



WHITE PAPER

Why your medical microelectronics development partner needs both particulate- and microbial-controlled clean rooms



Microelectronics technology is increasingly ubiquitous, even within the human body, as medical researchers develop new approaches to monitoring and treating a growing array of illnesses and injuries. A variety of implantable medical devices are now used routinely, ranging from intraocular lenses to electroencephalography (EEG) recorders and many others. The companies that design these devices require specific capabilities and qualifications from a potential medical device manufacturer. These requirements typically cover topics like experience in medical device manufacturing, the types of equipment necessary to manufacture, assemble, and package the product, parts tracking methods, employee qualifications and/or specialized training, required industry and governmental certifications, etc. However, as comprehensive as these requirements might appear, some of them fail to include an aspect that's critical for some categories of medical microelectronics device manufacturing: a microbial-controlled clean room.

In-house Microbial-Controlled Clean Rooms

A microbial-controlled clean room allows medical device manufacturers to handle the complete manufacturing process. By eliminating the need to ship finished devices to a third-party vendor for cleaning or packaging prior to sterilization, an in-house clean room helps to shorten the supply line, save time, and contain costs. Choosing a manufacturer without one increases the potential for production/delivery delays, product routing/tracking confusion or errors, accidental device contamination, and other problems. Having in-house clean rooms of this type streamlines the production process and reduces opportunities for finger-pointing if a question arises with a product in the field.

Why Device Sterilization Alone Isn't Enough

For microelectronic devices designed for either permanent or temporary implantation in the human body, the use of a microbial-controlled clean room to control the microbial (sometimes referred to as bioburden) level during final device assembly and pouching is essential to avoid exposing patients to danger. Bioburden refers to the number of contaminating bacteria on a certain amount of material before it is sterilized. Although implantable medical devices are thoroughly sterilized prior to shipment to the healthcare facility where they will be used (typically using gamma radiation or ethylene oxide [EtO]), sterilization should be thought of as a "necessary but not sufficient" step. Yes, sterilization will kill any living molds, bacteria, etc. on the device and its packaging. However, even after sterilization, pyrogenic (fever-causing) substances can remain in the cell walls of these dead organisms, posing an unacceptable risk to the patient after the device is implanted.

Clean Rooms Defined

It is a common misconception that clean rooms clean things but this is not the case. A clean room can be defined most simply as an enclosed environment with a low level of pollutants like dust, airborne microorganisms, aerosol particles, and chemical vapors. Clean rooms can only be as clean as the people, products, packaging and cleaning materials introduced into them. The facilities, people, tools, cleaning chemicals, and the product being manufactured can all contribute to contamination. All potential sources of contamination must be tightly controlled. A quick overview of the different types of clean rooms that medical device manufacturers may have in their facilities may be helpful.

Clean rooms are widely used in semiconductor manufacturing, biotechnology, the life sciences—anywhere there are products or processes that are sensitive to environmental contamination. The air entering a clean room is filtered to exclude dust; once inside, it is recirculated constantly through high efficiency particulate air (HEPA) and/or ultra-low penetration air (ULPA) filters to remove particulate contaminants generated inside the clean room itself.

In a typical city, the outdoor atmosphere contains 35 million particles that are 0.5 microns in diameter or larger per cubic meter, which corresponds to an International Organization for Standardization (ISO) Class 9 clean room. In contrast, an ISO Class 1 clean room allows no particles in that size range and only 12 particles that are 0.3 microns or smaller per cubic meter.

In order for a clean room to be certified by the U.S. Food and Drug Administration (FDA), it must meet the standards for controlled environments set forth in FED-STD-209E or ISO 14644-1. **Table 1** outlines the permissible particle counts for the various ISO 14644-1 clean room classifications. Although the US FED STD 209E was officially cancelled more than a decade ago, the classification numbers are still widely used, as outlined in **Table 2**.

ISO Class	Maximum Number of Particles in Air (particles in each cubic meter equal to or greater than the specified size)					
	Particle size					
	>0.1 µm	>0.2 µm	>0.3 µm	>0.5 µm	>1 µm	>5 µm
ISO Class 1	10	2				
ISO Class 2	100	24	10	4		
ISO Class 3	1000	237	102	35	8	
ISO Class 4	10,000	2,370	1,020	352	83	
ISO Class 5	100,000	23,700	10,200	3,520	832	29
ISO Class 6	1,000,000	237,000	102,000	35,200	8,320	293
ISO Class 7				352,000	83,200	2930
ISO Class 8				3,520,000	832,000	29,300
ISO Class 9				35,200,000	8,320,000	293,000

Table 1. ISO 14644-1 “Classification of Air Cleanliness”

Class	Maximum Particles/ft ³					ISO Class equivalent
	Particle size					
	≥0.1 μm	≥0.2 μm	≥0.3 μm	≥0.5 μm	≥5 μm	
1	35	7.5	3	1	0.007	ISO 3
10	350	75	30	10	0.07	ISO 4
100	3,500	750	300	100	0.7	ISO 5
1,000	35,000	7,500	3000	1,000	7	ISO 6
10,000	350,000	75,000	30,000	10,000	70	ISO 7
100,000	3.5×106	750,000	300,000	100,000	700	ISO 8

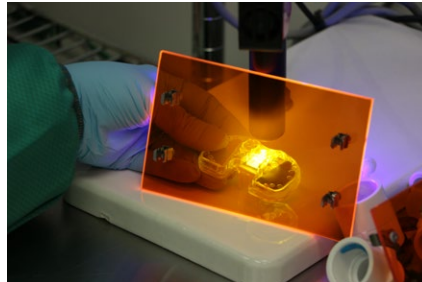
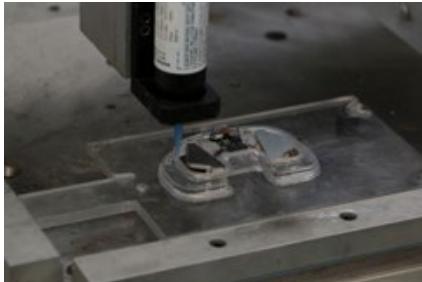
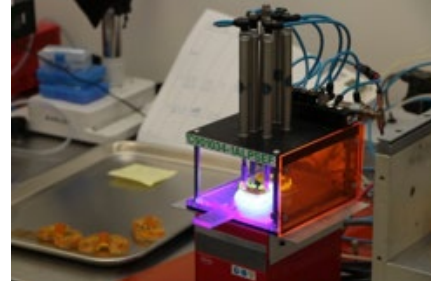
Table 2. FED-STD 209E Clean Room Classes

Valtronic Clean Rooms

Valtronic operates a variety of classes of clean rooms in its manufacturing facilities around the world. The newest one, which went into service in 2013, is an ISO Class 8 microbial-controlled clean room located in Valtronic's Solon, Ohio, manufacturing facility. This clean room combines temperature, humidity and contamination controls designed to prevent both particulates and microbes (dust, pollen, fibers, germs, yeast, molds, etc.) from making contact with implantable devices during final assembly and pouching, prior to EtO sterilization. Although this clean room was constructed to serve the packaging requirements of a single product, it is also suitable for use by anyone who needs microbial control for their implantable medical devices. For more information, see the section titled "Valtronic and OrthoSensor: Working in Partnership."

A double positive-pressure air flow design constantly forces particulates out of the clean room. Mini helix gauges are monitored to ensure this outward air flow is maintained. When added to Valtronic's decades of microelectronics design, manufacturing, and assembly experience, this new clean room completes the production chain, making it possible to provide a complete contract manufacturing solution for active implants in one building.

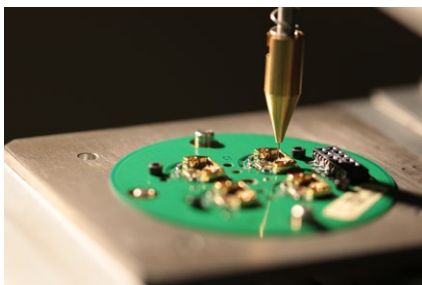
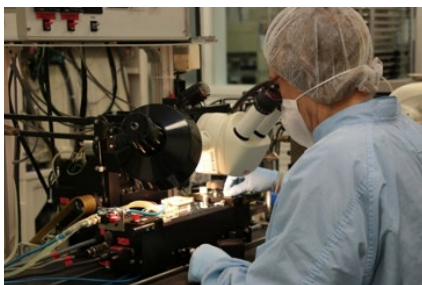
Wood pulp fibers shed from paper are one potential source of contamination, so minimal paper is allowed in the clean room; all component routing and tracking information is provided in electronic form. The activities of clean room technicians can also pose a risk of contamination. Everyone who works in the Solon Class 8 clean room follows standardized procedures to prevent this, including proper gowning procedures, which involve wearing hair nets, face guards, ESD smocks, rubber gloves, and ESD booties. To prevent bacterial transfer, technicians use antiseptic foam on their gloves before entering; work rules also ban them from entering the clean room if they're suffering from a cold or other illness.



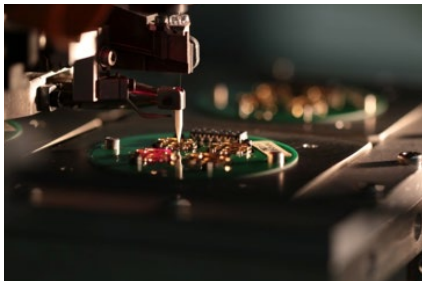
Workers in the ISO Class 8 microbial-controlled clean room at Valtronic USA follow strict protocols to prevent contamination of the devices assembled and packaged there.

Technicians follow a set of standard procedures and schedules for cleaning, HEPA filter maintenance, etc. Particulate counts are checked annually by an external auditor. Tables, walls, and floors are swabbed monthly and the residue is cultured to check for the presence of bacteria, yeasts, and molds.

The clean room houses a variety of testing, assembly and packaging equipment, including adhesive dispensing equipment for sealing devices and a helium leak tester for assessing their hermeticity, a load tester to confirm sensors are reading the applied loads properly, and a heat sealer for the plastic pouches in which finished devices are packed prior to EtO sterilization.



The ISO Class 7 clean room in Solon is used for microelectronics production tasks.



Valtronic USA also operates an ISO Class 7 clean room in the same Solon, Ohio, facility. Like the Class 8 microbial-controlled clean room, it employs a double positive-pressure design to force particulates out rather than drawing them in. The focus in the Class 7 room is on controlling particulates—dust, pollen, fibers, etc.—rather than organisms. Technicians working inside must wear bunny suits (coverall garments designed to contain any skin or hair shed) as well as hairnets and face guards. They follow similar cleaning, filter maintenance, and particulate auditing procedures but may use special ESD particle-free paper routers designed for clean rooms to track the progress of product “builds.”

Because it is used for production and assembly of a broad range of miniaturized electronic devices, the Class 7 clean room houses a variety of production and assembly equipment for use on a wide range of microelectronics devices, including an adhesive dispensing machine, die encapsulating machine, two wire bonders, and two plasma ovens.



The ISO Class 7 clean room in Valtronic's Swiss facility includes flow boxes where workers can reduce contamination to ISO Class 5 levels as needed.

Valtronic's Class 7 clean room in Les Charbonnières, Switzerland, is designed for producing electronic modules that require die assemblies (including those used in cochlear implants or neuro-implant systems to prevent glaucoma). It offers international customers access to a wide range of equipment, including stoves, adhesive dispenser, wire bonders, a heavy wire bonder, die bonders, flip chip bonders, interferometer, UV oven, plasma system, vacuum oven, pull testers, die shear testers, centrifuge, screen printers, and nitrogen cabinets. This facility also has a microbial-controlled environment used for lens manufacturing that occupies roughly one-quarter of the space in the Class 7 clean room.

The company's Class 7 and Class 8 clean rooms in Morocco are used in the production of active implants as well as a wide range of other medical devices, including bronchoscopes (instruments for examining the interior of the tracheobronchial tree), therapeutic goggles used for drug diffusion for those suffering from dry eyes, and other miniaturized electronics.



Valtronic Morocco operates both ISO Class 7 microbial-controlled and Class 8 clean rooms.

Your Partner in Medical Device Innovation

Valtronic is an FDA registered medical device manufacturer, and its operations are ISO 13485:2003 and ISO 9001:2008 certified. For more than three decades, Valtronic has helped thousands of companies develop and produce Class I, II & III medical devices and advanced miniaturized electronic assemblies from its worldwide facilities in Switzerland, the United States and Morocco. Customers include leading global suppliers of medical implants and devices, diagnostic imaging equipment and sensitive aerospace and industrial assemblies. As a global provider of engineering, industrialization and manufacturing services for medical devices and related high reliability products, Valtronic innovates and manufactures electronic products for its trusted medical device partners.

Valtronic can help you pioneer the next generation of healthcare innovations. With its extensive manufacturing and clean room facilities and highly trained personnel, Valtronic can be your partner in the development of medical technologies that help improve patient outcomes.

For more information, visit Valtronic at <http://www.valtronic.com>.

Valtronic and OrthoSensor®: Working in Partnership

Valtronic built its microbial-controlled clean room with one special partner in mind: OrthoSensor, Inc., a company that develops and commercializes intelligent orthopaedic devices and data services that provide quantitative feedback to surgeons and hospitals. In fact, the clean room was built at OrthoSensor's request and to their specifications for a new product. The VERASENSE™ Knee System includes a single-use intelligent tibial insert trial (the component that Valtronic manufactures) used in knee replacement surgery.

The Valtronic/OrthoSensor partnership works, in part, because of the good synergistic fit between OrthoSensor's business in implants and Valtronic's experience as a manufacturer of miniaturized electronic devices with experience in developing implantable medical products. Paul Birmingham, Senior Director of Operations for OrthoSensor, stated, "OrthoSensor is very excited about the partnership with Valtronic. Valtronic is a well-established contract manufacturer of medical devices and has demonstrated the ability to align with OrthoSensor's Best in Class requirements."

For the VERASENSE™ Knee System project, Valtronic performs incoming inspection, automated surface mount assembly of components on circuit boards, hand assembly of the sensors, and battery attachment. The sensors are tracked throughout the assembly process with routing codes that can be read electronically, eliminating the

need to bring paper into the microbial-controlled clean room. Inside the clean room, Valtronic technicians glue the sensor's PCB assembly into a plastic enclosure, perform a helium test to check for leaks in the glue joint, and perform a final load test of the sensor assembly. After a final cleaning, sensors are double-pouched in Tyvek bags. Shims used with the insert during surgery are also cleaned and sealed in separate double pouches. Outside the clean room, both sensors and their accompanying shims are boxed and labeled, then shipped to an ethylene oxide sterilization facility. After sterilization, products are shipped directly to OrthoSensor to await orders from orthopedic surgeons.

To maintain sterility, after the product is received at the hospital where the surgery will be performed, the shipping box is opened outside the surgical suite. Once inside the surgical suite, the outer pouch is opened and the surgeon removes the inner pouches. The inner pouches remain sealed until the surgeon is ready to use them.



OrthoSensor markets multiple versions of the VERASENSE insert design under different brand names and in a range of sizes.

The VERASENSE system is designed to take the guesswork out of knee replacement surgery by giving the orthopedic surgeon real-time, quantitative feedback on how the load on the knee is balanced. It gives the orthopaedic surgeon the data necessary to quickly achieve optimal tissue balance, component positioning and limb alignment. In the past, achieving the correct load balance required lengthy experimentation by the surgeon. The VERASENSE insert is designed to be placed in a patient's body for a maximum of 40 minutes during surgery. Small load sensors located on each corner of the insert allow the surgeon to see where the weight is being applied to ensure that it is correctly balanced. An improperly balanced load will lead to uneven wear and a significantly shortened knee replacement lifespan, potentially requiring a second surgery to correct the problem.

Load signals from the insert are transmitted wirelessly to a computer controller. The surgeon manipulates the patient's knee through a series of movements that allow evaluation of the load. Based on this information, the surgeon can adjust the soft tissue around the knee to achieve optimal balance. The insert can then be removed and replaced by the permanent knee replacement implant.

VALTRONIC™

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