Stevanato Group

LEVERAGING INTEGRATION AT EACH PHASE OF A DRUG DELIVERY SYSTEM PROJECT

In this article, Steven Kaufman, Vice-President Drug Delivery Systems, and Adam Stops, PhD, Drug Delivery System Product Manager, both of Stevanato Group, describe how an integrated offering can help customers at each phase of a drug delivery system project.

For more than 70 years, Stevanato Group has been renowned as a leading provider of primary packaging, producing cartridges, syringes and vials to the highest technological standards. The SG Fina, SG Nexa and SG Alba product lines are part of a wide range of glass solutions that embody Stevanato Group's long history of quality and reliability.

Today, as a full-service partner, Stevanato Group provides a suite of products, technologies and services for pharmaceutical companies. Customers can source their glass primary packaging, assess their formulation stability through analytical testing services, select one of the many proprietary drug delivery devices or even develop a new breakthrough device, and have their combination product manufactured to the highest standard using state-of-the-art injection moulding and automated assembly equipment with integrated inspection technologies. As a result of this comprehensive offering, Stevanato Group has established itself as a partner of choice within the industry.

A crucial aspect of Stevanato Group's business model is that customers can access these products, technologies and services independently. This flexibility enables clients who may be partnering with multiple suppliers to engage with Stevanato Group for any phase of their project and benefit from the resources, expertise and knowledge that the group offers within that discipline (Table 1).

However, as more and more primary containers are integrated into drug delivery devices, Stevanato Group's wide range of capabilities provides an advantage for building end-to-end solutions for pen injector, autoinjector, wearable and inhaler projects. By forging deeper partnerships with customers, the full depth and breadth

GLASS PRIMARY PACKAGING	ANALYTICAL SERVICES	CONTRACT MANUFACTURING	ASSEMBLY EQUIPMENT
SG ALBA®	CONTAINER SELECTION	DESIGN & DEVELOPMENT	SUB-ASSEMBLY
SG NEXA®	CONTAINER COMPATIBILITY	PRECISION INJECTION MOULDING	FINAL ASSEMBLY
SG FINA®	DRUG DEVICE OPTIMISATION	ASSEMBLY	PACKAGING & SERIALISATION
		REGULATORY AFFAIRS	
		IP	

Table 1: Customers can access a suite of products, technologies, services and capabilities independently or as a full package, for an integrated, end-to-end solution.

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of Stevanato Group's knowledge, experience and competencies can bring benefits to a project at multiple levels.

BENEFITS OF AN INTEGRATED APPROACH

Having evolved from a producer of pharmaceutical glass to a full solution provider, Stevanato Group understands how a pharmaceutical product, container, closure and drug delivery device interact with each other and work together to form a cohesive system. With this unique perspective, Stevanato Group has the ability to solve problems holistically. The primary container, the design of the drug delivery device and the manufacturing processes can all be optimised in a coherent approach with a common goal of producing a market-leading product.

For example, if a customer requested a design of an autoinjector with a unique technical requirement around dose accuracy, or if they wanted to increase overall cost efficiencies, Stevanato Group could approach this from several different angles:

- Primary container – is it possible to customise the container or adapt production techniques to better suit the new requirements?
- Device design – is it possible to refine the design of certain components?
- Plastic manufacturing – is it possible to tighten moulding tolerances, assembly processes and quality controls?
- Final assembly equipment – which are the critical assembly steps that need to be monitored to ensure device functionality?

As a single entity with control over multiple aspects of a project, Stevanato Group says it can take advantage of technical and commercial synergies. For example, a designer of a drug delivery device will spend a considerable amount of effort on a detailed tolerance analysis to ensure all the plastic components are well toleranced. However, for the most important component – the primary container – there is often a lack of information on process capability and reliability (Cpk and Ppk) because either the information is proprietary and/or the information required is new and unique to the device design. In both cases, the designer is in a compromised position and has to make estimates. This leads to inefficiencies in both device design and project timelines and, in worst case scenarios, can even compromise the robustness of the final product.

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At Stevanato Group, the device designer has access to all the necessary information, including the process performance and capabilities of the glass production line, and can work directly with the glass containers manufacturing team to develop solutions. This also applies to the manufacturing of the device itself: the designer works closely with manufacturing colleagues in Germany and the US who have market-leading expertise in injection moulding, as well as colleagues in Denmark who are world-renowned in automated assembly equipment suppliers. Communication between internal lines of business is transparent and information sharing is fluid. This powerful combination opens the door to smoother projects, more reliable products and improved customer relations.

To further illustrate some of the benefits of this holistic approach, what follows is a description of a typical project flow, according to Stevanato Group's development process. This approach facilitates communication between different departments and functions, so that knowledge, experience and synergies can be maximised for the benefit of customers, their projects and the resulting end products.

DEFINITION PHASE

Regardless of whether a pharmaceutical client seeks to customise a platform product, such as the SG Alina disposable pen injector, or develop an entirely new device concept on demand, the first step is the definition phase. This phase is where ideas, concepts and notions of what a product might be start to take shape. An interdisciplinary team will perform background research, early explorations and experiments which either compare platform device characteristics to customisation requests or – for a new concept – help define gaps in the market, technology capabilities and user needs, which often represent the key drivers for a particular project. This phase may include business case analysis, early technology explorations or other screening exercises.

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The goal before progressing to the next phase is to justify and define the project via preliminary technology risk assessment, intellectual property assessment, manufacturing assessments, and market and business assessments. Although many aspects are preliminary, these foundational activities are essential for providing the team with direction and framing the areas of work for the project.

Even in this early phase, the value of the Stevanato Group's integrated approach can start to be seen. From extensive knowledge in regulatory affairs, to supply chain and manufacturing know-how, to wide product line offerings and industry expertise, the Stevanato Group team can include experts from a wide range of functional areas. This team can help shape the project and identify future risks to be monitored and develop ways for them to be mitigated. At the culmination of this phase, a first draft of the product specifications and definition provides direction of what the product will do, how it will do it and what it could look like – setting the stage for the product performance focused development to come.

CONCEPT AND FEASIBILITY PHASE

The concept and feasibility phase is where the product really begins to take shape. Whilst the exact activities will vary depending on whether the project involves feasibility of a customisation request or concept generation for a new technology,

early shape models, human factors explorations and studies may be performed to start exploring the external design, while laboratory and breadboard prototypes may be built to develop the functional design. Early drafts are created, and early prototypes or models may help visualise the product concepts.

Thanks to Stevanato Group's integrated approach and long-term experience in glass container design and manufacturing, the core project team works in harmony with the internal glass primary container and laboratory teams to leverage the group's broad capabilities. This includes a comprehensive range of technical and analytical services available through its SG Lab (Italy) and its Technology Excellence Center (US TEC) in Boston (MA, US) – supported by a network of collaborations and partnerships with prestigious universities, research institutes and scientific organisations.

With a comprehensive understanding of the science behind glass primary packaging, Stevanato Group has the scientific and technological expertise to support pharma companies from early-stage formulations to device integration. As a direct result of these capabilities, Stevanato Group has devised a line of cartridges specifically for autoinjector, pen injector and wearable programmes. SG Nexa syringes are specifically designed to meet the dimensional requirements of device programmes and provide excellent mechanical resistance.

Highly qualified and experienced specialists can guide clients through the container selection process and optimisation options, while design engineers concurrently provide feedback on how the different container options may impact the device concepts and functionality. SG Lab and TEC provide testing and analytical expertise to support risk mitigation and development efforts. The input from the manufacturing team will be incorporated to ensure a viable scale-up plan.

While the full details continue to be developed in the next phase and changes can continue to be made, this phase ends when the customer agrees on the product concept, feasibility, prototypes and other information needed to deliver the product.

DEVELOPMENT PHASE

Once the selected concept and feasibility have been approved, the team dives into all the project details in depth. The development phase incorporates all the engineering, testing, analysis, refinement, iterations and modifications necessary to ready the product for production implementation.

Common activities during this phase can include laboratory functional testing, early stability studies, usability and formative human factors studies, measurement system development and small prototype production. The design is now fully analysed and detailed to ensure expected function, usability, manufacturability, cost and safety profiles. As product prototypes are evaluated to verify intended functionality and user feedback is incorporated, the designers can close in on final product performance requirements and specifications.

The engineering teams at Stevanato Group have access to a wealth of proven manufacturing and product knowledge and experience to ensure products can be produced and assembled efficiently and reliably at volume. This feedback can inform final design choices and features so that the design and manufacturing approach are iterated together; ensuring smooth technology transfer and manufacturing scale-up in the next phase.

By the end of the development phase, the design is considered frozen. All the product specifications have been finalised, the product is fully defined and the design has undergone engineering verification and formative user studies. Manufacturing plans are written and ready for implementation. Any IP submissions are finalised and the regulatory strategy is locked in.

DESIGN QUALIFICATION AND CLINICAL BATCH PRODUCTION

The next phase of the development is design qualification through verification testing and user validation studies. To enable this, manufacturing processes equivalent to the final production methods are initiated. Typically, these manufacturing methods will use single-cavity tooling and semi-automated assembly methods, depending on the project and the customer requirements. Stevanato Group uses moulds (Figure 1) produced to the highest quality and precision, which are then validated for part-to-part consistency using in-house metrology expertise.

In-house engineering teams also design each element of the assembly line, including part feeding, assembly, labelling and packaging, to ensure the chosen design at this phase can be scaled up to commercial volumes in the future. It is imperative that the choices made at this phase, for both injection moulding and assembly, are made with a view to commercial manufacturing processes. These manufacturing processes are qualified through installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ) protocols, based on a set of robust and efficient protocols, built from a long history of manufacturing.

By leveraging Stevanato Group's integrated capabilities and holistic approach, issues that might arise are immediately investigated and resolved by a team of experts from all functional areas under one

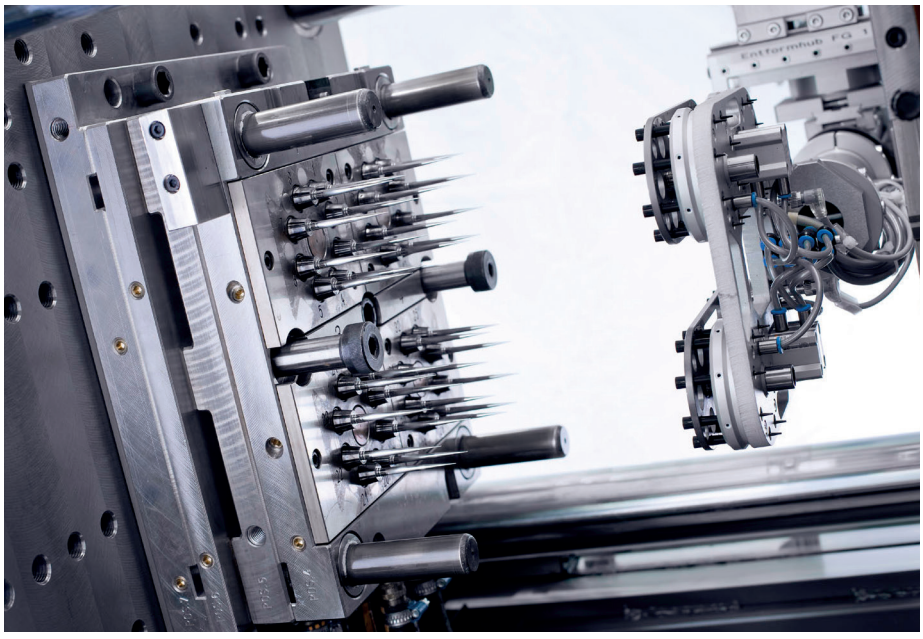


Figure 1: Stevanato Group boasts in-house expertise in tool design and maintenance, providing high-quality and precision moulds.

roof. This is extremely valuable, especially at a time when the pressure to succeed is high.

Following the validation of the manufacturing line, the device is then fully verified through design verification testing following international standard protocols and using in-house testing capabilities. Stevanato Group has invested heavily in device testing capabilities, in both its headquarters in Piombino Dese (Italy) and its primary device manufacturing site in Bad Oeynhausen (Germany).

Upon successful completion of design verification, the device is validated through user studies, including summative human factors studies, depending on the customer requirements – Stevanato Group can perform these activities on behalf of customers or support them during these phases. Subsequently, clinical batches are produced, typically in the range of 10,000 to 100,000 samples, to enable the customer to either perform clinical trial studies or stability testing, depending on the needs of the customer.

SCALE-UP AND INDUSTRIALISATION PHASE

Upon completion of the design qualification and clinical batch production, the focus is on scaling up production for commercial quantities. Commercial tooling and fixtures are commissioned, built and debugged. During this time, process engineers will challenge each operation to monitor critical processes and parameter sensitivities to optimise them for commercial production success. Operators are trained and begin operating the production machinery. Larger scale product verifications are performed to confirm reliability and overcome any issues revealed at scale. The team will revisit earlier risk plans and compare current product performance to support a final determination of safety and appropriateness for use.

By continually building on its contract manufacturing track record that includes over 50 years of injection moulding experience, Stevanato Group uses moulds fabricated to the highest quality and precision which are then validated for part-to-part consistency at scale. In-house engineering teams design each element of the production line, including part feeding, assembly, labelling and packaging. The entire line is laid out, built and then debugged, while overall quality and inspection methods are validated.

Figure 2: Stevanato Group has more than 160 injection moulding machines at three locations in the US and Germany for GMP, ISO 8 and ISO 7 cleanroom production.

As the initial launch lines are finalised, long-term production solutions are concurrently being planned and ramped up. For example, a product may launch with an initial process which produces lower quantities, while a full production line producing five or 10 times the throughput is being built. Stevanato Group has extensive experience in designing, building, programming and qualifying high speed assembly and packaging equipment. With hundreds of installations worldwide, Stevanato Group has become a proven partner for scalable, modular assembly and packaging solutions featuring state-of-the-art inspection technologies.

PRODUCTION PHASE

With the initial launch line validated and ready, the first production batches can be produced. During early production, engineers keep a very close eye on all operations to make sure things are running smoothly and as expected.

Stevanato Group's manufacturing sites in Germany and the US have a combined 16,900 m^2 of controlled and cleanroom production areas (Figure 2) – and those areas are being expanded to make ready for new projects. This includes GMP or Class ISO 5, 7 and 8 cleanrooms, depending on the project requirements. There are over 160 high precision moulding machines managed by production engineers experienced in running up to 128 cavity tooling. With in-house tool shops, tooling experts can maintain, refurbish and repair tools on-site, ensuring production continuity. Additionally, there are over 40 assembly installations in-house, ranging from manual stations to fully automated equipment. Many of these systems are built internally to provide modularity and flexibility for different device projects.

With 24/7 production capability, Stevanato Group's manufacturing sites are accustomed to both high-volume projects and small-scale production. This includes extensive experience in producing low-volume, highly complex products with or without electronics, such as electronic pill dispensers or large-volume plastic components for medical devices. Thanks to its worldwide footprint, Stevanato Group has links to logistic hubs close to its customers' reference markets and can rely on a global platform of suppliers for strategic sourcing solutions.

QUALITY

Rooted deep within Stevanato Group's culture is a commitment to deliver the highest quality products and services to all partners. The company operates an ISO 15378 and ISO 13485 certified quality management system and has a US FDA audited site in Germany. Additionally, the US operations are compliant with FDA design controls, including the requirements set out

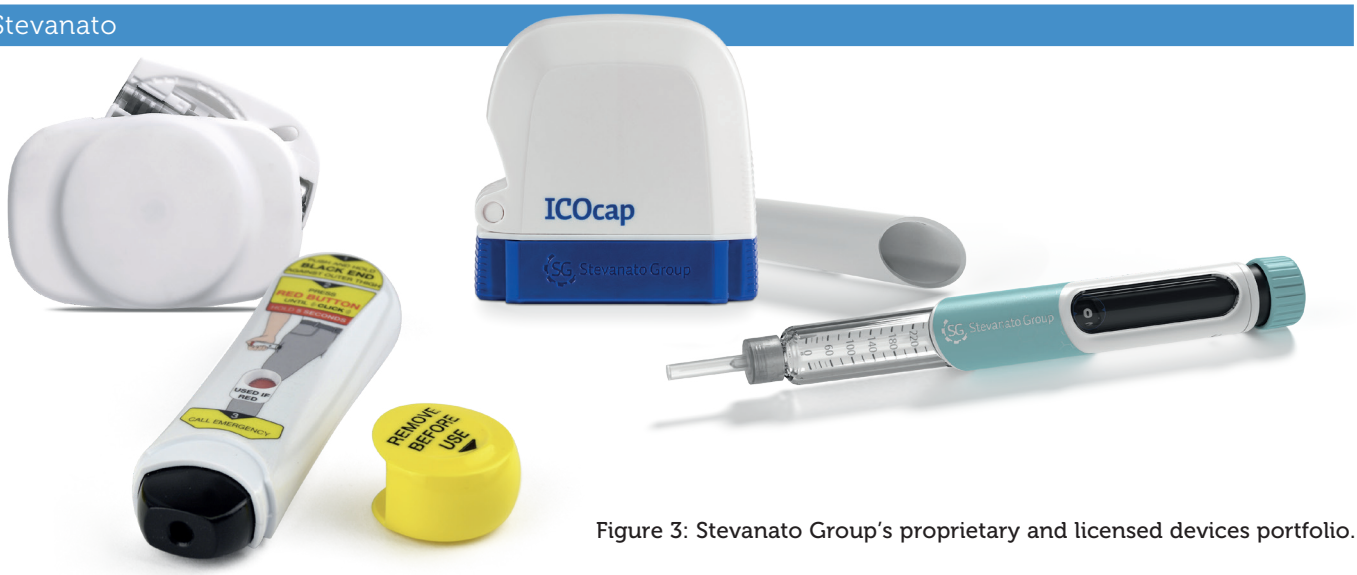


Figure 3: Stevanato Group's proprietary and licensed devices portfolio.

in 21 CFR Part 820.30. Product and process quality, risk management and user feedback are at the forefront of all decision making.

CONCLUSIONS

Through its comprehensive range of products, technologies and services, Stevanato Group has the capability to support pharmaceutical companies in taking their medical device projects from concept to launch. Its business model enables customers to access the products, technologies and services required or opt for a full end-to-end solution where all the benefits of Stevanato Group's integrated offering come into play.

Many pharmaceutical companies are attracted to the reduced overheads required to manage an integrated solution provider. This can be a significant advantage for smaller biotech firms that do not have the internal capacity to oversee various aspects of the project and co-ordinate multiple suppliers. Even for larger organisations that do have these resources, there are many benefits to a simplified supply and distribution chain.

By implementing a proven, methodical project management process, Stevanato Group leverages the synergies and knowledge from different lines of business to deliver the best possible solutions for customers. Any challenges can be handled efficiently by a single entity which sees the full picture and can solve problems from multiple angles.

Stevanato Group continues to invest in integrated solutions for contract manufacturing and in collaborations with industry partners to expand its portfolio of devices (Figure 3), including through licensing and collaboration agreements. Examples of this approach include a partnership and collaboration agreement with Duoject Medical Systems (Quebec, Canada) for the promotion and contract manufacture of Maverick, an emergency-use autoinjector; an exclusive agreement with Haselmeier (Stuttgart, Germany) related to its Axis-D technology for the development of SG Alina, a pen injector for diabetes care with support from Cambridge Design Partnership (Cambridge, UK); and ICOcap, a licensed inhaler from Iconovo (Lund, Sweden) for asthma and chronic obstructive pulmonary disease (COPD). SG EZ-be POD is a proprietary wearable device developed in-house. These examples illustrate the power of Stevanato Group's integrated approach and growing capabilities, as well as the flexibility and willingness to incorporate strong outside contributions to supplement and leverage internal capabilities to build class-leading devices for patients.

As an experienced partner serving internationally recognised pharmaceutical, diagnostic and medical companies, Stevanato Group is fully committed to providing the best combination of products, technologies, services and capabilities for an integrated solution, under one point of contact.

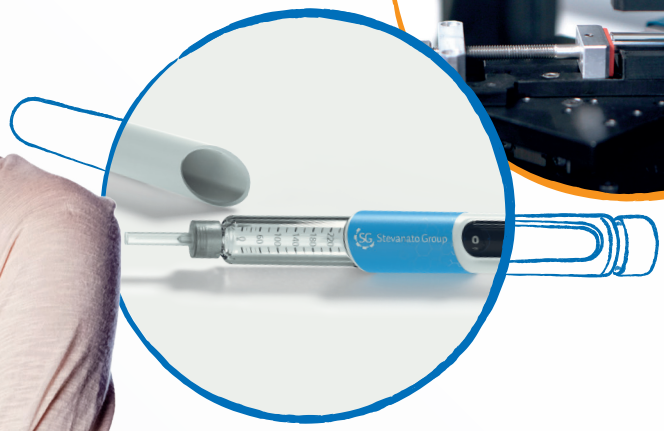
ABOUT THE COMPANY

Established in 1949, Stevanato Group is the world's largest, privately owned designer and producer of glass primary packaging for the pharmaceutical industry. From its outset, the group has developed its own glass converting technology to ensure the highest standards of quality. The group comprises a wide set of capabilities dedicated to serving the biopharmaceutical and diagnostic industries: from glass containers with its historical brand Ompi, to high-precision plastic diagnostic and medical components, to contract manufacturing for drug delivery devices, to vision inspection systems, assembly and packaging equipment. Stevanato Group also provides analytical and testing services to study container closure integrity and integration into drug delivery devices, streamlining the drug development process. Thanks to its one-stop-shop approach, Stevanato Group is able to offer an unprecedented set of solutions to biopharma companies for a faster time to market and a reduced total cost of ownership.

ABOUT THE AUTHORS

Steven Kaufman is Vice-President, Drug Delivery Systems at Stevanato Group, responsible for managing business development, proposal management and project management as well as strategic initiatives in the group's drug delivery systems business. He has been active in the drug delivery device field for more than 15 years, working with leading multinational biopharmaceutical companies to provide pen injectors, autoinjectors and wearable injection systems, as well as test equipment, assembly equipment and final device assembly services.

Adam Stops, PhD, is Drug Delivery Systems Product Manager at Stevanato Group, managing autoinjectors, prefilled variable and fixed-dose pen injectors, large-volume wearable injectors and inhalers. With a PhD in mechanical engineering and an MBA in business management, Dr Stops has broad experience in the design, development and product management of devices and parenteral products. Throughout his career, he has worked with innovative multinational companies, leading teams of experts in device research, design and industrialisation.



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