CELL AND GENE THERAPY: CONVERTING A ROLLS-ROYCE INTO A FORD?

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Many believe, writes Dr David Seaward, 3P Founder and Engineering Director, that what semiconductors and computers were to the latter half of the 20th century, biotechnology will be to the 21st.

The process of bringing new pharmaceuticals and biotechnology to market requires significant creativity from humankind's most gifted scientists and engineers. The COVID-19 pandemic has shown what small numbers of these hard working and gifted people can achieve in what might have been impossible until recently. In less than 2 years, the scientific world created numerous effective COVID-19 vaccines, retroviral medications and diagnostic tests that cost less than a cup of coffee.[1]

As pharma found a new paradigm for "warp speed" delivery (pun intended!), cures for many life-limiting diseases, such as cancers and genetic disorders, now appear to be within our grasp. Scientists have learnt how to manipulate genes and cells in what would have been science fiction just a decade or so ago. There has been an explosion of activity within what is now known as ATMPs.[2,3]

This may not be "breaking news," but you might wonder why a group of UK-based automation engineers have taken such a keen interest in ATMPs ... and why we have ongoing projects to address many of the unmet needs in this sector. 3P was founded to commercialise novel medicaments for which the associated manufacturing equipment simply didn't exist. 3P develops highly customised automation solutions for life science clients, which has led our engineers down a very interesting and quite unique path!

Many of the products we've helped to develop have been so-called sustained release devices, whereby the medicament elutes into the body during a period of time, which can be days, weeks and, in some cases, months. These devices need equipment that can extrude, mould, mix and shape a product. Typically, it is formed around a biodegradable plastic (such as PLGA) or elastomer/copolymer (such as silicone rubber or EVA), which is mixed with the active pharmaceutical ingredient (API).

The resultant device is typically an implantable depot, injection, implant or a vaginal ring. Much of the production equipment for these therapies doesn't exist or requires significant customisation.

Combination products, such as injector pens and inhalation devices, also need our specialist automation during assembly and, quite often, unique powder and liquid filling solutions to get the medicament into the final device. To add a further layer of complexity, the fill-finish process of injection devices requires the control of particulates (if terminally sterilised) and often needs to be undertaken aseptically (when the drug product cannot be terminally sterilised)[4,5]. These niche automation skills are essential when bringing a novel drug product to market.

To paraphrase a client presenting at our double Queen's Award Ceremony in late 2021: "When you're trying to disrupt a $93 billion sector, it helps if you can actually manufacture your disruptive technology … and this is where 3P come in!"

But, getting back to those ATMPs, these novel products often spin out of university labs on the back of some unique and highly protected intellectual property. Companies are then formed and initially occupy incubator space at, for example, university science parks. Initially funded by government grants, these potentially billion-dollar firms subsequently attract a mix of venture capital and Big Pharma money to commercialise their life-saving product.

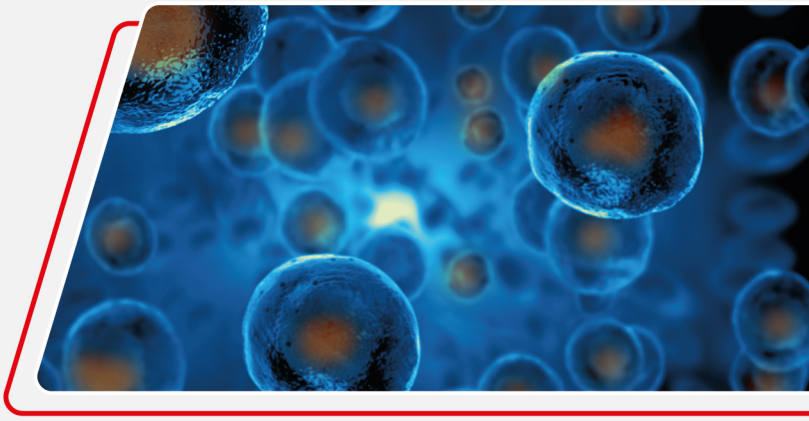
Some ATMP company deals have been "eye-watering." Although the core technology may be life changing for patients, there remains an issue that still needs to be addressed: currently, the cost of goods and price are also, ahem, eye-watering.

TAMING COST OF GOODS

To cite an example, the UK's BBC ran a story on the last day of 2021 about the one-year-old, Edward Willis.[5] His life has been transformed after receiving the world's most expensive drug for spinal muscular atrophy (SMA).

He received a one-time infusion of Zolgensma (manufactured by Novartis), which has a list price £1.79 million! It creates a new copy of a gene to make the missing protein that causes the disease, and is delivered by a genetically modified adenovirus (the same viral vector that was used in the Oxford-AstraZeneca and Johnson & Johnson COVID vaccines).

Young Edward Willis (image courtesy of www.justgiving.com/fundraising/edward-willis-hall



Whereas the list price of ATMPs is usually calculated based on "value" in terms of improved patient outcomes during many years of extended/enhanced life, the cost of production is also extremely high. Articles and conference papers list the need for automation as one of the top constraints on the sector[7,8,9,10,11]. These costs are driven by the complexity and number of production steps in a highly regulated industry. In many cases, the production process is essentially a sequence of "tidied up" and well-documented lab processes, which require significant operator involvement and intervention (which can lead to operator error and, potentially, very expensive and life-limiting errors). It should be noted that for some ATMPs, one patient represents one batch … and losing a batch through error may mean the death of that patient.

Nothing could be further away from the status quo of automation in pharma, such as that employed to produce a tablet; for example, a carton of blister-wrapped aspirin costs around £0.10 per tablet and a modern tablet press can produce well over 20,000 tablets each and every minute.

It would be naïve to assume that the cost of goods for ATMPs will ever get close to that of an aspirin tablet. First marketed by Bayer in 1899, aspirin has had more than 100 years to develop the associated high efficiency manufacturing processes and machinery. And that, hopefully, should explain why a group of pharmaceutical automation engineers have been active within the ATMP space!

THE NEXT FORD?

It might be worth, at this stage, to consider an analogy from the early years of the automotive sector. Before the introduction of the moving assembly line, the US-produced Ford Model T was priced at $825 (1908): after revolutionising the manufacturing line, it was priced at $260 (1925). At the same time, employees also saw their weekly working hours reduce and hourly pay increase, despite the lower level of skill required to assemble each vehicle.

1925 Ford Model T touring, built at Henry Ford's Highland Park Plant in Dearborn (MI, US) (Collective Commons by ModelTMitch)

1914 Rolls-Royce Tourer chassis with coachwork by Barker (Collective Commons Tomislav Medak)

During this period, the UK Rolls-Royce company had large teams of highly skilled artisans hand crafting Silver Ghost chassis. Let's think of these craftspeople as well-trained laboratory technicians and/or the PhDs often involved in the preparation of ATMPs. It should be noted that whereas Ford was producing entire cars, Rolls Royce was only producing a chassis and an engine, and leaving it to other companies to manufacture the coachwork. A Rolls-Royce chassis in 1914 cost $7000. During the 1908–1925 period, Ford produced around 16 million cars compared with approximately 8000 Rolls-Royces.

Right now, ATMPs fall into the hand-crafted Rolls-Royce camp. Cars revolutionised transport and Ford revolutionised their production. Similarly, ATMPs are about to revolutionise the treatment of many life-limiting diseases.

Industry growth is being constrained by a worldwide lack of life science laboratory technicians and phds to both develop the therapies and then produce them at commercial scale.

One must remember that automation serves humankind to provide a number of benefits:

- It reduces the number of operators required for production
- It reduces the skill required by those operators
- It improves the consistency of the product (and reduces faults and scrap)
- In many cases, it performs tasks a human simply cannot undertake.

3P posits that some cunning automation engineering is required to revolutionise the manufacture of ATMPs to reduce both the cost of goods and overcome the severe lack of skills currently constraining the sector. Who will be the first to turn ATMPs into mass market "Fords"? This series of blogs digs into the background of ATMPs and some of the challenges associated with their production. It will also suggest where possible solutions might exist.

The next blog will provide a "primer" on ATMPs, looking at what are they and why do they matter? The third blog will examine some of the megadeals in the ATMP sector, given that it's become abundantly clear that investors believe there's a significant return to be made from the technology. It is worth remembering that Zolgensma mentioned above was originally developed by AveXis Inc. Initially they raised ~$75m in 2013-15 in venture capitalist funds.

A few years later in 2018, they raised a further $460m and a few months later Novartis bought them for $8.7bn. These are good returns by anyone's standards. In the first half of 2021 $14.1 billion was invested in the sector[3], investors may, however, be disappointed to learn that there is currently a worldwide skills, and facility shortage compounded by a lack of efficient automation constraining the sector's growth.

The fourth blog will set the scene for automation with a reprint of a tweaked 2013 paper discussing the costs and scale-up risks for medical devices. It's pertinent to this series of blogs and was originally written before much of the current ATMP sector (or the term ATMP) existed. The fifth blog describes how ATMPs are currently manufactured and what the future may hold for their automation.

SIDEBAR

ATMPs

Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues or cells. The European Medicines Agency

(EMA) classifies ATMPs as follows:

Gene therapy medicines: these contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting "recombinant" genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources.

Somatic-cell therapy medicines:

these contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases.

Tissue-engineered medicines:

these contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue.

In addition, some ATMPs may contain one or more medical devices as an integral part of the medicine, which are referred to as combined ATMPs. An example of this is cells embedded in a biodegradable matrix or scaffold.

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