A "KODAK" MOMENT FOR THE PHARMA INDUSTRY?

In this article, Pari Datta, PhD, Senior Innovation and Research Consultant, and Nick Rollings, CEng, MIMechE, Consultant Medical Device Engineer, both of Cambridge Design Partnership, discuss the concept of personalised medicine, with particular reference to oncology, and how it represents both an opportunity, for those who can solve its manufacturing conundrums, and a threat, for those who find themselves unable to adapt to a changing therapeutic paradigm.

The pharmaceutical industry we know today began with the synthesis of early, simple medicines. Pharma companies such as Merck and Bayer originate from individual pharmacies, the dye industry and fine chemical companies that started to bulk manufacture antiseptics and painkillers. The second industrial revolution made mass production of medicines possible – a development that has lasted to the present day, with antibiotics still manufactured in batches of hundreds of thousands to treat vast numbers of patients.

As the pharma companies grew, they moved away from broad portfolios of consumer products to the first mass-market pharmaceuticals such as insulin and penicillin. Several decades later, the idea of the blockbuster drug became key to many pharma companies – they began to look for drugs that could make US$1 billion per year, such as Tagamet (cimetidine) and Prozac (fluoxetine).

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ONE SIZE FITS ALL

As a blockbuster, Prozac was a wonder drug that could treat millions of people. It was taken by 40 million people across 100 countries at its peak, adopting a "one size fits all" approach that was the mainstay of the pharma industry for decades. Despite this approach being used for decades, increasing insight in the genomic era since 2000 identified that certain therapies will only work for certain sub-populations of patients, depending on the presence of specific genes in a patient's genome.

The "one size fits all" model has been a particularly thorny issue in oncology. Small-molecule chemotherapy drugs, such as platins and taxanes, are only effective on some cancers and specific patients, whilst causing extensive side effects. The term "personalised medicine" has arisen over the past 20 years – because one size does not, in fact, fit all, especially for cancer therapies. The classic example of this has been the monoclonal antibody Herceptin® (trastuzumab), which is only given to patients whose tumour over-expresses the HER2 gene.

There has been a boom in gene targets that can be used for drug selection in the same way, empowered by our greater understanding of the human genome. Resulting companion diagnostic tests now enable clinicians to prescribe the correct drug first rather than taking an empirical approach.

STRATIFIED MEDICINE

"Stratified medicine" is a term that has been used for the last decade. Whilst not truly "personalised" for individuals, the latest generation of cancer therapies is now heading towards treating specific individuals in an 'n=1' scenario rather than groups of people in the traditional 'n=millions'."

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approach identifies a specific but smaller sub-population of patients that can be treated by specific therapies. With Herceptin for instance, in the 20-30% of breast cancer cases that are HER2 positive, the benefit is that the therapy will be particularly effective against their specific form of cancer. Such biologic-based therapies with high specificity work for highly specific patient groups whilst still enabling blockbuster-type revenues. However, manufacturing challenges associated with biologics mean that they still need to be manufactured in relatively large volumes to make the economic unit costs acceptable.

TOWARD PERSONALISED MEDICINE

The latest generation of cancer therapies is now heading towards treating specific individuals in an "n=1" scenario rather than groups of people in the traditional "n=millions". Advanced therapies (ATs), such as cellular therapies, are being developed for multiple conditions, from neurological to ophthalmological, with nearly 50% of therapies in the pipeline for cancer treatments based on immune and blood cells.

Some cellular therapies are allogenic therapies, where immune cells are taken from one donor, manipulated and then administered to many patients. In some ways, these therapies can be treated like traditional biologics – scaled up using fairly standardised methods and cryopreserved until they are required. There are some challenges with preserving these over a long shelf life, but the model is still relatively scalable, and therefore pharma originally favoured this approach based on traditional biologics. Specific challenges remain, however – scale up, for example, is still not as straightforward as merely increasing the bioreactor volume, as cell lines can exhibit differing behaviour at larger volumes. As another example, there are challenges in controlling agitation rates in larger fermenters, which can damage cells – yet cell function and quality is crucial to preserve product efficacy.

A second category of therapies is autologous cell therapies. These therapies require harvesting of cells from each patient, processing them and then returning them to the patient with modifications – making the body more capable of fighting a particular disease or condition. Recently approved chimeric antigen receptor T-cell therapies, such as Kymriah® (tisagenlecleucel, Novartis), involve modifying T-lymphocytes (T-cells) from a patient to provide them with the ability to detect malignant B-cells within blood-based cancers. The modification involves the use of viral vectors to alter the genome of the T-cells to express an altered receptor (chimeric) to target CD19 proteins, which are expressed in malignant B-cells in blood-based cancer. The key advantage of autologous therapies over allogenic therapies is there will be no immunologic reaction, as the cells are sourced from the patient. Despite the manufacturing challenges, autologous therapies have become popular, with multiple candidates in development.

Autologous therapies form the majority of cellular therapies undergoing clinical trials. Kymriah® was approved last year to treat B-cell acute lymphoblastic leukaemia in young people whose cancer has either recurred or always been resistant to other therapies.

RESULTING CHALLENGES

With the emergence of autologous ATs, pharma companies are less acting as a mass manufacturer of medicines, but rather as a solution provider enabling the modification of cells. The resulting challenge here is scale-out rather than scale-up, whereby one manufacturing batch treats one patient and not whole populations. Cells must be initially harvested from each patient individually. The harvested cells require careful handling as they are patient specific and cannot be replaced during processing. The cells must then be transported to a cGMP-compliant facility, without suffering damage or disruption during transportation. At this location, the cells are modified within aseptic processes by highly skilled scientists. The cells are then stored before being transported back to the patient's bedside within the hospital, where they are infused back into the patient. Transport is vital to both harvesting and re-administration to the patient, so conditions must always be monitored and samples tracked. Sterility and traceability to the original patient is key at all stages of the process.

It is therefore no surprise that manufacturing autologous therapies is expensive. Kymriah® has been priced at $500,000 per patient, which is a large cost despite the resulting value – completely curing a patient's cancer – being clear. It is easy to see where the costs come from, the patient needs to be kept in hospital for long periods and cells need to be removed and

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manipulated with agents – such as viruses – which, in turn, have been specifically manufactured to activate them. This process is then carried out manually by a highly skilled team. Every step in the 22-day process requires monitoring and quality checks to ensure a high-quality product.

Manufacturing must be carried out in aseptic locations, using many manual steps that can only currently be executed by trained personnel and that carry a high risk of errors. Many of the errors in traditional pharma processes are due to human error, and in the case of cellular therapies, such errors can lead to non-functioning therapies and life-threatening results for the patient. Cells are much more sensitive to damage than traditional biologics, which in turn are much less robust than small-molecules. The cost of failed batches contributes to the high costs of cellular therapies.

This means that ensuring quality throughout each precisely controlled manufacturing step is vital. The high cost of cellular therapies means they can't be available to all who need them. It also becomes too challenging to sustain a high enough gross margin for commercial viability of the products.

POTENTIAL SOLUTIONS

Following regulatory clearance in 2017, attention is now turning to resolving these manufacturing challenges for ATs. There are many classes of solution which become immediately applicable to tackle the issues. Closed systems – separating operator from product – are one such solution, enabling the high costs associated with high-grade GMP and clean locations to be avoided. Closed systems allow production to remain aseptic and the overall classification of a manufacturing location to be downgraded. They also reduce the risk of contamination by operators and enable therapies for multiple patients to be manufactured simultaneously within the

same manufacturing facility. Single-use, disposable technologies also contribute to reducing the risks of contamination.

Automation will become key to reducing production costs, improving both standardisation and quality. By implementing automation, simple manual steps, such as shaking, opening vessels and counting cells, can be avoided. In the example of counting cells, operators must still use haemocytometers to count cells in grids to assess yields, making judgements which can still seem quite subjective. Automation will reduce the skill level required by operators, enabling manufacturing processes to be carried out in multiple locations whilst, crucially, maintaining product quality.

Automation will also enable the collection of significant data sets during the production process, which will in turn enable continual improvement and refinement of the production process, maintaining quality and reducing costs. The ability to characterise products during manufacture could be invaluable, e.g. enabling understanding of the nutrient consumption of cells, their metabolite production and concentration to monitor overall process quality. Data is generated throughout all steps of the process, including analytics and batch records.

However, there are still questions around what technologies can be used to collect data, how much data is necessary and how best to use it to improve the manufacturing process. Currently, process analytics are performed off-line at set points. There is considerable potential for greater use of in-line analytics for continuous monitoring. There is currently a lack of general monitoring technologies when cell numbers are being expanded. Together with developments in sensing and monitoring technologies, data processing techniques – ranging from classical signal processing to artificial intelligence approaches – could be used to turn measured data into insights and actionable information, such as giving a prediction of cell potency.

More fundamental challenges exist around process steps related to cell modification and cryopreservation. Cell modification is currently carried out using live viral vectors, which themselves are very delicate and need to be handled carefully. Viral vectors can become integrated in random locations within the cellular genome, which impacts robustness in manufacturing. Next-generation gene editing tools, such as CRISPR-Cas9, could solve this problem with more site-specific additions of genetic constructs. Cryopreservation is another key step, performed at the back end of the manufacturing process, increasing the shelf life of products and therefore geographic reach. However, if not managed, inadequate storage conditions could lead to a decline in cell viability and therefore reduced therapeutic effect.

THE NEED TO INNOVATE

At first sight, the quantity and degree of the challenges in manufacturing cellular therapies may seem intimidating. It is, however, worth reflecting on the bigger picture and the enormous potential ATs have to treat patients and cure diseases. In original clinical studies for Kymriah®, the overall response rate in the short term – based on a single infusion of Kymriah® – was above 80% for evaluated patients whose leukaemia could not be cured by any other means. Current manufacturing challenges and high costs could prevent such treatments being used widely, consequently there are considerable opportunities for companies that can solve these significant challenges through innovation and technology. Innovation methodologies such as user-experience mapping, jobs-to-be-done, technology mapping, TRIZ and intellectual property landscaping have proved useful in other applications and could help to elucidate the challenges and discover solutions.

The flip side is that we could be heading for a "Kodak" scenario for companies that remain wedded to legacy processes and miss the opportunity to innovate and embrace a new future. Currently, these challenges are yet to be fully understood and further clarity around the challenges will be required. Whilst this may seem daunting, this scenario actually provides an opportunity for innovative thinking that will enable the entry of new players into the market, with solutions and technologies from other industries. We are already seeing this happen with the intense investment by major Asian companies such as Samsung and Hitachi. These companies can bring insight and fresh perspectives, not wedded to traditional ways of therapy manufacturing.

There are many parallels between the emerging era of ATs and the Kodak story. New entrants eventually took over the photography market as it transitioned from film to digital. Digital photography disrupted Kodak's film-based business model to the point of its bankruptcy, despite once owning 50% of the global photography business and employing 60,000 people. The brutal irony is that Kodak invented the very technology which destroyed its business, through its invention of the original digital camera in 1975. It did not spot or react to the disruptive forces in its industry. It tried to prolong the life of film by creating products which acted as printer docks for its cameras.

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A similar scenario is playing out right now in the automotive industry as new entrant Tesla has popularised the electric vehicle and left incumbents with businesses based on legacy internal combustion engines racing to develop their own electric models.

In a similar way, sticking to the old way of thinking centred on blockbuster drugs could lead to a Kodak moment for even today's biggest pharma companies. It is now possible to envisage manufacturing of cellular therapies reaching the patient's bedside with automated, scaled-out manufacturing approaches and no centralised manufacturing facility required. Companies that innovate, solve challenges and think disruptively could avoid falling into the Kodak trap – and unlock the huge potential enabled by ATs.

ABOUT THE COMPANY

Cambridge Design Partnership is a technology and product design partner focused on helping clients grow their businesses. Some of the world's largest companies trust CDP to develop their most important innovations. Located in both Cambridge (UK) and Palo Alto (CA, US), CDP specialises in the consumer products,

healthcare, energy and industrial equipment markets. Its multidisciplinary staff have the expert knowledge to identify opportunities and tackle the challenges its clients face.

ABOUT THE AUTHORS

Pari Datta, PhD, is an innovation professional who specialises in identifying, building and validating new opportunities for major global companies and emerging start-ups. He has 10 years' experience in leading innovation and strategy programmes, including insight generation, opportunity discovery, commercial assessment, strategy development, concept generation, technology scouting, IP landscaping and the process of innovation. He has led projects in many industries including fast-moving consumer goods, drug delivery, surgical and critical care – specialising in life sciences and diagnostics. He has accumulated extensive technical and commercial knowledge through R&D/commercialisation of early-stage technologies and working as an innovation project manager for a global leader in diagnostics. Dr Datta holds a degree in Biochemistry and a PhD in Genetics.

Nick Rollings, CEng, MIMechE, is experienced in all aspects of multidisciplinary technology and medical device development. He has instigated and led technology creation and development projects in the diagnostics and life science instrumentation sectors and has co-authored papers on various different technologies. Mr Rollings' experience includes multiple biotechnology instrumentation developments. He was also a founding member of a spin off company from a large FTSE 100 technology firm developing a novel diagnostics technology for veterinary and clinical point-of-care applications. Mr Rollings is a chartered engineer and spent time earlier in his 20-year career as a manufacturing engineer, implementing new and modified designs into mass production.

ON drugDELIVERY

2018/19 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
Sep 2018	Wearable Injectors	PASSED
Oct 2018	Prefilled Syringes & Injection Devices	Sep 6th 2018
Nov 2018	Pulmonary & Nasal Drug Delivery	Oct 4th 2018
Dec 2018	Connecting Drug Delivery	Nov 1st 2018
Jan 2019	Ophthalmic Drug Delivery	Dec 6th 2018
Feb 2019	Prefilled Syringes & Injection Devices	Jan 3rd 2019
Mar 2019	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Feb 7th 2019
Apr 2019	Pulmonary & Nasal Delivery	Mar 7th 2019
May 2019	Injectable Drug Delivery	Apr 4th 2019
Jun 2019	Connecting Drug Delivery	May 2nd 2019
Jul 2019	Novel Oral Delivery Systems	Jun 6th 2019
Aug 2019	Industrialising Drug Delivery Systems	Jul 4th 2019
Sep 2019	Wearable Injectors	Aug 1st 2019
Oct 2019	Prefilled Syringes & Injection Devices	Sep 5th 2019
Nov 2019	Pulmonary & Nasal Drug Delivery	Oct 3rd 2019
Dec 2019	Connecting Drug Delivery	Nov 7th 2019