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Licence Agreements for Cell and Gene Therapies

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Cell and Gene Therapies (CGTs) are revolutionising the field of life sciences, providing new and exciting treatment possibilities for patients, particularly with rare and previously untreatable diseases. CGTs are the latest development in the field of biological products (biologics) and build on the successes of monoclonal antibodies and other biologics, which in turn have transformed medical treatments in recent decades, following on from traditional small molecule drugs.

Intellectual Property (IP), particularly patents and know-how, as well as biological materials such as cell lines and vectors, are key assets for companies developing CGTs. In this article, we discuss the various issues that can arise when licensing this IP as part of the development and commercialisation of these transformative, sophisticated and highly complex technologies.

What Are Cell and Gene Therapies?

Small molecule drugs and traditional biologics are generally off-the-shelf, one-size-fits-all products, taken as a pill or injection. By contrast, CGTs are highly personalised treatments and have the potential to deliver long-lasting improvements or cures for many rare disorders and complex diseases that traditional medicines are unable to treat effectively.

The term "CGT" encompasses two distinct, but sometimes overlapping, types of therapies: cell therapy and gene therapy. Gene therapy involves correcting, inactivating or replacing faulty genes in a patient's cells, enabling those cells to function correctly. Cell therapy, in simple terms, is where healthy cells are introduced into a patient's body to replace diseased cells or interact with other cells. These cells are commonly genetically modified before being introduced into the patient. The most well-known example of this is CAR-T cell therapy (short for chimeric antigen receptor T-cell therapy). In CAR-T cell therapy, a patient's own T-cells (part of the immune system) are extracted, and then re-programmed genetically to express a receptor molecule that makes the T-cells better at detecting cancer, before being re-infused into the patient. Using a patient's own cells in this way is known as an autologous cell therapy. Where donor cells are used, the therapy is known as allogeneic.

The CGT field is developing rapidly, with new types of treatments regularly being developed and launched. In December 2023, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) became the first regulatory agency in the world to approve a medicine based on the innovative gene-editing tool CRISPR (Casgevy, a new treatment for sickle-cell disease and transfusion-dependent β-thalassemia).[1]

There are an increasing number of IP licensing deals being negotiated in this growing field[2] and, while licence agreements are in many respects similar to those for traditional pharmaceutical products, there are some important issues to consider when drafting and negotiating these agreements.

Scope of the Licence

One of the most fundamental aspects of an IP licence is its scope. In other words, what products or services is the licensee permitted to develop and commercialise, and which downstream sales will attract milestone and royalty payments? The definition of "Licensed Product" is usually used to set these boundaries and is therefore one of the most important definitions in a licence agreement.

In patent licence agreements for small molecule drugs, the "Licensed Product" (often in pill form) is usually defined by reference to products covered by a

valid claim of the licensed patents or, in some cases, by reference to a product that incorporates, or whose manufacture makes use of, certain licensed know-how.

CGTs are much more complex than small molecule drugs, and product definitions must be carefully considered and reviewed when drafting licence agreements. CAR-T, for example, is not a traditional "product" that will be manufactured in a factory and packaged in a box. Rather, it is a complex treatment with many steps, involving harvesting cells from the patient, sending them away to be genetically modified and processed, before re-infusing them into the patient. It is therefore important to ensure that the "Licensed Product" definition accurately describes the likely end product or service.

CGTs are also complex in the sense that they often involve the in-licensing of a whole range of IP, and each licence agreement might cover only certain components of the therapy or the process of developing or manufacturing it. Examples include IP relating to viral vectors for delivery of a therapeutic gene into the body, gene editing technology, promotors to control gene expression, and cell lines used to manufacture an off-the-shelf cell therapy.

The definition of Licensed Product in CGT licensing is therefore typically very deal-specific and there can be significant variation between different licence agreements. Questions to consider include whether the delivery of the therapy itself will be covered by any licensed IP, or whether the IP covers only the manufacture of the therapy, or even just some of the upstream development. The level of the royalties and milestones will be heavily determined by the scope of this definition, which is the main reason it is often heavily negotiated.

Platform Technologies and Exclusivity

As set out above, the complex nature of CGTs means that, to bring a product to market, innovators often need to license-in IP from multiple external partners. Often the technology licensed-in is a "platform technology" (such as a viral vector or a cell line) which the licensor simultaneously licenses to many different partners to be used in multiple products.

Although licensing platform technologies is by no means unique to CGTs, it is a very common occurrence, and poses a number of questions for those drafting and negotiating IP licences in this field. Considerations include how the parties deal with exclusivity, how patent prosecution, maintenance and enforcement is controlled and co-ordinated, deciding who has access to the licensee's improvements to the platform technology and considering how a licensee can protect itself from being over-burdened by royalties due to multiple third parties.

Exclusivity and carving-up fields

One of the most fundamental aspects of any IP licence is whether it is exclusive or non-exclusive. It is generally understood (under English law principles) that an exclusive licence means that only the licensee has the right to exploit the relevant IP rights, to the exclusion of anyone else, including the licensor. A non-exclusive licence gives the licensor the right to exploit the IP itself and grant others the right to do so.

Full exclusivity can never be granted where an IP owner is granting multiple licences, so exclusivity in this context is achieved by carving-out exclusive fields or territories for each licensee.

In the context of a CGT licence, both licensee and licensor will need to carefully consider any field exclusivity and there are a number of approaches that could be taken depending on the type of technology, the product and the commercial deal. For example, an exclusive licence might be granted to develop and commercialise CGT products for "the treatment of disease X in humans", or, more broadly, for "the treatment of neurological disorders in humans". Alternatively, exclusivity might be expressed by reference to a defined product. The licence could be expressed as an exclusive licence to the IP to develop and commercialise a gene therapy product that incorporates gene Y, for example. Other options include defining exclusivity with respect to a particular biological target.

A licensor must also take care to define the field and territories carefully to ensure there is no ambiguity as to the scope of exclusivity. A simple example is an agreement that grants exclusivity in the field of "respiratory diseases" and another that grants exclusivity in the field of "inflammatory diseases". There is an overlap between these two fields, and asthma could fall into both categories. If a licensor inadvertently grants two parties an exclusive licence in regard to the same disease by virtue of a poorly worded "field" definition in the licence agreements, this could lead to both licensees having claims against the licensor. If the licensor has already granted a field-specific exclusive licence, it is worth considering expressly excluding that field in future licences for clarity. Licensors should also be mindful of how the CGT field may develop in the future. As more CGT products are developed, and the potential indications for which CGTs may be viable expands, licensors could find they have granted broad exclusivity covering promising indications they wouldn't previously have thought commercially valuable.

Considerations for non-exclusive licences

If the platform technology in question is of broad applicability to CGT products (e.g. vector manufacturing technology) the licensor may decide to adopt a non-exclusive licensing model. Although a licensor can in theory grant an unlimited number of non-exclusive licences in the same field, it is still important for licensors to carefully consider the field of use in a non-exclusive licence.

If the licensor grants a non-exclusive licence with no field limitation, this prevents the licensor from later granting an exclusive licence in *any* field. Where the licensor grants a non-exclusive licence in a particular field, this only prevents the licensor from later granting an exclusive licence in that field.

There may also be certain fields and territories that the licensor wishes to reserve for itself or for future exclusive licensing, or that have already been exclusively licensed. If this is the case, the licensor should ensure that these fields are expressly excluded from the scope of any non-exclusive licence agreement.

Patent Management

Another issue to consider where a platform technology is used in a CGT is how patent prosecution, maintenance and enforcement is controlled and co-ordinated when there are multiple licensees. In a traditional IP licence for a small molecule drug, there is often just one exclusive licensee who takes control of patent prosecution, maintenance and enforcement. Where there are multiple licensees, the issue becomes more complicated. The licensor is likely to want to retain control in these scenarios, although exclusive licensees who have a high-value licence in a particular field are likely to push for a reasonable level of control of patent prosecution and maintenance and will certainly wish to have the ability to enforce the patents in their exclusive field.

Pricing Issues

The complex and sophisticated nature of CGTs, their high development and manufacturing costs, complex supply chains and the requirement for specialised teams to administer them, make these therapies the most expensive medicines in the world.

CGTs are often designed to be a one-off single-dose treatment that can have a sustained effect for many years or even over a lifetime. However, their record-breaking and headline-grabbing list prices can be difficult for healthcare systems to budget for, even if the treatment is ultimately cost effective as compared to the care and less effective, alternative treatments that the patient would otherwise be given over a lifetime.[3]

Innovative pricing models have been developed to deal with the difficulties that healthcare providers and insurers face paying such large upfront costs. These include:

- an annuity-based model, spreading the cost across a number of years;
- outcomes-based approaches, or "payment by results", such as outcome-dependent instalments or rebates if the treatment does not lead to a positive outcome for the patient; and
- a blend of the above approaches.

The table below shows some examples of prices reported for a selection of cell and gene therapies (initial US list price) and the agreed pricing model.

Name and manufacturer	Therapy type and indication	Initial US list price	Reported Pricing model
Zynteglo by Bluebird Bio	Cell and gene therapy for transfusion-dependent beta thalassemia	$2.8 million	Payment up front with outcomes-based rebates
Skysona by Bluebird Bio	Cell and gene therapy for cerebral adrenoleukodystrophy (CALD)	$3 million	Outcomes-based model not offered
Zolgensma by Avexis (subsidiary of Novartis)	Cell and gene therapy for spinal muscular atrophy	$2.1 million	Instalments over five years with outcomes-based rebates
Kymriah by Novartis	Gene therapy for acute lymphoblastic leukaemia	$0.475 million	Outcomes-based, payment after one month
Hemgenix by CSL Behring	Cell and gene therapy for hemophilia B	$3.5 million	Currently negotiating outcomes-based model
Roctavian by BioMarin	Cell and gene therapy for severe hemophilia A in adults	$2.9 million	Outcomes-based warranty program (i.e. rebates)

At the time of negotiating the licence agreement, it is unlikely the parties will know the ultimate pricing model but there are a number of points to bear in mind which we have summarised below (and Bristows has previously written in more detail on this topic in a previous article in this journal.[4])

Annuity model challenges

One concern that has been raised with annuity payment models is that licensees may face difficulties in collecting payments over time because a payer stops complying with payment schedules or becomes insolvent. This may have the knock-on effect of reducing royalties due to a licensor. Licensors may seek to reduce this non-payment risk by asking that royalties are payable on sums invoiced by a licensee, rather than sums received (although this is likely to be resisted by a licensee or perhaps only accepted with caveats).

Annuity-based models are also typically more complicated and more expensive for a licensee to manage administratively and those costs are likely to be deductible from sales totals before a licensor's royalties are calculated.

From a legal drafting perspective, care would also need to be taken by the licensor when defining payment terms and the royalty term (which is commonly linked to patent expiry) to ensure that the licensor continues to receive royalties in respect of patients who are treated within the royalty term, even if payment may not be received until after the patents and royalty term has expired.

Outcome-based model challenges

Outcomes-based models can create a lot of uncertainty for licensees and licensors. If the licensee receives payments for the sale of a therapy, and makes royalty payments to the licensor, the parties have to decide what should happen to those royalty payments if the treatment does not meet the agreed outcomes and the licensee has to refund the payor, potentially months or years later.

To counter this risk, a licensee may seek to build in a royalty claw-back mechanism into the licence, or to delay the point at which royalties are payable until after the relevant patient has met the required outcome. However, a licensor is unlikely to accept a significant delay in payment of royalties, particularly where the licensee has itself been paid. Academic licensors, with an obligation to invest income from technology transfer activities into research and the provision of education, are particularly unlikely to agree a royalty claw-back structure which could force them to refund royalties or milestones a year or more after having received them.

One alternative option may be to agree that the licensee can make deductions against future royalty payments. A further alternative could be for some portion of the royalties paid to be retained in escrow for a period of time, to be released to the licensor upon achievement of a positive clinical outcome or expiry of a set period of time. However, escrow arrangements necessarily increase the complexity of agreements and are difficult to negotiate upfront when payment and reimbursement models and the associated outcome triggers have not yet been set.

A compromise

Although there are things each party can consider at the outset of negotiating a licence, having protracted negotiations about hypothetical scenarios is unlikely to be attractive to either party.

As an alternative, the parties may wish to include robust governance provisions giving the licensor visibility into pricing decisions, combined with a mechanism for proposing and agreeing amendments to payment provisions in the licence if necessary to accommodate pricing and reimbursement issues that were unforeseen at the outset. The success of such mechanisms will depend on the strength of the relationship between the parties and a combined willingness to work together and potentially compromise. The licence agreement would also have to deal with the scenario where the parties cannot agree, and options to deal with this include escalation mechanisms, expert determination, or simply preservation of the existing royalty clauses in the licence.

Milestones

In common with licence agreements for other technologies, CGT licences often contain high-value milestone payments due to the licensor when the licensed product achieves key milestone events. Common examples include the first dosing of a patient in a clinical trial, the first commercial sale of a product, and the achievement of specified sales targets.

It is therefore critical to consider the milestone events carefully in light of the type of therapy to ensure that they are appropriately defined to avoid disagreements in the future about whether or not a milestone payment is due. For example, drafters should be aware of the types of clinical trial that might be put in place for CGTs, and how these might differ from a traditional small molecule drug. For instance, the first clinical trial for a CGT is often

structured as a phase I/IIa study, enrolling critically ill patients, rather than a classic phase I study in healthy volunteers.

It is also important to consider how market access will be granted and how milestone payments will reflect this. CGTs are often granted conditional rather than full marketing approval to allow timely access to patients desperately in need, despite limited data sets on safety and efficacy, and the parties must consider how to reflect this in the milestone payment structure. Licensees might try to negotiate regulatory milestones to be payable on getting both a marketing authorisation (such as a conditional marketing authorisation) as well as pricing/reimbursement approval from the relevant health authorities, as the latter cannot always be negotiated.[5]

Royalty Stacking and Competitive Products

Royalty stacking

Royalty stacking clauses have been used in licence agreements for many years. Their purpose is to protect a licensee from being over-burdened by royalties payable to different third parties on the same product. If the licensee is contractually required to pay royalties to a third party in relation to the licensed products, these clauses operate to allow the licensee to deduct all (or some) of such royalties from the royalties payable to the licensor.

The development, manufacture and commercialisation of CGTs is complex and uses a lot of technologies such as cell lines, vectors, promotors and gene editing technology, some or all of which may be licensed-in from third parties. The parties to a licence agreement for a CGT must therefore think carefully about this issue when negotiating the breadth of the royalty stack.

Traditionally, licensors often limit the deductions that a licensee is permitted to make in a royalty stacking clause to royalties due to third parties in respect of third-party patents, and not other types of IP. In the CGT field, due to the importance of other types of IP and materials (such as manufacturing know-how and cell lines) licensees might have more of an argument for the royalty stack to cover payments to third parties in relation to other types of IP.

Biosimilars

In traditional small molecule licensing, it is common to see clauses reducing the royalties where generic versions of the licensed product have entered the market following patent expiry, and the net sales of the licensee's products have fallen by certain agreed amounts.

There may be similar clauses in licence agreements for CGTs that refer to biosimilars as opposed to generics. Although biosimilars are highly similar to the biologic that has already been approved (called a "reference medicine" in the EU), they are not generics. Biologics are much more complex than small molecule drugs and can never be an exact replica of the reference medicine. As a result, more studies are required for their approval and they are a lot more expensive to get onto the market than generics. As a result, licensees of biologics may not be as concerned about reducing royalties if biosimilars enter the market, and might be just as concerned about competition from other branded competitor products.

Conclusion

In many senses, licence agreements for CGTs are very similar to licence agreements for more traditional medicines, but there are some very important differences that parties should consider when drafting and negotiating their agreements. Care must be taken to ensure that the definitions and other clauses are tailored to reflect the technology and the regulatory framework, the complexity of the products and the range of third-party IP licences likely to be needed, as well as the potential pricing and reimbursement mechanisms. As more CGTs are approved and as time passes, there will no doubt be further discussion and potential disagreements about the interpretation of IP licence agreements that were drafted many years earlier, and the drafting of licence agreements for this sector will naturally adapt over time as this experience is gained.

1. *https://www.gov.uk/government/news/mhra-authorises-world-first-gene-therapy-that-aims-to-cure-sickle-cell-disease-and-transfusion-dependent-thalassemia*.
2. Data from the Alliance for Regenerative Medicine showed that in December 2023 there were 1,804 ongoing clinical trials for CGTs, 340 of which were in Europe (*https://alliancerm.org/wp-content/uploads/2024/01/20231220_Sector-Snapshot-Outline-Fall-2023_V2.pdf*).
3. There are detailed studies conducted into the lifetime cost effectiveness of CGTs. *See* for example the Institute for Clinical and Economic Review (ICER)'s report on Gene Therapy for Hemophilia (*https://icer.org/wp-content/uploads/2022/05/ICER_Hemophilia_Final_Report_12222022.pdf*).
4. Cell and Gene Therapies: Blockbuster Prices and Licensing Challenges, The Licensing Journal, August 2020.
5. In 2022, BlueBird Bio withdrew its product Zynteglo (a cell and gene therapy for transfusion dependent beta-thalassemia) from the market in Europe and the UK following a failure to agree pricing with European health authorities.