eliciting a metabolic/immunological response. As mentioned above bacterial endotoxin as a function of sterilised contamination also has the capacity to kill.

Environmental Monitoring
In medical device cleanrooms environmental monitoring is normally a combination of settle plates and contact plates. Less commonly active air monitoring is undertaken. Virtually all cleanrooms will monitor for bacterial contamination and better programmes will also include an assessment for yeasts and moulds. Settle plates monitor the fall out rate onto a surface and are a good monitor of the microbial air quality while contact plates directly measure the contamination present on a surface and give an effective measurement of efficacy of cleaning processes. Contact plates
should contain a neutralising agent against disinfectant residues that would otherwise mask microbial contamination by inhibiting growth of contaminants on the agar growth medium.

### Bioburden explained

Bioburden is the measure of the pre-sterilization viable population of microorganisms on a product. That is to say it is the measure of viable contaminants destined to be killed by the sterilization process. In practical terms this is a measure of bacterial contamination.

There are many classes of bacteria and it is impractical, if not impossible, to assess them all for the purposes of bioburden determination, unless there are specific circumstances to investigate. Bioburden is the counting of non-fastidious mesophilic aerobic bacteria, which simply means non-fussy nutritional needs, room temperature, oxygen respiring bacteria.

Similarly, unless there are compelling reasons to do so fungi (yeasts & moulds) are not assessed as it is the bacteria that are normally more prevalent and more important. Other microorganisms such as viruses, protozoa, algae and so on are very rarely assessed. It is important to note that bioburden is an assessment of the total count and not just disease causing microorganisms, pathogens. Bioburden does not include Prions, the causative agent of CJD and it does not include Endotoxin.

Bioburden is an important measurement, and is ultimately the final arbiter as to whether control measures have been effective, but as a final figure it is quite coarse since it measures the combination of materials and activities including:

- Raw materials
- Sub-assembly operations
- Sub-assembly storage conditions
- Assembly operations
- Packaging
- Cleaning processes
- Operators’ hygiene controls
- Cleanroom operation
- Cleanroom efficiency
- Storage time & conditions

For the majority of medical devices, bioburden is found on the surface of the device although for absorbable devices such as wound dressings, those containing open cell sponges or more complex devices the bioburden may also be found within the matrix
of the product. The devices used for bioburden testing must have passed through the routine and entire manufacturing process including packaging to be a true reflection of the bioburden on real products. It is acceptable to use reject products for testing providing the reason for the reject status does not impact on the bioburden. The product packaging material itself is not normally part of a routine bioburden test. Any contribution of contamination to the total product bioburden as a result of the packaging material will have been made during the packaging process. Determination of the bioburden of the packaging material itself may be useful during an OOS investigation.

The bioburden test must undergo recovery efficiency validation to determine the effectiveness of the bioburden method to allow adjustment of the figures from routine testing to give an accurate reflection of the true bioburden. The implications are that whilst having a low bioburden result may look good from a quality perspective, if this result is not a true reflection of the product bioburden then this may not allow the product to pass an ISO11137 Dose setting exercise or could lead to future dose audit failures.

**Control Measures**

Since 80% of all cleanroom contamination comes from personnel the majority of control measures surround people and their activities. Most human contamination comes from either respiratory activities or hand contact.

Effective hand washing with a bactericidal soap at the start of a shift is effective in removing gross contamination, both physical dirt and microbes, but in order for the biocidal activity of the soap to be fully effective, operators need to have due regard for the manufacturer’s stated contact time, i.e. the time the skin should be in continuous contact with the soap for the biocidal effects to be fully realised.

Although it may seem obvious, training in hand washing should be more than a tick box exercise and does have an impact on bioburden levels.

“We recently had a high routine bioburden result for a customer and were involved in investigating this as they were unable to find the reasons behind it. After walking around the cleanroom and watching the staff get changed it became obvious that a new starter was not aware of the hand washing requirements. This was therefore solved very easily and did not lead to product recall, but it could have and the commercial impact of this would have been significant.”
Gloves do have their place in cleanrooms, particularly for critical care and highly invasive devices; however beware of the illusion of no contamination from the gloved hand. People do have a sub-conscious habit of touching themselves during the day whether this is nose or ear picking, or a hand to the back of the neck or scratching an itch on the cheek all of these activities whether with a gloved or un-gloved hand have the potential to transfer large numbers of microorganisms onto the medical devices. Talking is often overlooked as a risk activity. The very act of talking gives out far more contamination than simply passively breathing since air is ejected from the lungs more forcefully and carried with it significant quantities of saliva and all that contains. Cleanroom operators sitting face to face during final inspection and discussing the day while they examine products close to, will be inadvertently spitting all over the products they are inspecting while they talk.

Personnel suffering from any respiratory disorder, dry skin condition or gastrointestinal disorder are not suitable for work in the cleanroom. If these are chronic conditions a cleanroom is not a suitable place of employment; if these are transient conditions then alternative duties away from the cleanroom should be undertaken for the period of the acute condition.

Cleanroom operators who have cut themselves are suitable for work in the cleanroom providing the cut or wound is not infected, small, completely covered by a clean dressing which itself is low-shedding and is not actively weeping. It is important that scabs are completely covered up too as they will be shedding microscopic blood particles into the cleanroom and onto the products. The same is also true for dried blood smears typically immediately adjacent to a cut site since these too will be shedding microscopic blood particles.

Larger and perhaps more obvious contamination is contained by the cleanroom facility itself with pre-filters and terminal HEPA filters providing a constant supply of clean air to the cleanroom at an overpressure helping to prevent the ingress of unfiltered air into the manufacturing environment. The risks against this are the passage of people in and out of the cleanroom. On the outside of the cleanroom tacky mats should be strategically located to remove gross contamination from footwear, change rooms should have step over benches and ideally ‘no-touch’ operated taps. Operators should wear mob hats to completely cover hair and beard snoods for anyone with facial hair longer than 24 hours growth. Cleanroom gowns and overshoes should be worn at all times with a change policy implemented based on the output of a risk assessment. Mirrors in the change should be available to check correct attire.
What is an OOS situation & how do you deal with it?
Out of Specification (OOS) situations should initiate immediate containment, both physical and electronic, of affected product, pending results of product impact assessments and investigations.

Beware the knee-jerk retest, which achieves very little since one ‘Pass’ result and one ‘Fail’ result is hardly conclusive. There must be a documented rationale to justify discounting original test result and believing the re-test result. Re-tests, are useful however, in determining the extent of the issue as part of the investigation process.

If high bioburden results are seen during a dose audit, but the product still passes then it is also important to still investigate this even though product recall would not be required. It is also perfectly reasonable to question the test laboratory, but doubt over the laboratory process must be evidence based. If the laboratory skill is deemed to be ‘in doubt’ then this doubt should be applied to all test results including those where tests have successfully passed.

Investigations for OOS results are not always straightforward and classic quality tools such as the Fish Bone (Ishikawa) diagram can be very effective in tracking down the root cause. Useful information can be obtained from a detailed review including one or more of the following:
• abnormal events
• normal bioburden contaminants
• normal environmental contaminants
• identification of OOS contaminants
• other environmental factors
• cleaning programme
• changes to:
  • Personnel
  • Sub-contractors
  • Supply Chain
• component bioburden analysis
• sub-assembly bioburden analysis
• production key stage bioburden analysis
• Supplier audits, both QMS and Technical
• Personnel screening, including:
  • Finger dabs
  • Hand prints
  • Glove swabs
Conclusion

The regulatory requirements for contamination control are quite general in nature yet the practicalities of effective control can be quite intricate. The impact of a lack of control can be minor but also has the capacity to be devastating and companies ignore proper control at their peril.

Because of the large number of inputs into a cleanroom environment a wide range of control measures need to be implemented, culminating in control that may be assessed through just a few practical monitoring tests. Medical device companies are encouraged to review and assess their control plans with expert microbiologist support to ensure safety and compliance.
Global Acumen
From A Single Source

- EU Authorized Representative
- Quality Remediation
- Global Regulatory Issues, 483s, Warning Letters
- CAPA
- Regulatory Compliance
- Regulatory Submissions
- Quality – Audits & Assessments
- Quality – System Implementation & Process Improvement
- Validation
- Strategies, Planning, & Execution - For all types - process, software, test method, etc.
- Complaints, Adverse Events & Recalls
- Sterilization/contamination control
- UDI
- Supply chain management
- Make/buy, distribution, test/quality, functions & delivery
- Supply Chain Risk Assessment
- Supplier Quality – Auditing, Qualification & Management
- Commissioning Of Facilities & Utilities
- Manufacturing engineering services
- Post-market surveillance
- Mock FDA Inspections
- Implementation & Validation Of Software Systems
- Organizational change management

White paper produced by Maetrics

For more information, please contact global sales
+1 610 458 9312  +1 877 623 8742  globalsales@maetrics.com

With offices around the world  www.maetrics.com