White Paper

Cell & Gene Therapies: Innovation to commercialisation

Can industry bridge the gap?

Thought Leadership, IMS Health
Introduction

Cell & gene therapies have been at the forefront of medical science, promising a hopeful future for many patients suffering from a wide variety of diseases. For over two decades they have been in the headlines for scientific rather than clinical breakthroughs, with the majority of trial results disappointing patients and some raising questions of safety.

However, 2014 was a turning point for cell & gene therapies, with many exceptional results coming out of clinical trials; large pharma has recognised the potential and is entering the area en masse. The next, pivotal, decade will see several therapies currently in Phase II/III launch into the market and begin to set the precedent for those that follow. Many of these therapies are particularly novel, and potentially curative, and will therefore face unprecedented hurdles when taken from clinical trial setting to real world practice.

In this paper we will discuss the challenges around cell & gene therapy valuation, reimbursement, commercialisation, manufacturing and logistics. Players entering at this early stage must actively navigate and overcome these challenges in preparation for a successful launch.
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Executive Summary

The power of cell & gene therapies targeted at the treatment of life-threatening, high unmet need diseases has been the driving force behind the academics, small biotechs and now large pharmacos investing time and resource in this rapidly evolving area. Underwhelming outcomes and headline grabbing adverse events have caused setbacks across the entire field. However, the area is blossoming, the first cell therapy cancer vaccine has launched in the US, and Glybera, the western world’s first gene therapy treatment has been approved for use in Europe. 2014 through to 2015 saw a record flurry of large pharma investment in cell & gene therapy, displaying confidence that current technology platforms will reach the mainstream. Not only has the number of cell & gene therapy deals spiked since 2014, the average value of deals has jumped by a factor of over 5\(^1\). What has driven them to become such sought after assets? We believe this is due to a step change in technology innovation, finally making strides in the clinic with impressive results utilising diverse therapeutic strategies to target a range of indications. Fast track and breakthrough statuses are plenty, with some trials showing curative results for chronic, debilitating and life-threatening conditions. Consequently, the benefits of these therapies may not be limited to clinical gains; curative treatments may enable healthcare systems to make significant savings from a reduction in long-term spending on chronic treatments, co-morbidities and social impairments, benefiting the economy as a whole. The clinical and economic benefits of cell & gene therapies are encouraging; and pricing will most likely be set accordingly, posing challenges for healthcare systems that may face high budget stress to treat a built-up pool of patients.

Given the lack of any discernible experience from analogue products, incumbent players will need to carefully prepare and plan their launch and access strategies. IMS Health has identified four key challenges to succeed in cell & gene therapies that stem from their novel and unique characteristics: Valuation, Reimbursement, Commercialisation and Manufacturing & Logistics.

Cell and gene therapies will mostly be one time or short duration treatments, customised to the individual, and often in small patient populations, manufacturers will seek premium prices for these therapies. Given this, these therapies will face valuation and reimbursement challenges. Pricing based on long term patient benefits and future savings made within the healthcare system will be viewed sceptically because clinical trials will provide inadequate evidence of long term benefit due to limited duration, small sample sizes, and in some cases, imperfect or no trial comparators. As Chiesi’s experience with Glybera shows, such therapies may even be required to delay launch in order to collect more data for payers. Current HTA systems are also not set up to incorporate the value of long term cost savings, and social and economic benefits into price setting.

Even if they accept the price, reimbursement will still be a challenge as the budget impact will be in the first year, while the benefits will be spread over time. This may create a funding challenge given the potentially large pool of existing patients. This is compounded by siloed budgets where individual payer entities may not see the savings reflected in the broader health system and society. These concerns are important for all high cost cell & gene therapies, but for several cell & gene therapies targeting diseases with large populations such as HIV, angina or beta-thalassemia, payers may further struggle to reimburse them broadly.

\(^1\) IMS Health Pharma Deals Dec 2014
EXECUTIVE SUMMARY

Innovative pricing and funding arrangements will be required to address the cost burden and the uncertainties associated with these therapies. These arrangements could be limited to spreading the cost across several regional payers, or could go as far splitting payments into annuities which are linked to sustained efficacy of treatment. Implementing an annuity based reimbursement agreement will, however, be challenging with feasibility depending on country and payer sophistication. Within the US and EU5, Italy has has the most experience in paying for performance and stakeholders are positive about the feasibility of annuity payments. Other stakeholders such as those in the US believe that annuity payments will not be necessary unless treatment costs reach the $1Mn milestone.

The cell & gene therapy commercialisation model will be very different from the conventional one. The lack of experience of therapy launches will inevitably lead to mistakes being made. Small biotechs collectively hold 83% of the cell & gene therapy pipeline; the current funding environment is enabling them to develop in-house manufacturing and commercialisation structure, allowing independent product launch. However, it is not likely that small biotechs will be as efficient and effective at launch in comparison to large pharma. Valeant’s acquisition of the relatively unsuccessful Provenge will be interesting as a more efficient structure, strong specialist sales force, increased capital and most importantly, diverse pharmaceutical experience, will better suit Valeant to foresee and act on unprecedented challenges on entering the market.

Manufacturing and logistics are uniquely challenging for cell & gene therapies, particularly for autologous therapies which make up 60% of the cell therapy pipeline. New sophisticated facilities are slow and expensive to set up due to stringent product specifications and Good Manufacturing Practice (GMP) guidelines. Finding efficiency in the production of autologous therapies is key to maintaining profitability; this must be achieved through designing automated manufacturing early in the product lifecycle. Accurate forecasting of product demand and maintaining flexibility in manufacturing scale will further increase efficiency while ensuring manufacturing capacity does not limit uptake.

Difficulty in finding efficiency in the provision of autologous therapies does not stop at manufacturing, but continues to the logistical requirements. Autologous therapies do not fit the traditional pharmaceutical delivery pathway. The practical implications of extracting cells from the patient, processing them at a facility then returning them to the patient can cause a variety of complications. This requires very strong communication between the physician, hospital and the manufacturer and will require significant organisation and process management. Responsibilities over intricacies within the treatment pathway have not been established and we may see manufacturers and their sales force taking a more active role in the treatment of the patient. Should all the steps be carried out by the manufacturer, and an end to end single price is agreed and paid for from a central fund, or should different stakeholders carry out different steps and get paid individually for those steps from different sources? It is not obviously evident which option is optimal for payers, providers or manufacturers, and if there are conflicting views, how these would be resolved. Within this decade we will see cell & gene therapies launching into market, setting the precedent for those that follow. Players that are proactive in their approach to the above challenges will be most successful.

1 IMS Health R&D Focus Dec 2014.
Understanding the Cell & Gene Therapy Pipeline

We will first introduce cell & gene therapies by defining them and exemplifying typical strategies of treatment in the pipeline. However, due to the innovative nature of the area, what is considered typical now may quickly become outdated.

Cell Therapy

Cell therapies are treatments in which intact, living, human cells are injected into a patient for therapeutic benefit. The origin of these cells can be autologous, coming from the patient; or allogeneic, off the shelf. Many cell types can be used for treatment, ranging from neural stem cells to genetically engineered immune system cells.

IMS Health’s R&D tracking database is able to track all cell therapies in which the cells have been genetically engineered. Unfortunately this excludes the majority of stem cell therapies, which typically are not genetically engineered but are simply cultured and implanted in to the patient.

Graphic 1: Cell therapy pipeline* and popular platforms

Within the pipeline for genetically engineered cell therapies there are a few key cell platforms which make up the majority of candidates: dendritic cells, CAR T-cells, tumour cells and T-cells. These platforms all utilise the immune system, either through antigen presentation (directing the host immune system to the disease) or effector lymphocyte utilisation (administered cells themselves actively target the disease). Much like monoclonal antibody and small molecule immunotherapies, these cellular immune modulating therapies mainly target oncology and autoimmune disorders. However they are also being developed for infectious
diseases that the immune system typically struggles with, such as HIV. A typical dendritic cell therapy such as Provenge works by presenting cancer associated peptides to the immune system in order to elicit an immune response against cells carrying the specific peptides. In contrast, dendritic cells can also be programmed to dampen pre-existing autoimmune responses in conditions such as Rheumatoid Arthritis.

**Gene Therapy**

Gene therapies are treatments in which genetic material is incorporated into the cells of a patient with an intended therapeutic benefit. The majority of gene therapy trials involve the use of an adeno–virus vector for genetic manipulation, often replacing faulty or missing genes in patients with genetic disorders. A typical example would be a gene therapy replacing the non–functioning enzyme in a patient with Sanfilippo Syndrome, a lysosomal storage metabolic disorder.

**Graphic 2: Gene therapy pipeline**

Due to the wide variety of genetic disorders and the versatility of genetic manipulation, gene therapy development spans several therapy areas. The gene therapy pipeline also has diversity in mechanism of action; they are not always corrections of faulty genes:

For example, CERE 110 is a treatment being developed for Alzheimer’s disease, in which a viral vector is used to insert an additional gene for Human Nerve Growth Factor into cholinergic nerve cells, thereby stimulating nerve growth to prevent memory loss and deterioration of cognitive ability.

Another interesting strategy is a gene therapy designed to selectively insert a pro–drug activating enzyme into tumour cells, e.g. JX 929. This would enable the metabolism of pro–drug into a cytotoxic compound, selectively within the cancerous cells, allowing use of much higher cytotoxic treatment dosages whilst reducing the impact on healthy cells.

The clinical promise of cell & gene therapies lies in the diversity of therapeutic strategies available to be employed when targeting a specific disease. This diversity has enabled researchers to specifically target cell & gene therapies at typically hard to treat, high–unmet–need therapy areas.

Clinical candidates currently in the pipeline represent only the few best understood therapeutic strategies of the multiplicity of creative therapeutic approaches under scientific investigation.
Cell and Gene Therapy Entering the Mainstream

Cell & gene therapy has historically been a fitful area of R&D; it has been littered with underwhelming outcomes and headline grabbing adverse events. Bumps in the sector have caused setbacks across the entire field due to loss of investor confidence that these therapies will play a role in future medicines. Events like the diagnosis of leukaemia in several patients after undergoing SCID gene therapy in 2002, and fatal overwhelming immune responses after CAR T–cell (Chimeric Antigen Receptor T–cell) treatment in 2010, led to more caution by industry and increased scrutiny by regulators, slowing progress.

However, much progress has been made in the clinic, and in improving the perception of cell & gene therapies. This decade has seen the first cell therapy cancer vaccine, Provenge, launching in the US, and a landmark for the EMA with the first gene therapy, Glybera, approved in the western world.

Graphic 3: Number and average value of cell & gene therapy deals, 2007-2005

In order to quantify industry interest in the sector we have utilised IMS Health’s Pharma Deals database to track the number and the deal value of cell & gene therapy product licensing and acquisitions. The number of cell therapy deals has been increasing consistently year–on–year, with the number of gene therapy deals also hitting a maximum in 2014. These deals have also accrued higher valuation; we observed a dramatic rise in the average value of a deal for both cell & gene therapies in 2014, largely driven by the large number of major players putting up large sums for small biotechs, which are progressing into later stage cell & gene therapy development. Historically, this is an area where niche biotechs have been the predominant
players; but in 2014 and early 2015, we have seen a flurry of the top 20 pharma companies incorporating cell & gene therapies in to their pipeline, a clear sign of optimism as these therapies begin to approach the mainstream.

Graphic 4: Timeline of large pharma investment and licensing in cell & gene therapies, 2010-2015

What has driven cell & gene therapies to become such sought after assets?
We believe that this is due to a step change in technology innovation, finally making strides in the clinic with some impressive results; Cell & gene therapies have been awarded with breakthrough & fast track statuses for a wide range of indications, including:

- **Merck Serono’s Phase II TCELNA**, an autologous T-cell vaccine used to target patients’ autoreactive immune cells in Multiple Sclerosis (MS). A phase IIb study of 129 patients with a more active MS (Annualised Relapse Rate (ARR) > 1) showed a reduction in ARR to 0.2, in combination with 73% of patients showing stabilisation or improvement in MS disabilities. These results showing halting and even reversion of MS progression are extremely encouraging for sufferers of the disease
- **Novartis** is developing CTL019, a Phase II CAR T-cell therapy for patients with relapsed/refractory CD19-positive Acute Lymphoblastic Leukaemia (ALL), Chronic Lymphoblastic Leukaemia and non–Hodgkin Lymphoma. Phase II trials for ALL have resulted in 36 of 39 paediatric patients (92%) experiencing complete remission. Similarly, Juno therapeutics is developing a CAR T immunotherapy for relapsed/refractory ALL and achieved a complete
remission rate of 91%; these are patients who would have typically had a 35–40% survival rate\(^3\).

- Bluebird Bio’s LentiGlobin is a Phase II viral gene therapy for Beta-thalassemia Major, a prevalent blood disorder requiring patients to have regular lifelong blood transfusions. Although bone marrow transplant can be curative, a suitable donor match is not always available. LentiGlobin is showing promising clinical results; four patients have been able to maintain haemoglobin levels without transfusion therapy.

Several companies are working on second and third generation products which may be able to further the already impressive results of these therapies. This can be seen with CAR T-cells where increasingly sophisticated generations are already entering clinical trials. Successive CAR generations increase the variety of co-stimulatory composition, as well as the use of multiple interacting CARs.

The variety of therapeutic strategies and the rapid development of further generations lead us to believe that cell & gene therapy treatments are still at the very beginning on the learning curve of technology development; current pipeline therapies are not the peak.

**Cell & gene therapies benefits for several stakeholders**

The great potential benefits for many of these therapies coming in to the market are twofold: clinical & economic.

**Clinical**

Treatments can be curative, life extending or life enhancing; patients suffering from life threatening or debilitating diseases such as ADA-SCID (Adenosine Deaminase Severe Combined Immunodeficiency) with very few treatment options may gain access to treatments giving them longer and healthier lives.

**Economic**

What is particularly unique about this group of therapies is that many of these treatments aim to cure or significantly improve patient health in their targeted diseases, the majority of which are chronic or life threatening. These diseases by consequence have significant negative impact on the healthcare system and the economy as a whole.

This enables the possibility for cell & gene therapies to provide economic benefit. These can be realised through the reduction in long-term spending in chronic disease areas. For example, in Italy, regular blood transfusions and other medications used to treat a sufferer of Beta-thalassaemia cost €15,000\(^4\) per year, equating to lifetime costs for the healthcare system of at least €900,000. Bluebird Bio’s LentiGlobin is showing promise as a curative treatment for Beta-thalassaemia, potentially enabling the Italian healthcare system to reap huge savings spread over the lifetime of each patient. Savings will also be realised with decreased burden from high-cost patients requiring fewer hospitalisations and developing fewer co-morbidities.

\(^3\) Hematology, 2012, 1:129–136, E. A. Raetz

Further economic benefits can be found in the wider social aspect; curing patients with debilitating diseases e.g. inherited blindness will enable a greater ability to work, pay taxes and contribute to the economy. With the increase in social mobility, patients may also no longer require help from support systems unlocking greater savings over time.

With so much potential in cell & gene therapy efficacy, the theoretical clinical & economic benefits of treatment are impressive; realistically not all cell & gene therapies will have a strong economic argument, but for those that do pricing will most likely be set accordingly. This poses challenges for healthcare systems that may incur huge budget stress to treat a built-up pool of patients. While there are long-term financial benefits, the immediate challenge is a large near-term bill.
Challenges and Hurdles for Current and Prospective Players

Cell & gene therapy has attracted many of the largest pharmaceutical companies investing for the future. Given the lack of any discernible experience from analogue products, incumbent players will need to carefully assess planning and entry strategy. IMS Health has identified four key challenges to succeed in cell & gene therapies that relate to their novel and unique characteristics.

Cell & gene therapy is a completely different commercial proposition to the traditional pharma model.
Valuation

We predict that the valuation of cell & gene therapies, in terms of price and cost benefit, will be a considerable point of contention. Perspectives on the method of valuation and the influence of different pricing strategies will differ greatly between stakeholders. This is particularly challenging due to the huge potential but uncertainty of the clinical benefits for cell & gene therapies. Manufacturers and payers will naturally debate, but patients seeking access to potentially life-changing therapies will also make their voices heard.

Key factors influencing price

- **The impact on patient lives**
  Key to the value of any medicine is the positive impact it has on the patient. An example of how this influences pricing is UK’s NICE reputation of capping spending to ~£30,000 per Quality Adjusted Life Year for non-end of life therapies

- **Savings as a result of treatment**
  Savings realised from lack of need for alternative treatments, social support and gains from increased social mobility will be useful in building a strong value argument. Difficulties arise as these savings will be diffuse (realised by several entities) and will carry some long-term uncertainty, whereas upfront payment for therapy is paid by a single entity and has no long-term uncertainty

- **Risk taken by the manufacturer**
  Cell & gene therapies have historically had a very high risk of failure. As a risky investment for manufacturers, pricing may reflect a greater uncertainty on return

- **Target patient population size**
  Smaller patient populations, particularly orphan ones, will warrant a higher price for the manufacturer to make a return. Reimbursed populations will likely be restricted to the most severe patients as there are inevitable cost escalation concerns when target populations are no longer small or well defined

- **How much can the payer afford?**
  For therapies with truly effective clinical results, even by payers own estimations, the population cost of therapy may exceed what is actually possible to fund— in any given year or possibly ever
Uncertainty in clinical benefits

Suitable data

Payers will be unwilling to pay large sums for treatments based on the benefits and cost savings derived from small carefully-selected patient groups in controlled clinical settings. The level of uncertainty of real world impact of treatment, which is particularly high for cell & gene therapies, will strongly influence pricing.

High quality data based on real world evidence will strengthen the valuation argument. Programmes such as the UK’s Early Access to Medicines scheme could be leveraged. The scheme allows distribution and treatment of promising phase II and III products to patients with life threatening or debilitating disease—free of charge to the NHS. The first therapy to pass the initial step of Early Access Designation was a dendritic cell therapy targeted against malignant gliomas, DCVax-L. Similarly many other cell & gene therapies are likely to be eligible for the scheme due to their targeting of diseases with high unmet need. This scheme would enable collection of real world clinical & pharmacoeconomic data. Collection of the data would start before approval and before launch, providing clear evidence and stronger positioning for payer negotiations.

Confidence in longevity

Many cell & gene initial clinical results have been efficacious; however, they will be unable to prove that the effect of therapy will persist for the duration of a patient’s life. Scientific principles describing the longevity of therapy will not satisfy payers; they will want clinical proof of lasting long-term efficacy in order to justify product pricing accordingly. Initial clinical trials will not be able to capture such long-term data and payers will look at examples of gene therapies where benefits have deteriorated due to the nullification of genetic insertions by cell death, gene regulation or other cellular mechanisms. Recently, during clinical trials for patients with inherited blindness run by the University of Pennsylvania, after having seen considerably improved sight for one to three years, patients' vision began to fade again.

The story of Glybera, the western world’s first approved gene therapy, is particularly relevant in the discussion around confidence of long term efficacy. Glybera is an ultra–orphan\textsuperscript{5} treatment for Lipoprotein Lipase Deficiency (LPLD), a disease for which there are limited treatment options and sufferers primary cause of mortality is acute pancreatitis. Treatment involves a one time series of injections of viral vector carrying an intact copy of the LPL gene. Initial clinical trials showed that Glybera does alter lipid metabolism; however, the longevity of these results was scrutinised due to the return of a disease-associated biomarker in treated patients. This caused Glybera to have a convoluted route to approval, requiring four submissions before finally gaining approval under exceptional circumstances by the European Commission in November 2012.

However payers will be key market access decision makers for gene & cell therapies. Over two years after approval, Glybera has only recently launched. In July 2013, Chiesi acquired the licensing rights to Glybera in Europe and chose to further delay launch in order to collect extended follow–up clinical data revealed in June 2014. The 6 year follow–up data showed that treated patients had no severe pancreatitis and a 45% reduction in less severe events equating

\textsuperscript{5} Ultra–orphan threshold prevalence, 1:50,000 population; NICE 2004, Citizen Council Report on Ultra–Orphan Drugs
to a 50% reduction in hospitalisation post treatment\(^6\). This data was well received, but we are yet to see if it is compelling enough to convince payers to reimburse the one-off €1.1 Mn price tag put forward to the German Federal Joint Committee.

Although the ultra-orphan indication will have impacted the price, as a pioneering gene therapy, and one of the world’s most expensive drugs, Glybera has set the tone for other potential one-off curative cell & gene therapies.

\(^6\) uniQure press release
Reimbursement

With the expected high initial pricing for cell & gene therapies, payers will find it difficult to cover reimbursement costs. Manufacturers that address payer concerns fully and realistically will reap the benefits of easier market access and larger patient population coverage.

Payer reimbursement concerns:

- **The benefits of therapy are not fully proven**
  A guarantee of lasting benefit is not possible. Current financing models require upfront reimbursement, exposing payers to risk

- **Savings are diffuse**
  The wider economic and societal benefits may be present but will not be directly realised by the payer. Even within healthcare budgets, slow long-term savings in a primary care budget may not be attractive to payers for the hospital budget facing imminent high costs

- **Savings are long-term but payment is upfront**
  A strong long-term economic argument for treatment cost may be irrelevant if payers are unwilling or unable to pay high sums up front, when future savings will take several years to balance the books

These concerns will be important for all high cost cell & gene therapies; however, they are particularly daunting when these therapies target large patient populations. Treatments such as Argos Therapeutics’ AGS004 dendritic cell therapy for HIV, and Taxus Cardium’s alferminogene tadenovec gene therapy for angina & cardiac ischemia will be seen as potential budget breakers. Reimbursement of treatments for very large patient populations will mean a huge cost burden within a very short time span; payers will have to heavily restrict initial access to such therapies, and even with patient restriction payers will need innovative solutions to spread the cost burden.

Innovative funding arrangements

Spreading the cost of therapy and sharing the risk of treatment failure is likely to be key in gaining payer reimbursement and widening the patient pool. We will describe three cell & gene therapy funding models which represent the types of financing arrangements that could be considered: national funding schemes, the annuity model and paying for performance.

**National funding schemes**

Firstly it will be important that the regional burden of treatment is spread. This may mean promoting the development of a national level budget across many regions. Similarly, in areas such as the US with multiple payers in the same geographic region, payers may need to pool
reimbursement funds in order to spread the cost across plans, especially as patients may change plans, with one payer paying for the therapy and other payers reaping the benefits. Although this type of model will ease local budgetary impact of the high one-off payment, large patient populations will still be problematic. It does nothing to address payer concerns over the upfront cost and flexibility in financing required due to the uncertainty of treatment efficacy. If the treatment fails, or the patient dies in treatment indication related or unrelated circumstances, payers will not see a return on their investment and may need novel financing systems to recoup payment accordingly.

**The annuity model**

The annuity model of reimbursement could be increasingly attractive with very high cost cell & gene therapies. Payment is broken down into annual instalments, enabling payers to reimburse manufacturers over the time of therapeutic benefit. This enables payers to reimburse a treatment in concert with savings realised as a result of treatment. This model allows for sharing of the risk of treatment failure with the manufacturer.

Naturally, manufacturers may be unwilling or unable to take payments in instalments or take the risk of treatment failure. This has not been a traditional pharmaceutical model, and could cause significant problems for companies in terms of forward R&D investment, and raising investment capital. A solution to this could be to bring in financial institutions that, for a fee could take on the risk and provide payment in lump sum to the manufacturer, and get annuity payments from the payer. This is similar to a mortgage model, however, with the additional risk that the payer could stop payment if the patient dies or has a remission. This risk will have a cost that would need to be borne by the manufacturer or payer. Over time, this risk may be better quantified and more predictable across therapies, thereby lowering the cost associated with it.

**Pay for performance**

Another interesting feature that could be implemented into the annuity style of reimbursement is paying for performance.

In this model Real World Evidence (RWE) is utilised to measure the efficacy of treatment over time on a patient-by-patient basis. Annuity payment could be linked to scores of efficacy, or payment could even be given as a proportion of RWE measured savings of treated patients when compared to those which remain untreated. This would mean that if the efficacy of treatment for a particular patient decreased over time, annuity payments for that patient would fall accordingly, as represented in Graphic 5.
Challenges to annuity based financing

These models of reimbursement are useful for us to understand how to best to fund cell & gene therapies in a fair and progressive manner. However, in practice implementing an annuity based model will be challenging and will vary in feasibility depending on country and payer sophistication.

The feasibility of annuity-based agreements can be broken in to two dimensions:

- **Capability to track patient performance**
  The historical experience in pay-for-performance schemes

- **Feasibility to pay in instalments**
  Assessed through interviews of national, regional and local payers of US and EU5
Among the US and EU5, Italy has the most promise for annuity-based agreements, with payers responding well to the idea of future implementation. Italy has also built up the most experience in pay for performance carrying out 36 individual schemes since 2000, many of which target oncologics, a therapy area which has typically concerned payers.

Given its disproportionate importance to the global success of high value and specialist therapies, the challenge for annuity payments is that payers in the US are largely of the opinion that annuity payments are not as feasible and would not be considered unless drug cost is over the $1million milestone; however, with the entrance of economically sensible but high up-front cost drugs and increased experience in drug performance tracking, perception and the appetite for annuity models may improve.

7 External stakeholder interviews 2015
8 University of Washington PBRSA database June 2014
Commercialisation

We have considered two key aspects of cell & gene therapies which challenge the commercialisation model:

- Small biotechs leading development
- Sales force specialisation

Commercial challenges facing small biotechs

The current competitive landscape for pipeline cell & gene therapies is heavily dominated by small pioneering biotechs, which collectively develop 83% of projects in the pipeline.9

High activity of deal-making in this area has driven up the market capitalisation of these small players, giving several of them the opportunity to continue clinical development independent of collaboration with larger players or even enter commercialisation alone.

**Graphic 6: Prolific small players in cell & gene therapy**

<table>
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<tr>
<th>Therapy</th>
<th>Player</th>
<th>Market capitalisation</th>
<th>No. of Therapies</th>
<th>Latest phase</th>
<th>Large player-lead product licensing</th>
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Source: IMS Health R&D focus; company websites; google finance Feb 2015

Many of the above cell & gene therapy companies have recently undergone public offerings; some, including Kite Pharma and Juno Therapeutics, have already invested in their own

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9 IMS Health R&D Focus Q4 2014
expansion by building or buying their own sizeable manufacturing facilities and making acquisitions of smaller biotechs to increase in-house development capabilities.

One interesting example of a company that opted to complete development and go to market alone is Dendreon, which in the year of its first and only product launch, 2010, had a market capitalisation value of over $7 Bn. Dendreon was the first company to obtain FDA approval and launch of an autologous dendritic cell vaccine, Provenge. Provenge is used for the treatment of metastatic castrate resistant prostate cancer. Treatment requires the extraction of patients own dendritic cells, these cells are then pulsed with cancer–associated protein, allowed to mature, then are re-infused in to the patient. Provenge is not a curative therapy; however at the time of launch it extended overall survival by 4.1 months over standard of care.

Although the approval of Provenge was a clear milestone in the history of cell & gene therapies, the commercial story of Provenge is not a hugely successful one.

Graphic 7: Provenge company reported sales (2011-2014)

In 2010 expectations for Provenge were high with analysts projecting peak sales over $2bn. Dendreon being a small and relatively inexperienced company faced several challenges starting at launch preparation:

- In 2010–2011, Dendreon did not have sufficient manufacturing facility for Provenge demand; their second and third manufacturing facilities were not online until late in 2011. Consequently the sales effort for Provenge was

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10 Google Finance, 30th April 2010
12 Brean Murray Carret & Co IMS Health White Paper: Cell & Gene Therapies
COMMERCIALISATION

slowed down in order to not disappoint patients. If demand had been forecast accurately, and more timely investments made, launch may not have been compromised

• In 2011 it became increasingly apparent that complications in the reimbursement process were holding back physician willingness to treat patients. Providers who treated patients with Provenge paid the $93,000 cost of treatment and were made to wait several months to recover the upfront cost as reimbursement was only provided once all treatment cycles were completed. This became a limiting factor for Provenge uptake and was eventually rectified; however, creation of a proactive finance solution is crucial; to do this, it’s essential to invest in early in-depth payer and provider research and ensure communication with all relevant parties

• After 2012, sales of Provenge were strongly impacted by the advent of alternatives; clinically strong new oral agents entered the prostate cancer market with global sales of Zytiga breaking $1bn blockbuster status in 2013. This illustrates the challenge that cell & gene therapies are always likely to face where there is, or shortly will be, a conventional therapeutic alternative. Healthcare infrastructure, clinical, payer and possibly patient preference will most likely default, without persuasive arguments otherwise, to conventional therapies

In 2014 Dendreon filed for bankruptcy having accumulated $2.3bn of debt without reporting profit for a single year. Soon after, serial-acquirer Valeant bought the company for $495mn.

The future success of Provenge will become an important case study for other cell & gene therapy small biotechs. As a larger and more experienced company, Valeant is likely to contribute several valuable attributes to Provenge and its business model:

• More efficient new structure & strategy
  Dendreon restructuring to maximise synergy, cut manufacturing costs and gain benefits from tax domicile

• Strong specialist sales force
  Valeant’s sizable sales force in ophthalmology & dermatologics can be repurposed to expand Provenge uptake

• Pharmaceutical experience
  Valeant believes its business model and commercial expertise will enable it to re-ignite this brand

• Capital
  Large investments are required for expansion to Europe, develop clinical data or increase manufacturing capacity

A large company with many of these characteristics will be better suited to building and growing a market for cell & gene therapies. This is particularly significant in times of product uncertainty; when investors in small biotechs will aim to constrict funding, while larger companies may have the resources to ride through rough periods if necessary.

The lack of precedent in cell & gene therapy commercialisation will inevitably lead to mistakes to be made by all companies. However, companies that have diverse experience and a strong commercial market access model, such as Valeant, will be better suited to predict and act on
these mistakes. If Valeant is able to transform Provenge in to a more successful product, it will send a clear message to other relatively inexperienced players about the challenges in cell & gene therapy commercialisation.

The typical cell & gene therapy commercialisation force

The complexity and variety of mechanisms of action within cell & gene therapies will demand a new type of sales force, hyper specialists, in some ways more similar to a Medical Science Liaison or to Medical device sales representatives than the traditional conception of the pharmaceutical sales rep. This would require a smaller force, targeting efforts to few specialist hospitals likely to carry out treatment.

Many cell & gene therapies make use of novel and varied administration devises and procedures, necessitating the training of doctors through from sales representatives and manufacturer run courses. For example, the administration of Glybera requires ~60 intramuscular injections optimally placed to maximise the proportion of skeletal muscle that becomes genetically engineered. In some cases sales representatives may have to advise the physician in the operating room while conducting the procedure. An interesting analogue for a hyper specialist sales force can be found when looking at pacemaker implants; the device sales force has the responsibility of custom programming the pacemaker alongside the physician pre-implantation. This level of communication between the sales force and specialist physicians may be required for the more complex cell & gene therapy administration procedures.
Manufacturing and Logistics

The manufacturing and logistics of cell & gene therapies has been difficult to carry out efficiently, much like the now simple biologics of the past. In the near future there will be a step change in these difficulties arising from the increase in development of personalised autologous treatments which currently make up 60% of pipeline cell therapies.¹³

Manufacturing

Appeasing strict GMP guidelines makes the building of manufacturing facilities slow and expensive. They can be bought, but requirements are stringent and few facilities will be viable. The manufacturing of autologous therapies is particularly difficult to accommodate as each individual patient’s treatment must go through the entire manufacturing procedure independently, heavily impacting efficiency. This has historically been done manually with only one patient’s cell samples being processed on a clean bench at one time. However automation of the manufacturing process is a clear solution to improving scale and this should be considered early in the product lifecycle in order to maximise efficiency.

Three years after launch, a significant portion of the Provenge manufacturing process was being carried out manually, although a change to automation is now being pushed by Valeant.

Maintaining flexibility in order to match manufacturing capacity and patient demand is key. Manufacturers may have to set up contracts enabling the lease of facilities in order to expand or contract output efficiently. Maintaining flexibility was challenging for Dendreon; at launch, capacity fell short of demand, but in 2015 they had an “infrastructure in place for a billion dollar product” Valeant CEO Michael Pearson.

These shortfalls in efficiency heavily impacted the profitability; 67% of Provenge revenue was spent on producing and delivering the product.¹⁴ This is far above typical industry values for biologics, original brands and generics: 15%, 25% and 50% respectively.¹⁵

Difficulty in finding efficiency in the provision of autologous therapies does not stop at the manufacturing process, but continues to the logistical requirements.

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¹³ IMS Health R&D Focus; Thought Leadership analysis;*Excludes all non genetically engineered therapies
¹⁴ Dendreon 10k filing, financial year2013; figure based on revenue from 2011-2013
Logistics

Autologous therapies do not fit the traditional pharmaceutical delivery pathway where the product is manufactured, shipped to wholesalers, distributed to providers and then administered to the patient.

We have used Provenge as an example of an autologous therapy logistical chain. The chain begins with sample being taken from the patient by the provider, and sent directly to the manufacturer. As these are living cells their therapeutic efficacy is often time dependent, for Provenge, cell samples have 18 hours to go from patient to manufacturer. Due to the wide distribution of Provenge patients in the US, this was done utilising commercial flights to carry cold boxes of patients’ cells cross–country to one of three Provenge manufacturing sites. Dendreon would then aim to fully process the cells and fly them back to the provider, to be infused in the patient within 18 hours of manufacturing completion. This must be done three times over six weeks for each patient.
There are numerous complexities with this distribution model. Firstly carrying out this process even once for each patient will be very costly and there is no doubt it had great effect on the profitability of Provenge.

Perhaps most daunting is the necessity to perfectly execute the logistical movements of every patient sample. This must be done in a time sensitive, per patient request manner; mistakes cannot be made in the chain as patients are heavily dependent on receiving their therapies, not to mention the costs associated with each sample. Logistical planning for predicaments, such as airport closures due to poor weather or power outages, must be prepared for in advance.

This chain will require a great deal of communication between the provider and the manufacturer, Dendreon tackled this with an effective online platform connecting them with certificated physicians using Provenge. Further integration may also be useful with managing logistics. Some Monoclonal Antibody (MAb) oncology products in Europe are utilising dedicated project managers to help key accounts solve organisational problems. Similar services may be required for organisation of the treatment pathway in cell & gene therapies; however, stakeholder responsibility over intricacies within the treatment pathway has not been established.

How far will companies have to go? Which parties will bear which costs in the treatment pathway, and should these costs be included as part of a full treatment package?

Bringing the patient to the manufacturing site

Complexities and possible complications associated with the cell transport chain drives innovation for an alternative solution. Could you bring patients to the manufacturing site and avoid the transport chain? We describe two novel models for carrying this out:

A large company run treatment facility

Specialist physicians and manufacturing facilities located on a single treatment site. Patients may even travel internationally to be treated at these specialist centres. Apart from the elimination of cell transportation logistics this has the advantage of having access to the most experienced and best informed physicians, savings from economies of scale and easier GMP approval. The main hurdle will be patient burden from the need to stay at the facility for some time and the costs associated with patient travel and accommodation; however, given the likely high price of therapy these costs may be insignificant.

Distribution of cell processing devices

Larger hospitals in regions could use a scaled-down user-friendly cell processing device. Physicians could extract patient cells, input them in to the device, add in disposable reagents such as tumour antigens and cell maturation factors (provided by the manufacturer). This model resembles a more conventional therapy chain of distribution, as the product provided remains off the shelf until reaching the hospital, while also easing the burden on the patient.
Hurdles include the cost of the device, uncertainty over device GMP approval and the technical difficulty in producing a device capable of reliably altering patient cells.

These are two extreme examples of alternatives to the logistical chain associated with cell & gene therapies. Ultimately, patient population size and the specific requirements of each therapy will determine what kind of strategy is most efficient, but what is clear for autologous therapies is that efficiency will have to be developed, not borrowed from the traditional pathway.
Conclusion

Cell & gene therapies are more popular than they have ever been; pipeline product valuations and deal activity spiked in 2014 with no signs of slowing through 2015. This activity is being driven by large pharma taking increased interest in the area due to the prevalence of efficacious and potentially curative treatments making it in to late stage development, many of which are breakthrough or fast-track designated.

Given the lack of experience in the field, cell & gene therapies will pose novel and unique challenges for players to understand and overcome in order to commercialise successfully.

Product valuation will be a point of contention due to possible clinical and economic justifications for high cost. Steep prices will be particularly concerning for payers who will find difficulty in financing the high upfront cost of these products when savings as a result of therapy may take years to balance the books. Payer confidence in the efficacy, safety, reproducibility and longevity of treatment will need to be addressed. Use of innovative funding schemes to overcome reimbursement challenges could be necessary for high cost cell & gene therapies, in order to aid market access and potentially increase patient population groups reimbursable by the payer.

Developing a strong commercial model for cell & gene therapies will be complex and difficult to execute. Although many smaller players may utilise the high levels of investment in the area, raised capital may not be a suitable replacement for diverse pharmaceutical experience when it comes predicting and navigating novel challenges. The cell & gene therapy commercialisation sales force will require greater training and higher levels of specialisation than is conventional for pharmaceuticals, and may have more in common with medical device sales representatives in terms of training and approach.

Manufacturing and logistical challenges will be plenty, particularly for autologous cell therapies. Maintaining cost efficiency whilst providing personalisation will require ambitious strategies for both manufacturing and logistics. Effective automation of the manufacturing and logistical process is a must if the patient population is non-orphan.

Within this decade we will see cell & gene therapies launching in to market, entering in to relatively unchartered waters with respect to valuation, reimbursement, commercialisation and manufacturing. Cell & gene therapies are a different game to traditional pharma and should be approached as such.

Five questions that companies which either are, or are considering investing in cell & gene therapy should ask themselves:

- What will be the unique clinical advantage of the cell or gene therapy being developed? Innovation in the technology platform alone is not sufficient. These therapies must be able to compete on clinical efficacy with current and future conventional pharmacotherapies. In fact, given the other challenges cell and gene therapies bring to healthcare systems, a clear margin of clinical superiority to any conventional therapies that are or will be on the market is probably desirable
CONCLUSION

- What are the uncertainties in the value proposition, and how can those be dealt with clearly and effectively in making the initial price to payers? Uncertainties on the duration of clinical effect, side effects or response need to be transparently identified, acknowledged, and addressed from the earliest discussions with payers and providers. Ducking or downplaying issues holds a greater danger of adverse consequences.

- What healthcare system logistical and funding challenges is the introduction of this therapy likely to cause? By early Phase III, build a 360 degree view of the path to patient for the therapy, from the perspective of patient, prescriber, payer and other key parties. Identify how it is different to the current path these patients travel. Build an action plan to address the differences and gaps between the two which supports any changes in the path for patients, payers and providers.

- What type of commercial model is needed for success? Customer facing individuals may need a different skill set to the conventional pharma rep, with training, work alongside healthcare professionals, relationship building and technical expertise a greater priority than is usual. These individuals may therefore be closer to MSLs or some types of medical device sales representatives. Other aspects of the commercial model may also be novel.

- What are reasonable expectations in terms of uptake and investment to create the market? There is no market for cell and gene therapies. It needs to be created, and creating markets takes time and sustained effort. Companies need to be prepared for a long haul, even if they are owners of a revolutionary therapy, because by its very nature their therapy is likely to challenge, and if successful, transform disease areas and healthcare provision, and healthcare systems contain a great deal of inertia.
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