CAMBRIDGE PHARMA
An SMC Ltd. Company

Precision Medicines and the Manufacturing Challenges for the Pharmaceutical Industry

Biopharmaceuticals are generating a paradigm shift towards treating many conditions by targeting patient population subgroups. This shift is bringing precision medicine closer for many patients.

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INTRODUCTION

The development of biomarkers has enabled the differentiation of phenotypes and identification of patients suitable for specific targeted therapies. The US National Institute of Health calls personalised medicine "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." Precision medicines are a step removed from personalised medicines, but do target small patient populations that have a common cause in complex conditions like cancer.

There are many drugs on the market for which biomarkers have aided the development of specific treatments for cancers, including Herceptin for the treatment HER2-positive breast cancer, Keytruda for the treatment of advanced melanoma, Opdivo for the treatment of advanced non-small cell lung cancer and Lynparza for the treatment of advanced epithelial ovarian cancer.

More recently drugs for the treatment of severe asthma which affects only 5% of asthmatics have been launched including Nucala, Cinqaero and Fasenra.

In recent years, the trend has been towards a dominance of biologics in pharma pipelines, and there is also a growing trend towards precision medicines for smaller, targeted patient populations, which provide better outcomes for patients. Moreover, many of the current top selling drugs are biologics. Of the 10 top-selling drugs in the US in 2018, 8 were biologics as were 13 of the top 20. This accounted for over 85 per cent of the

revenue of the top 10 and 72 per cent of the revenue of the top 20 respectively.

In 2016 of the projects in clinical development, 822 were determined to be covered by an orphan drug designation awarded by the FDA. These medicines treat populations of 200,000 or fewer, examples include ALS (amyotrophic lateral sclerosis) and cystic fibrosis. 17 percent of Phase III projects and 22 percent of projects undergoing regulatory review by FDA, fell into this category. *

Many of these new medications are first in class and will treat conditions in areas of previously un- met need and distributed across many therapeutic areas from cancer, cardiovascular disease, and neurology. For example, in 2016, 739 clinical development projects were in neurology alone, including 143 in Alzheimer's disease, 67 in Parkinson's disease, and 29 in ALS (amyotrophic lateral sclerosis, or Lou Gehrig's disease.1

These medicines developed for small patient populations are dominated by biologics and will result in low annual production demands but will command high prices and generate substantial revenues.

During the pandemic there has been a need to take many treatments to patients, as hospitals have had to cope with COVID and many patients were reluctant to go into hospital for routine treatments, for fear of becoming infected. This change has made health care providers aware that there are many benefits to getting treatments out of hospital settings, including reduced costs and this philosophy is expected to continue post-pandemic.

Pharmaceutical companies will have to react to this change in the market and consider home treatment regimens wherever possible. Many pharmaceutical companies are already looking at moving treatments from hospital into the home and we are seeing this strategy being implemented as part of product life cycle management for marketed drugs. At-home treatments are not only cost effective for health care providers, but they are also widely preferred by patients.

These shifts will have many benefits for patients but will prove challenging for pharma companies. Biologics can be difficult to formulate, since they are comprised of large molecules and formulations can be highly viscous and delivered volumes can be high, to achieve the therapeutic effect. Since oral administration is not possible, most of these formulations require aseptic manufacture and must be must be administered via the sub-cutaneous or intramuscular routes. New delivery technologies will be needed to provide the best possible patient experience and small patient populations will require flexibility in manufacturing especially with respect to sterile small batch fill-finish processes.

Products already in R&D pipelines include difficult to deliver formulations. Biologics, especially gene therapies are large fragile molecules that are administered either by the subcutaneous or intramuscular routes. Formulations containing large molecules can be very viscous or must be delivered in larger volumes than those typically injected by the subcutaneous or intramuscular routes. New formulation technologies are available that allow up to 10 mL to be administered subcutaneously, avoiding the need for infusions. Halozyme's Enhance technology is being adopted by several pharma companies and marketed products are available that involve high volume sub-cutaneous injections (> 3mL).

Developments in autoinjector technology have been made that enable the delivery of volumes of up to 10mL and can also deliver very high viscosity formulations including gels and suspensions. Injections are preferred by many patients as an alternative to infusions and Pharma companies are turning their attention to higher volume injectors for administered volumes of up to 10 mL

1 The Biopharmaceutical Pipeline: Innovative Therapies in Clinical Development- Analysis Group

This trend towards the development of drugs for small patient populations is driving the demand for small batch fill finish manufacture, not just for clinical trial supplies but also for commercial manufacture. Small batch sterile fill finish requires flexible filling processes that can handle a range of primary drug containers including prefilled syringes and custom designed vials and cartridges. Dedicated filling lines for small batches and relatively low annual sales volumes of less than 2 million units per year, are not a cost-effective way forward for pharmaceutical companies, given the associated capital investments and expertise required.

Where a product range may contain, very viscous formulations and suspensions, broad expertise in fill finish process development is required. These developments when only needed periodically can prove challenging and can lead to extended development times. The development of flexible equipment and the related fill finish processes requires specific expertise, that can be difficult for companies to maintain for periodic developments.

Pharma companies will have to address these issues to take full advantage of the innovations in precision medicines and to provide their patients with new products that can be administered at home. Success in building flexible manufacturing for fill finish will allow companies to remain competitive in this changing market.

SMC GROUP

The SMC is a global services provider helping Life Science innovators. Our world class drug delivery technologies and manufacturing solutions support our customers to develop and launch successful pharmaceuticals, biologics, diagnostics, and medical devices.

We have built an advanced range of technologies and capabilities offering precise quality combined with flexibility and security. We are dedicated to enabling a better and faster customer journey from product development to patient.

SMC Group has developed a business model that utilises the strengths of its three associated companies to provide both new technologies in drug delivery and contract pharmaceutical development services to provide a full end-to-end solution for our customers.

The group consists of Oval Medical Technologies Ltd, that designs and develops drug delivery devices; SMC Ltd Contract manufacturing which has wide experience in the manufacture and assembly of device components and the integration of filled drug containers into a final device; Cambridge Pharma Ltd provides full pharmaceutical development services.

The group provides the documentation required for IND and NDA applications and the established Programme Management Office provides a single programme manager to plan the programme with your teams and to manage the programme to keep your clinical trial and NDA applications on track. Programme slippage inevitably occurs at company interfaces and this single programme approach can save time to market and hence increase competitive advantage and increased revenues.

OVAL MEDICAL TECHNOLOGIES LTD.

Oval Medical 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 approach is built around two key areas; establishing a deep understanding of the cognitive, physical and emotional needs of each patient group; and the comprehensive characterization of formulation behaviors under a range of conditions. With Oval's experience in developing novel primary drug containers, which enables true design freedom, this approach allows us to customize our advanced autoinjector technologies to create truly optimized devices which drives patient choice and sustainable competitive advantage.

As more treatments are moving from clinic to home, it is becoming more important for drug delivery devices to be simple and intuitive to use. Elimination of user errors will make treatments more effective. Health care professionals, treating patients at home, want

to minimize the time to deliver treatments and therefore the fewer the number of steps required to deliver the treatment, the better the device will be accepted by HCPs.

Oval's design approach is to study the potential user group to determine the best possible user interface for the delivery device. In addition, we characterize the formulation, which enables the device design to be optmised in terms of, injection force, delivery time and needle gauze for a formulation of a given viscosity. This characterization is undertaken in parallel with user group research, at the early stages of a programme. Animal injection equipment can be provided such that PK studies can be undertaken while replicating the clinical delivery performance. This service is particularly useful for very viscous formulations and suspensions, where bolus shape and surface area impact PK.

Oval has developed device platforms and technologies that enable a range of intramuscular and subcutaneous presentations to be optimised for the route of administration for a range of formulation viscosities and delivered volumes, for both subcutaneous and intramuscular administration.

SMC LTD.

is a contract manufacturer that is focused solely in manufacturing product for the healthcare industry. Our teams specialize in

Autoinjector Platforms

Subcutaneous

Intramuscular

ArQ®

ArQ®-Bios

ArQ®-Vita

Low-Medium Viscosities
< 100 cP
0.5 – 3 ml

Low-Medium Viscosities
< 100 cP
3 – 10 ml

High - Ultra-High Viscosities
< 100 – 10,000 cP
0.5 – 3 ml

0.5 – 3 ml

launching medical devices, diagnostic product, and drug delivery devices. We work with our customers closely to review the design of the devices in respect to molding, tooling, and assembly to ensure the design is as robust as possible in production. Our service offerings have been established to ensure we offer as much value to our customers as possible. In addition to molding and assembly, we offer handling of drug product, final kitting and packaging.

For Oval's devices, SMC produces the device components and undertakes the manufacture of device subassemblies. For the US market SMC integrates the primary drug container with the autoinjector and can provide final packaging and shipping.

CAMBRIDGE PHARMA LTD.

CPL specialises in filling liquid formulation batches of circa 100 to 15,000 units for a range of presentations, including syringes, cartridges and vials with the highest standard of quality to ensure sterility assurance. We can work with non-active biologics and small molecules including cytotoxics. Our high-quality flexible service offers customers development of the fill finish process including analytical methods development for QC release and stability testing. We can accommodate non-standard primary drug containers and we can also develop and validate container closure integrity testing and provide 100% testing of filled batches. We operate a fast and flexible service to meet your clinic critical deadlines.

Our staff are experienced in the development of fill finish processes and can meet the challenge with difficult to fill formulations and we have the equipment and facilities designed for smaller flexible manufacturing runs. Specialising in this service ensures that development timelines can be minimised, and cost savings can be made by our customers.

Our QC department has experienced analysts that can develop and validate test methods and can receive and upgrade methods for early clinical trials supplies manufacture and stability testing.

Our teams will provide reports required for CTX and IND applications and our QPs can release product for your clinical trials.

We can provide scale up and technology transfer for commercial supply or we can supply low annual demand for sales of up to 2 million units per year.

ABOUT THE AUTHOR

Barbara Lead is the CEO of Cambridge Pharma Ltd and Oval Medical Technologies. Barbara has held senior positions in three Pharma Companies and has experience in the R&D and Industrialisation. Working in the field of asthma and allergy she has experience of working with many drug device combination products and in solving manufacturing and design issues with drug delivery devices.

" Over many years I came to realise the importance of good device design, risk assessment and human factors in the development of delivery devices to ensure effective drug delivery and correct use by patients. Oval aims to provide Pharma Companies with innovative delivery devices for precision medicine and SMC Group can provide an end to end solution for parenteral drug device combinations".

SMC Group can provide end to end solutions for delivery device development, fill finish process development and fill finish for clinical trials. The group also has the capability to provide market supplies for products sales of up to 2 million units per year. This capacity is likely to increase over the next few years.
This service solves the problem of developing flexible inhouse fill finish for small annual demand and the investment risk can be outsourced unless and until product sales can justify internal investment. Visit us at **www.smcltd.com**, **www.ovalmedical.com** and **www.cambridgepharma.com** .

SMC Group

Thank you