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ACCELERATING NOVEL THERAPIES TO THE CLINIC – CUSTOM SOLUTIONS

In this article, Asmita Khanolkar, a Senior Director at SMC Ltd, discusses the key offerings necessary to accelerate "speed to clinic" for custom manufacturing solutions.

Pharmaceutical trends today are shifting towards targeted therapies, precision medicine and personalised treatment for smaller patient populations. With the growth of novel therapeutics, "speed to clinic" is more critical than ever. These novel therapeutics target a more specific indication, resulting in a smaller potential market. The overall revenue projection, along with available clinical study patients, are reduced – as seen in markets for oncology.

The formulations involved are more complex biotherapeutics, and large yet fragile molecules pose many unknowns and uncertainties throughout development. Bioavailability and immunogenicity are often not well understood, which means multiple iterations for therapy optimisation. In addition, delivery of these formulations is difficult, as they are often non-Newtonian or high viscosities and require custom high-pressure primary drug containers and devices. This requires flexibility to support adaptive and flexible sterile manufacturing towards an integrated approach for a path from development to small-batch manufacturing and commercialisation that can save time to clinic.

PHARMA SUPPLY CHAIN

The pharma supply chain still overwhelmingly represents the legacy needs of large-scale launches of blockbuster drugs with more "off-the-shelf" delivery options. In contrast, novel therapeutics often require customised delivery solutions for more targeted therapies. This gap or lack of alignment can increase the time required for development of novel therapeutics.

> "Novel therapeutics often require customised delivery solutions for more targeted therapies."

The unique combination of skills and expertise of the SMC Group (SMC Ltd, Oval Medical Technologies and Cambridge Pharma) aligns with the need for delivery customisation and results in reduced time to clinic for challenging novel therapeutics. With the combined offerings of SMC, Oval Medical and Cambridge Pharma, a portfolio of integrated services is provided – from the exploratory, preclinical stage through to clinical development and registration – to help accelerate the combination product development process from early stages onwards.

This includes formulation characterisation, drug product compounding, drug scale-up, innovative drug delivery device autoinjector platforms, animal testing, human factors studies, clinical sterile fill-finish and commercial

> "Speed to clinic is more critical than ever for novel therapeutics due to potentially reduced market sizes."

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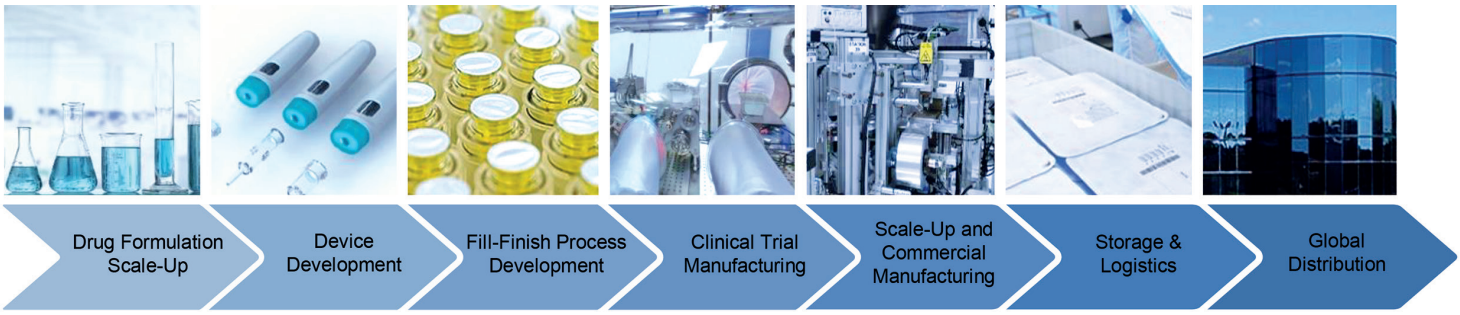

Figure 1: Integrated manufacturing from early research to commercial launch.

manufacturing (Figure 1). Speed to clinic is more critical than ever for novel therapeutics due to potentially reduced market sizes, which impacts both return on investment and available clinical study patients – but, more importantly, the need to bring critical solutions to patients faster.

The following are the key offerings necessary to accelerate speed to clinic for custom manufacturing solutions:

- Vertically integrated development and manufacturing services to iterate quickly and cost effectively and avoid lengthy delays later in the development cycle.
- Enabling drug delivery solutions that can help early characterisation of formulations for optimised delivery of novel therapies.
- Small-batch manufacturing flexibility from clinical trials to commercial scale-up
- State-of-the art facility for GMP fill-finish with flexibility to handle legacy and customised delivery solutions for novel therapies.
- Specialised isolator equipment and filling experience to optimise fill-finish while maintaining container closure integrity (CCI) for challenging formulations.
- Experience providing solutions for challenging formulations including high viscosity, suspension and non-Newtonian fluids.
- Dedicated process development laboratory for process engineering solutions.
- Analytical laboratory solutions for test-method development and stability studies.
- Broad expertise across multiple facets of regulatory, clinical and commercial strategy.

SMALL-BATCH MANUFACTURING

Small-batch manufacturing requires flexible filling processes and innovative equipment that can handle a range of primary drug containers, including prefilled syringes and custom-designed vials and cartridges. Fast, flexible fill-finish isolator-based filling suites including qualified person (QP) release set-up is needed for handling small batch sizes ranging from 100 units to 10,000 units.

In contrast to dedicated high-volume lines, small-batch manufacturing requires flexibility for changeovers. However, due to the complexity of these formulations, there may be conflicting requirements for specialised equipment. Thus, the need for innovation through single-use systems, automation, non-contact processing, robotic inspection and CCI testing (Figure 2).

Novel therapies, including biotherapeutics, have special manufacturing needs and may need special processes developed for drug compounding, scale-up and fill-finish processes. Different pump technologies and fill methodologies can help tailor filling suitable to the drug. Depending on the application, peristaltic pumps for use with sensitive products like biotherapeutics and contact-free or single-use applications, for example, versus rotary piston pumps and special heads, which are suited to highly viscous formulations. Separately, optimisation of aseptic drug filling, stability, storage and delivery profiles for custom devices while maintaining CCI requires significant process mapping steps. In addition, quality control (QC) and analytical test methods for biotherapeutics need significant development (Figure 3).

Adaptive manufacturing is a strategy that supports customisable processes and adjustments as the process is developed and unknowns of novel formulations are revealed. A true adaptive manufacturing process can enable adjustments to improve quality at each step as the process is developed from lab scale to GMP scale. For custom primary drug containers,

Figure 2: Small-batch sterile manufacturing.

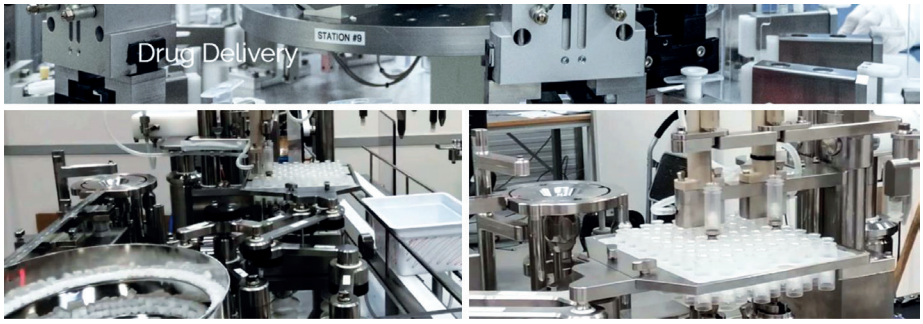

Figure 3: Speciality processes.

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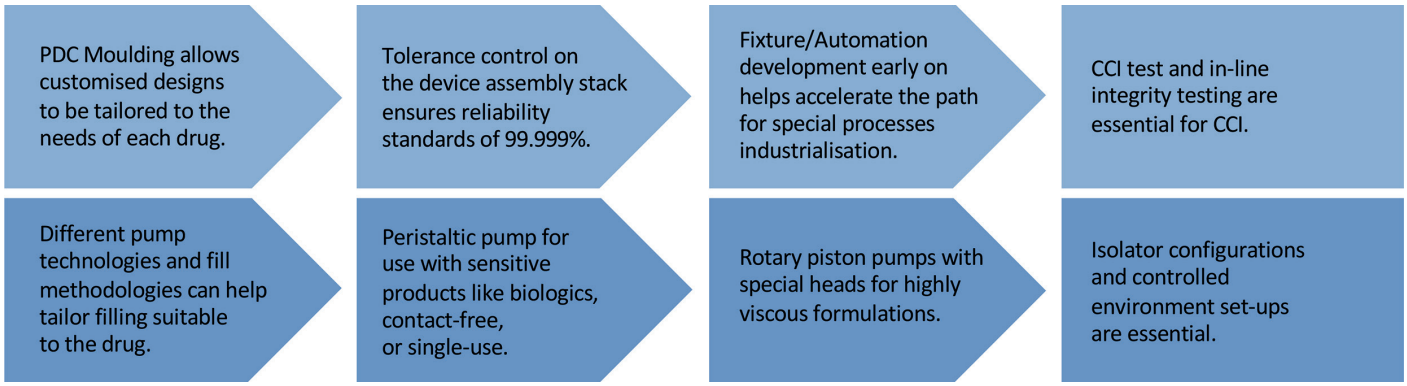


Figure 4: True adaptive manufacturing from start to finish.

mould design and tolerances can be adjusted to meet the needs of the drug. Flexible isolator configurations and controlled environment set-ups are essential for developing GMP similar processes from the beginning (Figure 4).

BROAD TECHNICAL EXPERTISE

Alongside the GMP manufacturing facility, process engineering laboratory and analytical laboratory capabilities allow the experienced scientific team to carry out process development work, analytical method transfer and validation, QC release and stability testing and, if required, QP certification to clinic. This type of process development work requires a holistic cross-functional approach and broad expertise looking at various facets of development and streamlining.

It is time consuming and challenging when engaging with multiple different suppliers and many items are missed at process hand-offs and interfaces. A single source partner with in-house expertise to support novel drug development from pre-clinical to commercialisation eliminates any fragmented approach and streamlines development. Process engineering and development information is leveraged for clinical production to eliminate risks early on, which reduces time to clinic (Figure 5).

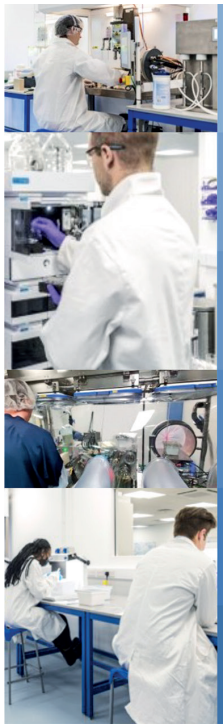
CUSTOM IS THE NEW NORMAL

Novel formulations require characterisation for various aspects of drug filling, storage and delivery. Early characterisation at the start of a project eliminates lengthy delays at later stages in the programme (Figure 6).

STATE-OF-THE-ART FACILITY

The regulatory requirements landscape for GMP facilities is stringent and newer facilities have to meet the latest requirements for compliance as well as sustainability. Cambridge Pharma has state-of-the-art facilities with optimised material and people flow. Two filling suites are available for flexible small-batch manufacturing, including a clinical isolator line and a commercial semi-automated isolator line.

> "Continuing trends from hospital to home treatment have changed the clinical trials landscape."



Formulation	• Bulk vessels per capacity, Reusable versus single-use • Impeller options for homogeneity and sensitive products • Special requirements shelf, filtration, inert gas head space
Filling Process	• Filling process development for new formulations • Standard versus custom PDC development • Stopper position control for downstream assembly
Container Closure	• Closure system selection for custom device and process • Validation of closures including stability/shelf life • Inspection; CCI method development
Sterilisation	• Sterilisation strategy development • Bio burden and sterility assurance planning • Control of primary hermetic closure
Final Assembly	• Assembly steps must not compromise container closures • Sub-assembly drug paths must maintain sterilisation
Secondary Packaging	• Secondary packaging development to align with sterility • Sterile seals identified and validated • Stability/shelf life determined

Figure 5: Streamlined process development interfaces.

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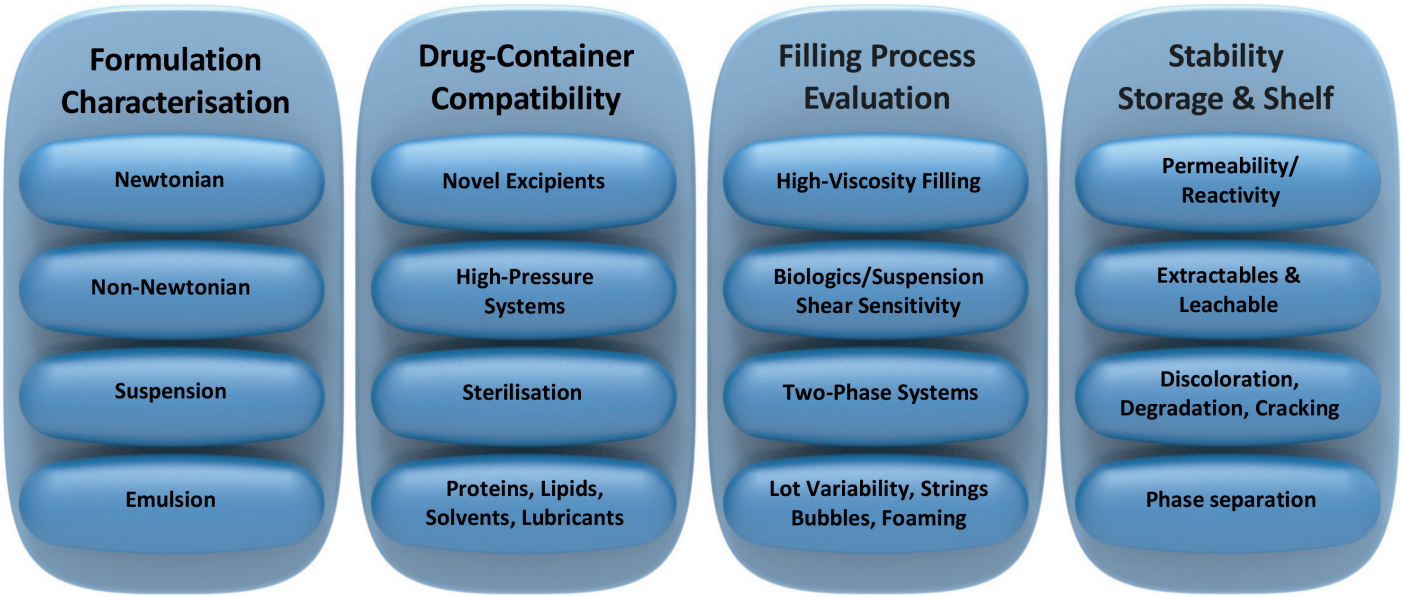

Figure 6: New drug formulation considerations.

Not only do the suites have innovative cleanroom control systems, enabling real-time monitoring and energy-efficient heating, ventilation and air conditioning systems, but they are also controlled separately so the suites can be operated independently.

NEW LANDSCAPE FOR CLINICAL TRIALS AND REGULATORY PATHWAY

Continuing trends from hospital to home treatment have changed the clinical trials landscape. This is driving the industry to focus more on the self-administration of therapies and the need for devices in clinical studies earlier in the cycle. The cost of therapy is also lower when delivered at home rather than in a hospital setting, which puts additional importance on speed to market. New regulatory pathways allow faster avenues for breakthrough therapies and emergency use. This means less time to commercially scale and a shorter development cycle.

In summary, as a single-source supply partner with small-batch manufacturing capabilities, SMC can substantially improve speed to market and de-risk programmes. A state-of-the-art facility with innovative equipment and systems provides the specialised systems needed for novel therapies. In addition to a GMP facility, a process development and analytical lab provides an adaptive manufacturing model and increases speed to clinic.

ABOUT THE COMPANY

The SMC Group comprises SMC, Oval Medical Technologies and Cambridge Pharma. The group provides end-to-end integrated services for clinical and commercial manufacturing of combination products for drug delivery.

SMC, with more than 35 years of experience, provides product services from initial concept through to the final packaged device, including programme management, design and development, product manufacturing, clinical/commercial manufacturing, electronics integration and global supply chain management. SMC has global GMP manufacturing sites in the US, the UK, Costa Rica and India.

Oval Medical Technologies specialises in the development of patient-centric autoinjectors that meet the most challenging requirements arising from diverse patient groups and novel drug formulations. Oval's technology platforms can be customised to deliver a wide range of drug formulations, including fragile molecules and biologics for both subcutaneous and intramuscular injection with high viscosities and large volumes. Oval's patented primary drug container technology provides the design freedom to create truly optimised devices for patient benefits.

Cambridge Pharma specialises in pharmaceutical services, sterile fill-finish batches for a range of presentations, including its own primary containers, as well as syringes, cartridges and vials with the highest standard of quality to ensure sterility assurance. It can work with a wide variety of formulations including small molecules, proteins, peptides and biologics. Its flexible, broad service offers clients development of the fill-finish process including CCI method development and testing, analytical methods for QC release and stability testing. The company provides fast and flexible services to meet clinical and commercial critical deadlines.

ABOUT THE AUTHOR

Asmita Khanolkar has a master's degree in Materials Science & Engineering from Worcester Polytechnic Institute in Worcester (MA, US). With more than 25 years of manufacturing experience, specialising in the medical device and pharmaceutical industry, she has managed various device projects from concept to commercial launch. Her product portfolio includes single-use, wearable and implantable devices, drug-device and device-biologic combination products for drug delivery, biotech, biotherapeutics and pharmaceutical applications. Ms Khanolkar has held various engineering and management roles in new product development, manufacturing engineering, advanced quality planning, operations, supply chain and product lifecycle management.

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