



MEETING DEMAND BY BRINGING MANUFACTURING IN-HOUSE

In this article, Bentsi Algazi, Vice-President of Operations, and Anna Kalika-Rodin, Quality Manager, both of Sorrel Medical, discuss the process of developing and implementing in-house production facilities at Sorrel Medical, including cleanroom facilities. The authors discuss the regulatory requirements involved, practical considerations of the design and construction, and the benefits the establishment of in-house facilities confers to Sorrel and its pharmaceutical partners.

Growing recognition of the need for patient-centric drug delivery devices, combined with the increasing prevalence of biologics and a general trend towards home care and self-administration, has led to greater demand for disposable and easy-to-use wearable injectors. As such, pharmaceutical manufacturers are increasingly investigating wearable drug delivery solutions as an option for launching new products to market, as well as for lifecycle management of combination products already in circulation. Consequently, device manufacturers and technology vendors must

align themselves with pharma's evolving development needs – to deliver devices that meet pipeline expectations, while ensuring all the quality controls and necessary standards are maintained.

With an understanding of the direction in which the industry is moving, Sorrel has established its own independent manufacturing and cleanroom facilities to accommodate scalable production of wearable drug delivery devices (Figure 1). As demand from multiple customers increases, it is essential that Sorrel's manufacturing capabilities can scale-up accordingly, while still maintaining a level of quality that meets the highest requirements throughout the production process. Customisation and adaptable manufacturing capabilities allow for Sorrel to manufacture devices according to customer requirements, either in-house or outsourced to third-party providers.

"Throughout the construction and implementation process, consistent monitoring, evaluation, and revaluation was required to ensure that all cleanroom standards were being upheld."

THE DECISION TO IMPLEMENT IN-HOUSE MANUFACTURING

Looking to expedite the transition from initial design and development, with low-



Bentsi Algazi
Vice-President of Operations
T: +972 73 238 8867
E: bentsi.algazi@sorrelmedical.com



Anna Kalika-Rodin
Quality Manager
T: +972 73 238 8884
E: anna.kalika@sorrelmedical.com

Sorrel Medical
29 Yad Haruzim St
PO Box 8639
Netanya 4250529
Israel
www.sorrelmedical.com



Figure 1: Sorrel has established its own in-house cleanroom facilities as part of its development of scalable in-house manufacturing capabilities for its wearable injector platform device.

volume manufacturing, to medium- and high-capacity production of wearable drug delivery devices, in line with the needs of global pharma, Sorrel began the process of establishing a dedicated in-house manufacturing facility. The cleanroom (an integral component for the manufacturing process, scientific research, and quality control) required careful consideration with respect to both the design phase and the actual use of the facility once established.

The primary motive for establishing facilities for in-house manufacturing was



to ensure that Sorrel meets manufacturing demands with the proper level of quality for future products, whether developed for R&D purposes, clinical studies, or ongoing

commercial device production. In conjunction with establishing in-house cleanroom operations, Sorrel engaged leading contract manufacturing organisations (CMOs). The option of utilising a third-party CMO can be examined, either in parallel or in addition to commercial in-house manufacturing, on a partner-by-partner basis.

The International Organization for Standardization (ISO) standards ISO 14644/14698 (Table 1) and EudraLex GMP Annex 1 served as guiding requirements for the cleanroom setup and operation, as well as for microbial monitoring during manufacturing. Therefore, beginning with the design phase, careful consideration was necessary to determine:

- How the cleanroom would be used
- Where the cleanroom would be located
- The permitted particle concentration
- The manufacturing process requirements
- The cost.

Sorrel sourced and continually engaged with cleanroom consultants in order to review the process and ensure complete compliance with all required standards. Concurrently, it was necessary to liaise with pharmaceutical partners to establish

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

Table 1: ISO 14644-1:2015 cleanliness requirements.

a All concentrations in the table are cumulative, e.g. for ISO Class 5, the 10,200 particles shown at 0.3 µm include all particles equal to and greater than the size.

b These concentrations will lead to large air sample volumes for classification. Sequential sampling procedure may be applied.

c Concentration limits are not applicable in this region of the table due to very high particle concentration.

d Sampling and statistical limitations for particles in low concentrations make classification inappropriate.

e Sample collection limitations for both particles in low concentrations and size greater than 1 µm make classification at this particle size inappropriate, due to potential particle losses in the sampling system.

f In order to specify this particle size in association with ISO Class 5, the macroparticle descriptor M may be adapted and used in conjunction with at least one other particle size.

g This class is only applicable for the in-operation state.

their specific development expectations and pipeline needs. From there, Sorrel began a process of constant knowledge acquisition, application, implementation, and evaluation, to build the facilities that would best serve the needs of both Sorrel and its strategic partners. The result was an ISO-7 level (Grade C, per EudraLex GMP Annex 1) cleanroom integrated within the new manufacturing facility, which also includes a front warehouse, Incoming Quality Control (IQC) lab, washing room, and ISO-8 (Grade D)-rated gowning room.

THE IMPLEMENTATION CYCLE

The ISO provides the guidelines for cleanliness requirements, and according to that the cleanroom classification is set. Throughout the construction and implementation process, consistent monitoring, evaluation, and revaluation was required to ensure that all cleanroom requirements were being upheld. The extensive testing – including smoke tests, air uniformity, recovery tests, microbial counting, and particle counting – were performed to ensure compliance with the highest standards required for implementation. The new facility will exclusively manufacture Sorrel's own fully disposable wearable injectors (Figure 2)

“Making the transition from outsourcing manufacturing to third-party providers to establishing in-house production for clinical trials and commercial output allows for greater control of production and improves device manufacturing processes from both a regulatory and quality perspective.”

for design and development activities, feasibility studies, clinical studies, and commercialised products.

The decision to include the 80 m² cleanroom within the facility enables Sorrel to begin production with a capacity of hundreds of thousands of units per year, with the flexibility to further increase output as necessity dictates. As an ISO-7 class environment, the production cleanroom is specifically intended to reduce particulate and microbial contamination in accordance with ISO 14664-1:2015 and EU GMP Annex 1 requirements, as well as controlling other environmental parameters, such as temperature, humidity and pressure.

One of Sorrel's top priorities in establishing the facility was to focus on the future growth of the company. The decision was therefore made to invest in and build a facility that would be able to support the company's rising production forecasts. In due time, as more sections of

the assembly line are brought online and existing features are changed or upgraded, regulations and standards are to be monitored and internal processes updated accordingly. Thus, implementation is a constant cycle of learning, appraisal, and adjustment. Sorrel's Quality Management System (QMS) certification, granted by a notified body, ensures annual inspection of the implementation process, thus ensuring compliance with up to date cleanroom regulations and company quality policies.

COMPLIANCE IS KEY

Once a cleanroom is up and running, it needs to be meticulously maintained to guarantee its continued integrity. Great care must be taken to minimise contamination risks, including restricting access to a select number of specially trained employees, as well as carrying out constant cleaning, maintenance, and monitoring, with frequent inspection of particulate and microbial matters. This requires intense quality control measures to be implemented and adhered to on an ongoing basis. Any non-conformance or misalignment with the monitoring of the cleanroom environment must be mitigated immediately according to established processes, protocols and corrective actions.

As Sorrel's devices are intended for direct, self-administration of medication by patients, the manufacturing environment requires airborne particle control to mitigate any risk of contamination during the assembly process. All products must therefore undergo further sterilisation via ethylene oxide (EtO) by a certified supplier, after being packed in the cleanroom in Tyvek and blister packages, specially designed for each product (Figure 3).

Making the transition from outsourcing manufacturing to third-party providers (primarily for R&D purposes) to establishing in-house production for clinical



Figure 2: The Sorrel Medical wearable injector platform.

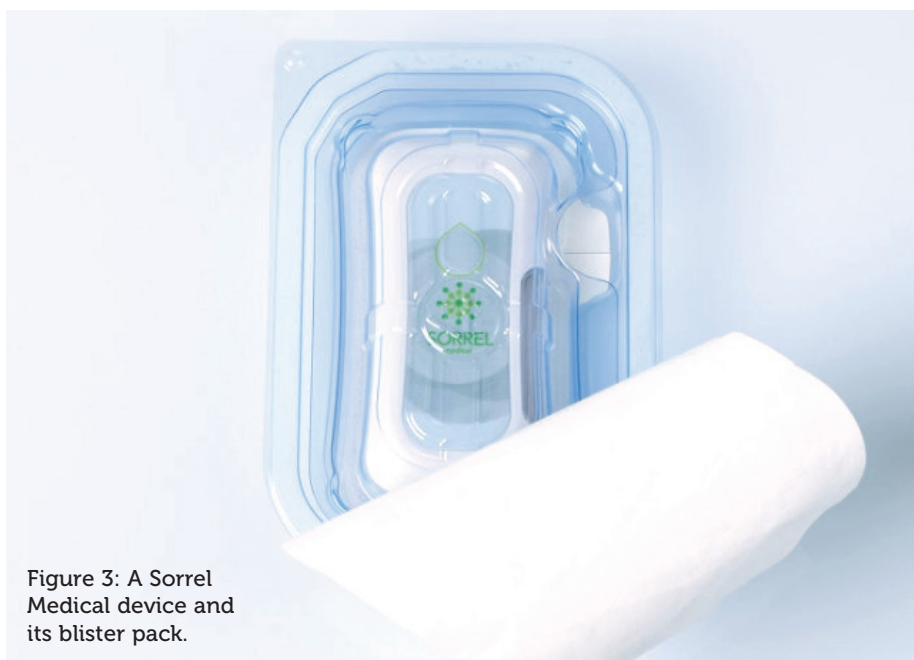


Figure 3: A Sorrel Medical device and its blister pack.

“Establishing and maintaining one’s own manufacturing facility requires significant commitment and demands that the manufacturer is invested in the process on a daily basis. While the challenges involved in this are considerable, the benefits are tangible.”

trials and commercial output allows for greater control of production and improves device manufacturing processes from both a regulatory and quality perspective. With respect to operational and quality considerations, the facility must be of a suitable size, construction, and setting to ensure that cleaning, maintenance, and operations can be performed as stipulated. Additionally, the facility must have adequate space and operational flow design to prevent potential errors and cross-contaminations; surfaces that are easy to clean; and the capability to control temperature, pressure, and humidity. Air within the room is kept at a positive pressure and is HEPA-filtered, environmental conditions are constantly monitored, and all equipment, as well as the cleanroom itself, is regularly cleaned and disinfected to maintain the ISO Class 7 requirements.

All employees need to undergo specific training to understand the importance of behaviour and proper disinfection in a controlled environment. The operation and maintenance of the cleanroom has necessitated numerous additions to Sorrel’s QMS, in the form of procedures,

dedicated work instructions and additional controlled processes, to comply with all the standards and requirements for cleanroom certification. Final accreditations – including Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) – were required to ensure that all components are correctly installed, that the installation meets its design requirements and specifications, and that it operates as intended.

CHALLENGES AND BENEFITS

Establishing and maintaining one’s own manufacturing facility requires significant commitment and demands that the manufacturer is invested in the process on a daily basis. While the challenges involved in this are considerable, the benefits are tangible.

Ensuring that production remains within close proximity to R&D and operations means that all associated activities can be performed in-house. This grants Sorrel considerably more control over processes, as well as facilitating quality assurance, which is required on a continual

basis. Additionally, as a development project nears the design transfer phase (in which the R&D engineers essentially pass the responsibility of the device over to the operations and manufacturing teams), the proximity between the R&D offices, quality team, and manufacturing site proves to be imperative for quick and efficient resolution of any issues that may arise.

Another key benefit that in-house manufacturing provides is a considerable saving of time and resources. In-house manufacturing allows for frequent audits and inspections of the cleanroom to be conducted internally, rather than Sorrel having to audit external suppliers. Additionally, the opportunity to directly manage all manufacturing processes independently eliminates the reliance on, and waiting time for, other contractors, enabling a much faster turnaround for initiating full-scale production.

Finally, having a dedicated and independent facility enables it to flexibly cater to Sorrel’s specific needs, granting Sorrel autonomy to run the production line and develop customised tools and fixtures for production automation to best serve its clients.

The same goes for capacity – if so desired, Sorrel can potentially extend manufacturing to round-the-clock production. The fact that all technicians and lab personnel involved in production are now dedicated Sorrel employees, with a vested interest in the company’s success, engenders greater commitment and professionalism that further enhances quality and productivity. Not only that, but in an industry where partnerships between device manufacturers and pharmaceutical companies are often confidential by nature until commercial launch, having these activities take place within the company’s premises ensures confidentiality is maintained.

INCREASING CAPACITY THROUGH AUTOMATION

Increasing the capacity of a production line is dependent on numerous contingencies, but Sorrel will continuously improve its capabilities with time as production is increasingly automated. High capacity, already achieved through the introduction of both semi- and fully automated tools to assembly lines on a consistent basis, positively impacts the quality and consistency of the entire manufacturing

process. This has already resulted in Sorrel's increased production of higher quality products.

As the company continues to expand, increased manufacturing capabilities will enable Sorrel to support global pharmaceutical and biotechnology partners in bringing the highest quality of wearable drug delivery solutions to patients.

ABOUT THE COMPANY

Sorrel Medical is a medical device development and manufacturing company focused on prefilled wearable, on-body injectors. Its technology platform, based on a robust patent estate, is prefilled and preloaded, and is intended for the subcutaneous delivery of biologics,

biosimilars and small molecules (doses of 1–25 mL). The platform is suited for multiple configurations, molecules, and indications, and is digitally integrated with Bluetooth and NFC connectivity.

Sorrel is one of three privately held companies operating under the Eitan Group, all in the field of drug delivery devices, including Q Core Medical, Avoset Health and Sorrel Medical. Q Core Medical develops and manufactures the Sapphire infusion system, on the market in both hospital and homecare environments. Avoset Health is developing a connected homecare infusion pump, available for pharmaceutical companies in a dedicated application configuration.

The joint experience shared amongst the Eitan Group's three companies includes development, commercialisation and manufacturing of drug delivery products across the continuum of care; multiple US FDA approvals; market presence in over 20 countries; and an R&D team with experience in parenteral drug delivery, accuracy, flow control, human factors and cybersecurity.

ABOUT THE AUTHORS

Bentsi Algazi is the Vice-President of Operations at Sorrel Medical. As such, Mr Algazi oversees all of Sorrel's supply chain, engineering, production, and vendor management activities. Prior to Sorrel, he was Micro-Infusion R&D Site Manager at West Pharmaceutical Services, leading the team responsible for bringing the company's SmartDose® wearable injector to commercialisation. Before joining West, he served as COO at PowerPaper, a developer of micro-electric solutions for cosmetic & RFID applications. He holds an MBA and a BSc in Physics and Mathematics from the Hebrew University of Jerusalem.

Anna Kalika-Rodin is Quality Manager at Sorrel Medical. As such, she leads the company's quality activities and ensures Sorrel's QMS complies with all the latest standards and regulations. Ms Kalika-Rodin and her team are responsible for the company's QMS, documentation, audits, and more. Prior to Sorrel, she worked as a Quality Engineering Team Lead at Q Core Medical, a manufacturer of drug delivery devices. She holds a BSc in Quality Engineering from the Technion-Israel Institute of Technology.

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- **GAIN** insights into the use of wearable injectors and devices in clinical trials

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