nibrt

National Institute for
Bioprocessing Research
and Training

The case for supporting Cell and Gene Therapy Manufacturing in Ireland

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Contents

1 Introduction

Ireland is a recognised global Centre of Excellence for Biopharma Manufacturing. The last 10 years have seen tremendous success in attracting foreign direct investment (FDI) associated with MNCs establishing their biopharmaceutical manufacturing operations to our country. In this period capital investments of ~€10bn have been made and the number of biopharmaceutical manufacturing sites has grown from 3 in 2003 to 22 in 2019. Over 30,000 employees are directly employed in the sector, contributing €40bn+ in exports. Much of this success is predicated on the availability of highly educated personnel, a track record of operational excellence and the existence of a thriving ecosystem supporting the sector.

While this national strategy has clearly been successful, the sector is evolving rapidly and we must again take proactive measures to ensure our position. The majority of current activity relates to the production of recombinant therapeutic proteins such as monoclonal antibodies. Recently there has been a global surge in interest and investment in cell and gene therapies (also sometimes referred to as ATMPs - Advanced Therapy Medicinal Products). This interest is supported by the large number of clinical trials (1028 globally in 2018 with a target enrolment of 59,000 patients), the increase in venture capital investment ($13bn globally), the increase in capital investment in new facilities and the number of partnerships and acquisitions in ATMPs[1].

This document outlines the case for why Ireland needs to take immediate steps to respond to these new developments and how we are ideally placed to capitalise on our existing success as a destination for Biomanufacturing excellence.

1 http://alliancerm.org/wp-content/uploads/2019/03/ARM_AR2018_Web_FINAL.pdf

2 Executive Summary

The National Institute for Bioprocessing Research and Training (NIBRT), through its in-house expertise and global network of industry contacts, monitors emerging trends in the Biopharmaceutical sector. This activity led to the initiation of a process to assess the opportunities presented to Ireland by the huge growth in a new group of therapies referred to as Cell and Gene Therapies (CGTs). This commitment was catalysed by feedback from numerous individuals with global leadership roles in some of the world's largest Biopharma companies who strongly recommended that Ireland should be positioning itself to capitalise on this growth. The process was initiated with a preliminary meeting in December 2018 in NIBRT involving representatives from relevant national stakeholder groups including academic researchers, Biopharma manufacturers, regulators, funding agencies, indigenous SMEs, data/logistics specialists, HEIs, industry associations, specialist equipment vendors and engineering design companies.

Vision

Ireland will build on its reputation as a global leader in Biologics manufacturing to become the lead destination for Cell and Gene Therapy production. To achieve this we will target the development of a highly trained workforce with skills relevant to producing these new medicines and support research into technologies and tools to overcome the challenges associated with safe and economical manufacture of Cell and Gene Therapies.

Cell and gene therapies encompass a range of diverse, life-changing and life-saving therapeutic modalities based on using cells and genes to address some of the most grievous human illnesses. Some extraordinary clinical results in recent years have led to an explosion in the number of new companies developing these therapies or technologies related to their production and delivery[2]. Several of these have been the subject of multi-billion dollar acquisitions by some of the traditional big Biopharma companies, underlining the excitement and anticipation around the promise CGTs represent for the future[3]. Furthermore, major investment is now under way globally by both private and public entities to create manufacturing capacity and capability.

Ireland has proven itself over the last decade as one of the premier Biopharma manufacturing destinations globally with all of the top 10 Biopharma multinationals having significant operations here. That success has led to thousands of high-value jobs, billions in FDI, a thriving service industry and €46.3bn in exports (~33% of total) in 2018[4]. The technologies and facilities required for the production of many CGTs are similar to those currently in place in Ireland for the manufacture of existing protein-based therapies, therefore there is the potential that these manufacturing processes could be encouraged to come here in the future.

The question is, are we ready? Will Ireland be attractive to companies making investment decisions around CGT production?

In composing this paper we set out to explain, in brief, what CGT therapies are, the recent growth in activity around them and some of the challenges related to manufacturing them at commercial scale. We attempt to assess the opportunity and outline why Ireland, with appropriate investment, can capitalise on its existing reputation as a Biopharma manufacturing destination as well as to become an innovation hub for technologies related to CGTs and their production and develop an action plan to progress the opportunity.

2 https://alliancerm.org/wp-content/uploads/2018/08/ARM_Q2_2018_Web.pdf

3 https://www.forbes.com/sites/mergermarket/2018/06/19/demand-for-gene-therapies-to-prompt-surge-in-pharma-ma/

4 https://www.cso.ie/en/releasesandpublications/er/gei/goodsexportsandimportsdecember2018/

This plan identifies actions in the following areas:

1. workforce development
2. developing a world-class, scientifically excellent research community
3. enhancing key infrastructure to support training and research
4. the role of government and state agencies

Many other countries are investing in supports for CGTs, for example the £50m+ UK investment in a Cell and Gene Therapy Catapult in 2014. Ireland's early entry into and success in Biopharmaceutical manufacturing is now being replicated by other jurisdictions including China, Korea, India and Singapore. Many countries have and will have similar ambitions around CGT manufacturing.

While Ireland's existing reputation will be important, simply put, if we don't address the training requirements and demonstrate a commitment to supporting innovation around the challenges associated with manufacturing this new wave of medicines now, this opportunity will pass us by.

In summary:

- The strong growth in cell and gene therapies represents an opportunity to underpin the next wave of FDI
- Very significant manufacturing and supply chain challenges represent an opportunity for Ireland due to existing ecosystem
- Investments are already underway in competing jurisdictions
- There is an immediate need to define Ireland's value proposition for cell and gene therapies manufacturing

3 What are Cell and Gene Therapies?

Cell and gene therapies is an umbrella term for a broad group of therapies that are otherwise referred to as Advanced Therapy Medicinal Products (ATMPs). These terms encompass gene therapies (viral and non-viral – including liposome/polymer/exosome-based delivery of RNA and DNA), cells as therapies (modified or unmodified) and engineered tissues. They form a disparate group both in terms of application as well as the methods of producing them.

In the last couple of years the promise of cell and gene therapies has finally started to come to fruition. For the greater portion of the history of modern medicine we have relied on what are typically referred to as small molecule drugs. While these have been and will continue to be a critical part of the medicinal arsenal available to physicians for treatment of disease, the dawn of biotechnology in the early 1980's ushered in the next class of therapeutic modality – recombinant proteins or Biopharmaceuticals. These drugs are produced by living cells grown in large bioreactors and have revolutionised the way in which many diseases can be treated. For patients lacking functional versions of certain proteins e.g. Factor VIII or IX in haemophilia, these therapies provide a safe and reliable alternative to the traditional animal or donor blood-derived material. For patients with certain malignancies, antibody-based therapy has greatly reduced the severity of side-effects compared with chemotherapeutic agents and improved outcome due to their highly specific mode of action. Recombinant proteins now account for 40% of the pharma market and a further 40% of company pipelines[5].

While recombinant protein technology has revolutionised medicine, CGTs have progressed at a more modest pace over the same period of time. Partly that is related to the complexity of these new modalities but also to some negative outcomes in clinical trials in the early 2000's. However, while protein-base therapies have revolutionised modern medicine, CGTs have distinct advantages in some circumstances. For example, rather than periodically administering a functional version of a missing or faulty protein, supplying a correct copy of the protein-encoding gene has the potential to permanently fix the problem. This is often referred to as the 'one and you're done' concept. Or in the case of certain blood malignancies, genetically re-programming the patient's own immune cells to recognise and eliminate cancerous cells, using CAR-T cells, has proven very effective. In the last 2-3 years a small number of products that fall into this category have received market authorisation including, for example, a gene therapy (Luxturna™) for a particular form of blindness which has been commercialised by Spark Therapeutics.

As mentioned above these medicines are highly sophisticated and therefore present complex and unique challenges in order to produce them efficiently, effectively and safely. Indeed one of the first gene therapies to receive approval, Glybera™, was subsequently withdrawn having treated just one patient in Germany at a cost of €1m for a single dose. While the drug was a regulatory and therapeutic success, it was a commercial failure, mostly due to the very small patient population (it treated a rare enzyme-deficiency disorder) and associated high cost per dose.

The following section will briefly describe the nature of these modalities and some of the challenges related to their manufacture.

5 https://pharmaintelligence.informa.com/~/media/informa-shop-window/pharma/files/pdfs/whitepapers/rd-review-2017.pdf

- **Gene therapy** refers to the delivery of a functional copy of a gene that a patient is lacking or suppression of a gene that causes disease. This may be to specific cells where the encoded protein performs a specific function e.g. the gene *RPE65* in Leber's disease, an ocular disorder that leads to blindness, or to cells that secrete the protein to perform a function elsewhere, e.g. the Factor IX gene delivered to liver cells to help with blood clotting systemically. Gene suppression involves the use of rapidly expanding technologies such as RNA interference (RNAi) or genome editing using, for example, CRISPR-Cas. These gene therapies can be delivered using the same methods as used for delivery of a functional copy of a gene, i.e. using a virus or various non-viral methods. The most common viral vectors are Adeno-associated virus (AAV) or lentivirus (LV), both of which effectively deliver the therapeutic DNA or RNA into the target cells. Non-viral methods rely on either chemical delivery agents, such as liposomes, exosomes or synthetic polymers for example, or physical treatments, such as electroporation, to introduce the genetic material into target cells *in vivo*.
- **Cell therapies** in the broadest terms have been used for many years, for example blood transfusions or bone marrow transplants, however in the context of cell and gene therapies, cell therapy refers to cells that have been substantially expanded or modified through exposure to particular growth conditions *ex vivo*. Cell therapies can be further classified as autologous (where a patient is treated with their own cells) or allogeneic (where a patient is treated with cells from another individual). Often in the case of the latter, cells derived from a small number of donors may be expanded and used to treat many recipients. Takeda are currently building a facility in Grange Castle that will produce Alofisel™ - an allogeneic cell therapy approved for treating complications associated with Crohn's disease.
- A combination of both of the above approaches results in what often referred to as **gene-modified cell therapy** or *ex vivo gene therapy* where cells are genetically modified outside the body – typically by viral transduction – and then infused into the patient. This is the basis for CAR-T cell treatments where T cells (part of the immune system) are harvested from the blood of cancer patients and re-programmed with a gene (delivered by a viral vector) followed by expansion, formulation and re-infusion back into the patient. The gene allows the modified T cells to detect cancer cells and destroy them and, importantly, they can persist in the patient long after the cancer is effectively treated. An example of this approach is Kymriah™ from Novartis which was approved in 2017 and is used to treat paediatric B cell acute lymphoblastic leukaemia. Furthermore, Cellectis and Allogene are partnering to develop an 'off-the-shelf' (allogeneic) CAR-T cell therapy.[6]
- Finally **regenerative medicine** or *tissue engineering* is another approach with several products on the market particularly for cartilage (Chondron™) and skin replacement therapy (Stratagraft™). These products are usually generated from special stem cell populations that are subsequently expanded for administration or treated in some way to cause them to form specialised structures ex vivo before being applied. As with other cell therapies these can be either autologous or allogeneic.

6 https://pharmaphorum.com/news/allogene-raises-another-120m-to-develop-off-the-shelf-car-ts/

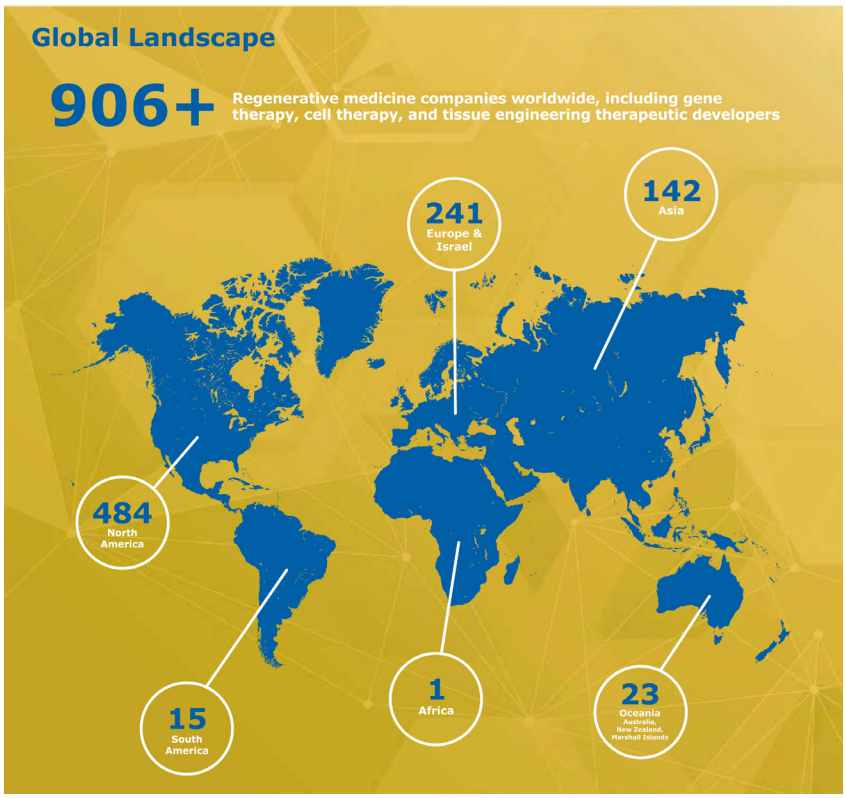
4 What is the state of play currently regarding these therapies?

The recent increase in approvals of cell and gene therapies and some very promising, in some cases striking, clinical outcomes in a number of trials has created huge interest in these approaches both in terms of new trials and commercial activity. It is estimated that there are >900 start-up companies in this space and many of the large pharma/biopharma MNCs are now actively entering the arena - via acquisition mainly (Fig.1).

The commercial value of CGTs is forecasted to be very substantial over the coming years (Fig.2)[7]. Interestingly, the majority of this growth will come from outside of the top 20 Biopharma companies thus leading to potential Foreign Direct Investment (FDI) opportunities from newer US mid-size Biotechs. Furthermore, given that many of Ireland's existing MNC clients are American, future acquisitions in this space by these MNCs will create further investment opportunities at Irish sites.

In Europe since 2009, ten cell and gene products have been authorized (4 have been withdrawn, such as Glybera)[8]. As of end 2018, there were over 1028 clinical trials ongoing or completed worldwide and this number is rising rapidly[9]. In January 2019, the US Food and Drug Administration stated that it expects to see more than 200 applications per year by 2020 requesting permission to begin cell and gene therapy trials. The agency already has more than 800 such applications on file and plans to hire some 50 clinical reviewers to handle the surge[10].

Figure 1. Global activity in CGT – company numbers[11].



7 Evaluatepharma World Preview 2018, May 2018

8 https://labiotech.eu/features/atmp-cell-gene-therapy-ema

9 http://alliancerm.org/wp-content/uploads/2019/03/ARM_AR2018_Web_FINAL.pdf

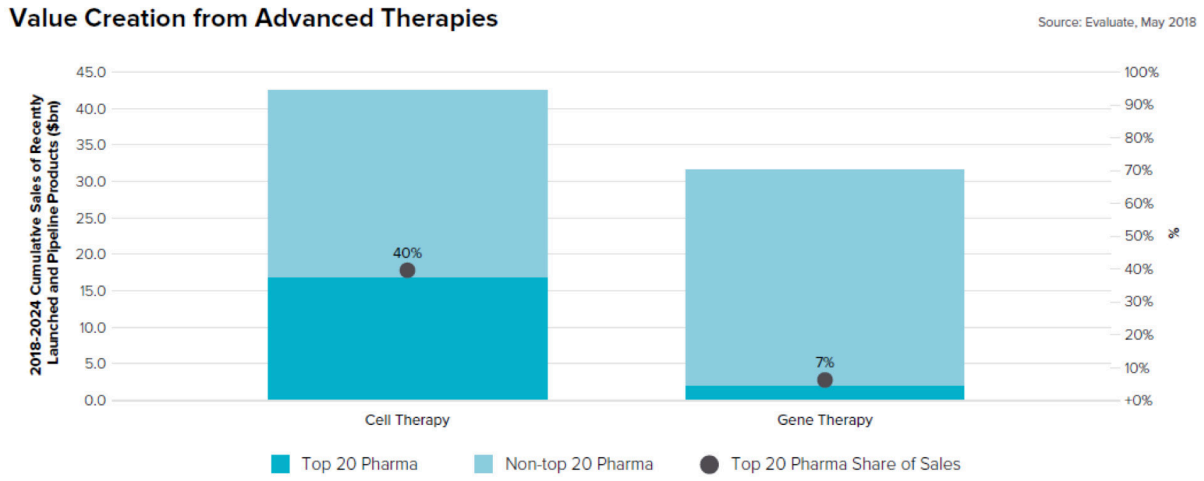
10 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm629493.htm

11 Data from Alliance for Regenerative Medicine 2018

Specifically, recent commercial activity in the CGT space includes:

- 2017 saw the landmark FDA approvals of the first two chimeric antigen receptor (CAR) T-cell therapies: Novartis' Kymriah and Kite/Gilead's Yescarta hailed as "a new frontier in medical innovation".
- 2018 saw Celgene paying $9bn to acquire leading CAR-T company, Juno Therapeutics[12]
- May 2018, Novartis acquired gene therapy developer AveXis for $8.7bn[13]
- In Dec 2018, Moderna had the largest ever biotech IPO valued in excess of $600m based on its mRNA therapeutics
- Jan 2019, BSM made a bid to acquire Celgene for $74bn[14]
- Feb 2019, Roche offer $4.3bn for Spark Therapeutics
- March 2019, Biogen signal intent to acquire Nightstar for $800m
- March 2019, Cellectis announces plans to build 82,000sq.ft. CAR-T facility in North Carolina and 14,000 sq.ft. facility in France
- In March 2019, Thermo agree to buy Brammer Bio a viral vector CDMO, in a $1.7bn cash deal
- In April 2019, Regeneron announce an $800m investment in Alnylam, who in Aug 2018 received the First-Ever FDA Approval of an RNAi Therapeutic[5]

Figure 2. Projected sales of licensed and pipeline cell and gene therapy products by company size[15]



12 http://fortune.com/2018/01/22/celgene-juno-deal/

13 https://cen.acs.org/business/investment/FDA-prepares-huge-growth-cell/97/i3?utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A+cen_latestnews+%28Chemical+%26+Engineering+News%3A+Latest+News%29

14 https://www.biopharma-reporter.com/Article/2019/01/09/BMS-and-Celgene-see-cell-therapies-as-future-of-oncology?utm_source=newsletter_daily&utm_medium=email&utm_campaign=09-Jan-2019&c=Hbej9aWL57tk0JwBBZc28MSYc74aktQD&p2

15 Evaluate Pharma World Preview 2018, May 2018

What are the challenges associated with each modality in terms of manufacturing?

While the promise of these therapies is obvious based on many of the clinical trial results there remains numerous challenges related to commercial manufacture and supply particularly to large patient populations. Each modality has its own unique challenges but some are relevant to all. Furthermore there is no universally accepted way of generating either gene or cell therapies – therefore each company is developing their own manufacturing capability often with limited in-house expertise which is time- and resource-consuming. It also may lead to a situation where the solutions to these complex manufacturing challenges become siloed in individual companies. This section will attempt to outline some of these issues in brief.

Gene therapy:

The technology currently employed to manufacture viral vectors is adequate for small patient populations (rare diseases) or to generate enough GMP material for clinical trials but significant improvements still need to be made to improve yield for more common indications. Dose can vary greatly also depending on the indication with ocular treatments typically requiring 10^{11} AAV particles per eye for example, but blood factor replacement or muscular dystrophy could require 10^{13} – 10^{14} particles per kg. Furthermore viral vectors (both AAV and LV) are produced by transfecting a human cell line growing in culture, typically adherent culture – which is difficult to scale – with 3 or 4 plasmids carrying the various genes required to generate the virus as well as the therapeutic gene. These plasmids must initially be made in bacterial cells and purified to GMP standards. The resulting viral particles must be harvested, purified and tested for purity and potency and formulated for delivery. At each of these steps there are challenges to solve and opportunities to improve the associated technologies. For example:

- generating high-yielding suspension culture cell lines
- generating chemically-defined media formulations for cell culture
- finding alternatives to large-scale transient transfections (for example creating stable, inducible cell lines akin to a mAb-producing CHO cell)
- reducing the incidence of 'empty' viral particles (where the therapeutic gene has not been packaged within the virus – a particular problem with AAV)
- finding novel separation technologies to purify correctly packaged virions from empty capsids
- Ensuring absence of replication-competent virus[16]
- new analytical techniques to monitor critical quality attributes of the viral product and improving stability after formulation

This is by no means an exhaustive list but illustrates some of the hurdles that must be overcome to ensure gene therapies are a commercial as well as a therapeutic success. NIIMBL have recently published a Technology Roadmap highlighting the challenges for CGT manufacturing in more detail[17]. It's obvious from the list above that the regulatory implications are significant also. Scott Gottlieb, M.D., outgoing FDA Commissioner commented that, *'In contrast to traditional drug review, where 80 percent of the review is focused on the clinical portion of that process, and maybe 20 percent is focused on the product issues, I'd say that this general principal is almost completely inverted when it comes to cell and gene therapy. The initial clinical efficacy is often established early, and sometimes in small series of patients. The more challenging questions relate to product manufacturing and quality...'*[18] Finally it is also worth noting that there is currently a global lack of clinical-grade manufacturing capacity available[19] which creates a bottleneck both for small companies and academia trying to generate material for early stage trials and larger entities anticipating market authorisation for more advanced leads.

16 https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM610800.pdf

17 https://niimbl.force.com/resource/1541788844000/NIIMBLGeneTherapyRoadmap?

18 https://www.fda.gov/NewsEvents/Speeches/ucm608445.htm

19 https://www.genengnews.com/insights/scaling-up-cell-therapy-manufacturing/

Cell and gene-modified cell therapies:

The challenges related to manufacturing cells as therapies are very much dependent on whether the treatment in autologous or allogeneic. Autologous treatments, such as CAR-T cells, by their very nature cannot be scaled-up (apart from production of the viral vector) as each individual treatment is essentially a unique batch produced from and for a single patient. Therefore the technical solution to delivering this type of therapy to large patient cohorts depends on scale-out, i.e. multiple small production units. Furthermore the individual nature of the treatment means that 'raw materials' – the patient's blood cells – are inherently and dramatically variable creating significant debate as to how QC can be applied. In addition, the process of harvesting a patient's T cells, activating and expanding them, transducing with lentivirus, harvesting, formulating and re-infusing must be achieved in a compressed timeframe – typically 10-15 days – which limits the opportunity to perform extensive product quality/safety or other traditional lot release assays. Allogeneic products are more amenable to scale-up, at least for part of the manufacturing process after which they can be stored, but once thawed they may also have a very limited timeframe within which they need to be administered. This last step must therefore either be achieved near to the patient which requires local specialist infrastructure and skilled operators, or more centrally which requires a reliable, fast and efficient logistics network. Finally, this creates challenges around data handling including supply chain management, product tracking, complex data privacy laws (GDPR) and increased trend towards linking remuneration structures to patient outcome.

5 What is the opportunity for Ireland?

Building on its pharmaceutical manufacturing legacy from the 1950s, Ireland was able to successfully compete for FDI investment in Biologics manufacturing winning over €10 billion of investment from 2008-2018. Government's strategic investment in NIBRT in 2005 to provide Biologics manufacturing training and research was especially helpful in winning and sustaining this investment. Cell and gene therapies manufacturing technology is still at a very early stage of development, equivalent perhaps to the manual roller-bottle technology of the 1980's for early clinical manufacturing of the first approved products from recombinant CHO cells (i.e., rtPA and EPO) or mouse ascites technology of the 1980's for manufacturing of the first approved mAb (OKT3)[20]. As with mAbs and other recombinant proteins, the manufacturing technology around CGTs must and will improve in order to meet market demand and to ensure affordability. Fundamentally, manufacturing many of these therapies requires similar infrastructure and skillsets as needed for mAb production, therefore it is likely that many of the existing facilities in Ireland could become locations for CGT production also. As mentioned earlier, the high levels of CGT activity and innovation in the US and the predominance of US big pharma companies with facilities in Ireland also represents an opportunity. However, while this is a good start, *it will not be enough for us to compete in the future unless we invest in aligned and appropriate scientific and engineering expertise*. To ensure this happens it will be necessary to create a supportive and proactive environment.

This includes:

- a commitment to ensuring small and large companies can source appropriately trained advanced manufacturing staff (NIBRT, Remedi and the HEIs);
- ensuring availability of scientific and engineering expertise within the national research system (HEIs);
- providing the necessary infrastructure to support investment or development (testbeds, incubators).

Ireland has a global reputation as an attractive location for biomanufacturing but we cannot afford to allow the opportunity provided by these new therapies to pass us by. Already other jurisdictions are investing heavily to attract and support this industry. The UK has invested in a Cell and Gene Therapy Catapult in Stevenage to give the country a head-start in attracting CGT development which provides facilities to scale-up production. A lot of smaller UK companies have been frustrated at the lack of manufacturing facilities available and the Catapult is a response to this. 30% of Europe's 400+ SMEs active in cell and gene therapies are based in the UK, and the UK have stated that the CGT Catapult will help build a £10bn industry[21]. It is worth noting that this facility took approximately 4 years from conception to active operation (anticipated sometime in 2019).

The opportunity exists for Ireland to leverage and further develop its existing capability to become a global leader in CGT manufacturing, characterisation and supply but we must act quickly. This will require the development of a strong CGT manufacturing research and training strategy and capability. This will be of critical importance for existing Irish manufacturing sites to win mobile opportunities to manufacture these products as they become more commercially mainstream within their parent organisations as well as supporting smaller indigenous companies with targets or technologies in this area. It should also be emphasized that to make a success of this will require a sustained effort that is developed pro-actively year-on-year.

20 Kelley, B. 2009. Industrialization of mAb production technology The bioprocessing industry at a crossroads. MAbs. 1(5): 443–452.

21 https://www.gov.uk/government/publications/cell-and-gene-therapy-develop-new-treatments-in-the-uk/cell-and-gene-therapy-develop-new-treatments-in-the-uk

6 How can Ireland create a supportive Ecosystem for CGT Manufacturing?

Currently Ireland is a recognised global Centre of Excellence for Biopharma Manufacturing, employing 30,000+ direct employees in the sector and contributing €40bn+ in exports. Much of this success is predicated on the availability of talent and track record of the operations here. This is accomplished by the existence of a thriving ecosystem supporting the sector.

The last 10 years has seen great success in FDI associated with MNCs establishing their biologics manufacturing operations here - €10bn in capital investment. Twenty two companies are now involved with biologics manufacturing from a base of three in 2003. The IDA's investment in NIBRT to support the growth of this industry in Ireland has contributed greatly to this success by ensuring a steady supply of appropriately trained personnel. Table 1 lists some of the supportive elements that underpin this ecosystem and identifies how these elements should be expanded or modified to avail of the opportunities that CGT manufacturing present. This was the starting point for discussions that led to the actions listed in the next section.

Table 1. Starting point for broader stakeholder input

	Existing Strength	Key Points
1	Strong output of STEM graduates from the Universities and Institutes of Technology	While skills related to recombinant protein manufacturing are relevant to CGT, there is a need for more graduates with appropriate skillsets. HEIs to ensure content relevant to CGT manufacturing in course curricula during programmatic reviews. NIBRT to partner with HEIs and other stakeholders to develop a range of training solutions to address the skills requirements for manufacture of CGTs, e.g. New MSc in Cell Process Technology at Remedi
2	Track record of the 75+ Pharma and Biopharma companies in Ireland	Opportunity for further FDI by existing MNCs based on their previous success. The move from Biologics to CGT is not as great a challenge as small to large molecule manufacture – but still *should not be underestimated*
3	Internationally renowned Services, Consulting, Construction and Specialist Equipment Vendor companies supporting the expanding MNC base	Some of these companies are already supporting the global CGT community - opportunity needs to be shared more widely
4	Proactive Government agencies supporting sector growth (IDA, EI, SFI)	Recognition and broad alignment needed by agencies of the opportunities presented and what their part to play is.
5	Excellent Regulatory track record (HPRA)	On-going effort both nationally and internationally to drive effective, innovative and proportionate regulation in the context of both product and manufacturing authorisation
6	A dedicated Training and Research Institute for biologics, NIBRT	A Pilot facility for training on CGT is needed. This could also provide for proof-of-concept studies and potentially small quantities of pre-clinical material.

7	Strong Trade Associations and Professional Societies (IBEC, AmCham, BPCI, EI, ISPE, etc)	Awareness of the opportunities and further consultation to determine the skillsets needed for future success, e.g. ISPEs *Workforce for the Future Initiative*[22]
8	A strong and growing research community focussed on key challenges associated with biologics manufacturing	Remedi (NUIG) and some other HEIs have been engaged with CGT research for some time, but this needs to be further expanded across all the relevant Universities and Institutes of Technology
9	A small, but renowned, research community involved in Basic Discovery, i.e. of new CGT solutions for disease, and in particular technologies around delivery	There is a growing awareness in the University research community around CGTs – this should be developed, supported and promoted further. Establish an academic forum focused on cell and gene therapies

Proposed National Strategy for Cell and Gene Therapy

For Ireland to capitalise on the opportunity presented by the growth in CGTs in the coming years the Cell and Gene Therapy Manufacturing Forum has defined a series of actions that we believe will be necessary to ensure this happens. The actions address different aspects of the ecosystem including:

As outlined in the previous pages the growth of CGT medicines has exposed a global shortage in personnel, expertise and capacity to ensure the delivery of all the new products that are emerging from research labs as well as at various stages of clinical trials. It has also exposed the many challenges involved in safely and economically manufacturing these therapies at scale. However, it is apparent that many of Ireland's traditional competitors in the protein manufacturing space have progressed with strategies and supports to attract further investment in the CGT manufacturing space. Many of these international competitors have already established National Centres to focus their efforts and compete for this growing industry. Without comparable focus and investment, Ireland will fall further behind in the race to secure some of this business. Investments in research and development of CGT manufacturing technologies and processes, coupled with initiatives in the HEIs and NIBRT to educate a skilled workforce should enable Ireland to compete successfully in this area.

We believe that the existence of a thriving, predominantly recombinant protein- and vaccine-based, manufacturing sector here means that Ireland should be well placed to compete for these investments, however there are many unique and specific challenges in manufacturing CGTs, therefore additional strategies will be needed to make a convincing case for companies to invest here.

By implementing the recommendations outlined in this document, we believe that Ireland can successfully attract investment in CGT manufacturing facilities and build a research community focused on novel and transformative solutions relevant to CGT production.

Table 2 outlines a range of recommendations from this group that need to be executed upon in order to prepare the ground to not only maximise the chances of Ireland's winning further FDI but to encourage indigenous innovation and growth in CGT-related activity.

22 https://ispe.org/initiatives/workforce-future

Table 2. ***Action Plan for CGT***

Workforce Training and Development		
Area	*Action*	*Implementation*
Increase STEM graduate numbers	HEIs to evaluate opportunity to offer CGT MSc courses.	NIBRT to communicate with stakeholders in all 23 HEIs. Promote existing MSc in CCMI
	HEIs to add CGT manufacturing content during programme reviews	HEIs to engage Heads of STEM schools/ depts.
	NIBRT to develop a range of training solutions	NIBRT to run joint programmes with Remedi and GE
Training facility for CGT manufacturing	Install Pilot Plant for CGT manufacturing at NIBRT	NIBRT to work with industry to further define needs
Proactive Government Agencies		
Area	*Action*	*Implementation*
FDI	IDA to define the value proposition to attract FDI in CGT	IDA to develop marketing collateral for CGT FDI in Ireland
	Targeted IDA marketing plan	Engage IDA project executives on CGT opportunity
	Ensure existing Biopharma MNCs are aware of opportunities	BPCI & IDA to assist site leads to pitch for site selection studies
National Strategy for CGTs	Inform DBEI of importance of CGT	IDA and BPCI
	SFI to make CGT a high priority area	NIBRT to engage with SFI
	Engage with EI to nominate CGT as high priority area	EI to communicate opportunity to relevant clients
Regulatory track record	Capitalise on exemplary regulatory track record of Irish manufacturing facilities and HPRA	Highlight in marketing collateral that EU is ahead of FDA on CGT guidelines
	HPRA to continue to build regulatory profile at EU level	Leverage RSI and HPRA's innovation office
	Supporting education and training in Regulatory Affairs	HPRA to continue to engage with and contribute to HEI programs
Building a Supportive Research Environment		
Area	*Action*	*Implementation*
CGT Manufacturing Research	Establish a working group focussed on CGT manufacturing technologies	NIBRT to initiate via sub-group of this Forum
CGT Discovery Research	Resolve issues such as: how to encourage further development of Irish SMEs; is an Irish Catapult required to support CGT innovation?; how to increase research funding levels for CGT	NIBRT to initiate establishment an academic forum focussed on CGT discovery and delivery. CCMI to assess capacity to provide Phase 1/2 material
Other Supporting Elements in the Ecosystem		
Area	*Action*	*Implementation*
Consulting, Construction, Equipment vendors	Ensure awareness of the upcoming opportunities amongst support industries	NIBRT to organise a conference on "Opportunities for CGT manufacturing"
Trade Associations and Professional Societies	Promote awareness of opportunities in CGT area (IBEC, AmCham, BPCI, EI, ISPE, PDA, etc.)	Invite stakeholders to Conference

Glossary

FDI	Foreign Direct Investment
CGT	Cell and Gene Therapy
ATMP	Advanced Therapy Medicinal Product
MNC	Multi National Company
NIBRT	National Institute for Bioprocess Research and Training
SME	Small-Medium Enterprise
HEI	Higher Education Institute
AAV	Adeno-associated Virus
LV	Lentivirus
CAR-T	Chimeric Antigen Receptor T Cell
RNAi	Ribonucleic Acid Interference
GMP	Good Manufacturing Practice
GDPR	General Data Protection Regulation
QC	Quality Control
mAb	Monoclonal Antibody
EPO	Erythropoietin
CHO	Chinese Hamster Ovary Cell
rtPA	Recombinant Tissue Plasminogen Activator
Remedi	Regenerative Medicine Institute
NIIMBL	National Institute for Innovation in Manufacturing Biopharmaceuricals
IDA	Industrial Development Authority
STEM	Science, Technology, Engineering and Mathematics
EI	Enterprise Ireland
SFI	Science Foundation Ireland
IBEC	Irish Business and Employers Confederation
AmCham	American Chamber of Commerce
BPCI	BioPharmaChem Ireland
ISPE	International Society for Pharmaceutical Engineering
CCMI	Centre for Cell Manufacturing Ireland
GE	General Electric
FDA	Food and Drug Administration
HPRA	Health Products Regulatory Authority
PDA	Parenteral Drugs Association

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