CELL AND GENE THERAPY LICENSING: COMPLEX REGULATORY PATHWAYS NECESSITATE CAREFUL SCRUTINY OF FINANCIAL MILESTONES

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Cell and Gene Therapies ('CGTs')[1] promise revolutionary and highly personalised treatment options for people living with rare and previously intractable diseases. Compared to traditional small molecule pharmaceuticals and even to other biological products such as antibodies, CGTs are newer and more complex products with regulatory pathways which are still evolving. In order to develop and commercialise CGTs, developers often need to enter into intellectual property ('IP') licences to secure rights to patents and know-how relating to CGTs (including IP in the various constituent elements of CGTs, such as viral vectors for delivery of a therapeutic gene into the body or promoters to control gene expression or lipid nanoparticle technology which is the subject of a number of ongoing patent disputes between Moderna and Pfizer/BioNTech). Those involved in drafting and negotiating CGT IP licences should be aware of how CGT products and their regulatory pathways differ from more traditional pharmaceutical products in order to ensure that their IP licences appropriately address the unique challenges of these cutting-edge technologies. One such challenge pertains to how nuances in CGT clinical and regulatory pathways and available regulatory exclusivities may impact the drafting of the financial terms of CGT IP licences, particularly the financial milestone provisions.

As with more traditional pharmaceutical products, the financial terms of CGT IP licences might typically include some combination of an upfront fee, royalties and/or milestone payments. Conventionally, milestone payments to the licensor are triggered upon the licensee's successful achievement of a particular regulatory or commercial event, such as commencement of specific clinical trial phases, obtaining a marketing authorisation ('MA'), first commercial sale, or hitting certain sales thresholds. It is crucial that the triggers for these milestone payments are clear.

However, as we explore in this article, when it comes to CGT products, the differences and uncertainties in regulatory pathways and blurring of boundaries between clinical trial phases means that achieving clarity regarding triggers for clinical and regulatory milestones can be challenging. In this article, we use examples of the clinical and regulatory pathways taken by certain CGT products in recent years to highlight key points that parties who are negotiating and drafting CGT IP licences should be aware of, and explore how such parties can consider addressing these challenges.

What are CGTs?

Whilst cell therapy and gene therapy are often referred to together under the umbrella term 'CGT', they are in fact two distinct, though sometimes overlapping, types of therapies.

Cell therapy aims to treat diseases or repair injuries by restoring or altering particular types of cells, or using cells to transport a therapy throughout the body. The cells are

1) For clarity, in Europe (including the UK), CGT medicinal products qualify as (and are regulated as) Advanced Therapy Medicinal Products and in the US, these are primarily regulated as Human Cellular & Gene Therapy Products and are the subject of a Biologics License Application.

cultivated *ex vivo* (that is, outside of the body) and may or may not be genetically modified before being introduced into the patient. Such cells may be autologous (meaning that the therapy uses the patient's own cells) or allogeneic (meaning that the therapy uses donor cells).

Gene therapy involves inactivating, replacing or introducing genes into cells such that those cells can function correctly. This process can also be done either *in vivo* (that is, inside the body) or *ex vivo*.

Clinical and Regulatory Milestones: The Traditional Approach

Broadly, the traditional clinical regulatory pathway for pharmaceutical products can be broken down into the following five distinct phases (although we note that these phases do not have set definitions so the following description should only be used as a rough guide):

- Phase 0 trials are the first-in-human trials of a sub-therapeutic dose to determine if a medicine engages its expected target. Such Phase o exploratory trials might involve 10 to 15 healthy volunteers (not patients).

- Phase I trials test a sub-therapeutic dose of the medicine in around 20 to 80 healthy volunteers in order to: (i) assess the initial safety/tolerability of the medicine to determine the safe dosage range; (ii) learn about any potential side effects; and (iii) elucidate any early measurements of therapeutic benefit.

- Phase II trials begin to explore the efficacy of a therapeutic dose of the medicine in a larger group of people with the relevant disease (usually between 100 and 300 individuals) to further evaluate safety while continuing to explore efficacy. Phase II trials are sometimes sub-divided into two parts, with Phase IIa typically involving the early exploration of optimal dosage and Phase IIb further determining efficacy at a given dose.

- In Phase III trials (sometimes called pivotal trials), the medicine will be given to a much larger group of people with the disease (usually between 1,000 and 3,000 individuals) to establish the medicine's safety and efficacy. Typically, the results of the Phase III trial form the basis for the approval of the medicine.

- Finally, Phase IV trials encompass post-marketing or surveillance trials of licensed medicines in order to collect data on the treatment's real world efficacy and safety across a considerably larger population. Not all medicines undergo a Phase IV trial.

IP licences in the life sciences sector typically include milestone payments that the licensee must pay to the licensor upon the achievement of specified events. Pre-launch milestones are usually linked to key clinical and regulatory events (with the achievement of each milestone generally representing a successive derisking of the product for the licensee). Typical milestones may be tied to events such as initiation (or sometimes successful conclusion) of a Phase I, Phase II and/or Phase III clinical trial (with separate payments due for initiation of each phase) and subsequently the grant of marketing authorisations in key markets.

For a traditional small molecule pharmaceutical product which is likely to follow the above clinical trial phases, linking a milestone payment to initiation or completion of a particular clinical trial phase should not be problematic (though care should of course always be taken to ensure that clear definitions are included for the relevant clinical trial phases and for terms such as 'initiation' or 'successful completion'). For a product following the traditional clinical pathway it should generally be clear when any particular clinical trial phase has been initiated.

However, as we seek to illustrate with the following examples, the same cannot always be said for CGT products.

Clinical Development of CGTs: Blurred Lines

A significant proportion of CGTs in development are for rare genetic diseases and certain rare cancers. Unlike traditional small molecule medicines, advanced therapies (such as CGTs) generally cannot be tested in healthy human volunteers (as would be the case for a traditional Phase 0 or Phase I trial) due to, amongst other things, the possibility of extended

or permanent effects on the study participants. Instead, advanced therapy trials always initially involve patients in a Phase I/IIa trial. It becomes immediately evident, therefore, that CGTs do not adhere strictly to the traditional clinical regulatory pathway outlined above.

One gene therapy, currently under development by US-based clinical stage biotechnology company Regenxbio Inc. ('Regenxbio'), provides a helpful illustration of the blurring of traditional clinical trial phases. Regenxbio's RGX-202 is an adeno-associated virus gene therapy designed to treat people living with Duchenne Muscular Dystrophy ('DMD'). DMD is an inherited genetic condition for which there is currently no cure. DMD predominantly affects boys (with symptoms typically presenting in children around two to three years old) and is characterised by progressive and severe wasting-away of skeletal muscle. DMD is caused by mutations in the dystrophin gene, which means that individuals living with DMD cannot make the dystrophin protein which plays a crucial role in protecting the membrane surrounding muscle fibres during muscle contraction. RGX-202 is a one-time treatment designed to produce microdystrophin, a smaller version of the protein that is absent in people living with DMD.

In 2024, Regenxbio announced positive functional results from the first five patients in the Phase I/II portion of its ongoing AFFINITY DUCHENNE trial. The company further announced that it achieved 'alignment' with the FDA to expand its existing Phase I/II AFFINITY DUCHENNE trial into a Phase I/II/III pivotal trial that can support an accelerated approval. This expanded Phase I/II/III pivotal trial is expected to support a Biologics License Application submission using the accelerated approval pathway in 2026.

This example of extending an existing clinical trial to include later phases highlights why traditional milestone payment triggers may not be appropriate (or at least may require careful thought and drafting) for CGT products. For example, typical milestones triggered by events such as 'successful completion of a Phase I Clinical Study', 'initiation of a Phase III Clinical Study' or 'first dosing of a patient in a Pivotal Study' are common but each may present difficulties in such circumstances. The combination and extension of clinical trial phases blurs the boundaries between different phases and, unless this is anticipated and clearly drafted for in clinical milestones, there is a risk of disagreement between the licensee and licensor as to when a clinical milestone could be payable.

Another example of a non-typical clinical development pathway which illustrates this point is the development and approval of the gene therapy Glybera. Glybera was a gene therapy for hereditary lipoprotein lipase deficiency first approved in 2012. Glybera was only ever the subject of open-label studies (that is, no placebo or blinding) in a very small number of patients (fewer than 40) and subject to annual safety updates for 15 years post-administration. In the context of drafting milestone triggers, it would be difficult to say whether these very small open-label studies for Glybera before its approval would have been considered Phase I, Phase IIa or Phase III studies (or something else), or when Phase II or Phase III was 'initiated'. As a further point, given that Glybera was subject to annual safety updates for 15 years post-administration, it could be arguable that it was not clear when the trials were 'completed' or 'concluded'.

Approval of CGTs

As noted above, it is also common for parties to agree to link a milestone payment to the grant of regulatory approvals (that is, an MA) (usually in one or more specified key markets). Of course, it is always important to ensure that milestone triggers are clearly defined. However, for those negotiating and drafting milestone triggers linked to grant of an MA for a CGT product, careful thought should be given to: (i) the type of approval that may be granted; (ii) whether this would be captured by the milestone trigger drafting; and (iii) in certain cases, whether it is even appropriate from a commercial perspective that a milestone would be triggered.

For example, parties should consider whether the relevant licensed product might be granted a conditional MA (rather than a full MA), which may be granted for medicines that address unmet medical needs on less comprehensive clinical data than normally required. By way of example, the Medicines and Healthcare products Regulatory Agency ('MHRA') and

the European Medicines Agency ('EMA') separately granted conditional MAs for Vertex Pharmaceuticals' CASGEVY, a CRISPR/Cas9 gene-edited therapy, for the treatment of sickle cell disease ('SCD') and transfusion-dependent beta thalassemia ('TDT').[2] A conditional MA may be granted for medicinal products for seriously debilitating or life-threatening diseases where the applicant can demonstrate: (i) the balance of benefit and risk of the medicine is positive; (ii) it is likely that the applicant will be able to provide comprehensive clinical data after authorisation with a view to converting the conditional MA into a full MA; (iii) the medicine fulfils an unmet medical need; and (iv) the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required. If it is possible that a conditional MA may be granted, the definition of Marketing Approval in the relevant CGT IP licence should be scrutinised to check whether a conditional MA would be covered. Licensors may expect to get paid a milestone upon the grant of a conditional MA but licensees should consider if this is appropriate, or if any distinction should be made from a full MA. For example, a licensee may wish to consider negotiating that a lower sum is payable to the licensor upon grant of a conditional MA due to the fact that: (i) a conditional MA is only granted for a period of one year and is subject to annual review; (ii) once granted, the holder of the conditional MA (that is, the licensee) must fulfil specific obligations within defined timelines, such as completing ongoing or new studies or collecting additional data to confirm that the medicine's benefit/risk balance remains positive. If the licensee is unable to comply with such obligations (for example, if the licensee is unable to obtain the required comprehensive clinical data) the conditional MA can be revoked or not renewed; and (iii) as further detailed below, there is a genuine risk that conditionally approved products may not receive positive reimbursement outcomes. Accordingly, licensees should be conscious of excessively high milestone payments to licensors that are triggered in CGT IP licences upon the granting of a conditional MA.

As a further example, Glybera, which we mention above, was only ever granted an MA in Europe under 'exceptional circumstances' (this is a particularly rare type of MA that may be granted where the applicant is unable to provide comprehensive data on the efficacy and safety of the treatment under normal conditions of use because the condition is rare, or because collection of such data is not possible or is unethical) meaning that the MA was vulnerable to annual review by the EMA. As such, the EMA could suspend or revoke the exceptional circumstances MA following such annual re-assessment if the benefit/risk profile of the medicine no longer justifies the continuation of such an MA. The Glybera example also serves as a useful reminder of the possibility (albeit a rare possibility) of MAs being granted under 'exceptional circumstances'. Unlike conditional MAs – which are granted on the basis that the clinical data is likely to be provided after authorisation – such 'exceptional circumstances' MAs may be granted where comprehensive efficacy and safety data cannot be obtained, even after authorisation. As with conditional MAs, it may be useful to determine whether such an 'exceptional circumstances' MA may be granted and to similarly assess the appropriateness of the Marketing Approval definition in the relevant CGT IP licence.

Due regard should also be given to pricing approvals since the product may potentially obtain an MA but not pricing approval. Using CASGEVY again as an example, despite the treatment being granted conditional MAs from both the MHRA and EMA for the treatment of SCD and TDT, NICE refused to recommend CASGEVY for treating SCD on grounds of the treatment being above the acceptable cost-effectiveness estimate as regards NHS resources, only recommending CASGEVY for the treatment of TDT as detailed above. More generally, reports suggest there is an apparent divergence between: (i) regulatory agencies, such as the EMA, that promote accelerated access to medicines through expedited approval pathways that rely on limited early phase clinical data (including through granting of conditional MAs); and (ii) health and technology assessment agencies that require robust clinical evidence to inform reimbursement decisions (such as NICE). It is therefore imperative that the mixed success rate of conditionally approved products receiving positive reimbursement outcomes is borne in mind by those

2) Vertex Pharmaceuticals has since announced a reimbursement agreement with NHS England for individuals 12 years or older with TDT to access CASGEVY, following the issuance of positive guidance from the National Institute for Health and Care Excellence ('NICE') recommending CASGEVY's use in the NHS.

negotiating and drafting any milestone triggers linked to pricing approval.

Further Considerations: Launch-related Milestones

In addition to the above key considerations regarding approvals, there are two other less common scenarios that practitioners should be aware of when reviewing and considering milestone triggers linked to the launch of a product. Licensors often expect to receive a milestone upon first commercial sale of a product. Again, careful thought should be given to the drafting of the trigger point, particularly for CGT products.

Firstly, a CGT product may be designated as a Promising Innovative Medicine (such designation being issued after an MHRA scientific designation meeting that will assess the non-clinical and clinical data available at the time): this indicates that such medicine may be eligible for the Early Access to Medicines Scheme ('EAMS'). EAMS gives authority for an NHS doctor, on an interim basis, to use the medicine prior to it being granted an MA (in line with the associated MHRA protocol) for patients living with life-threatening or seriously debilitating conditions. In this scenario, real patients will be being treated (outside the context of clinical trials). However, EAMS medicines have to be provided to the NHS free of charge by the company in the period between a positive EAMS Scientific Opinion and the granting of an MA.

Secondly, there are various other exemptions, such as the hospital use exemption or the 'specials' exemption, that may allow an unlicensed medicine to be on the market. Briefly, (i) the hospital use exemption applies for Advanced Therapy Medicinal Products (including CGTs) prepared and used on a non-routine basis in a hospital in accordance with a prescription for an individual patient; and (ii) the 'specials' exemption applies to a medicinal product to treat an individual patient's 'special' clinical needs where no licensed medicine is available.

For the purpose of drafting milestone triggers in CGT IP licences, licensees will wish to ensure that the EAMS and such exemptions outlined above are not inadvertently captured by a wide definition of 'first commercial sale', 'launch' or similar.

Practical Considerations

The CGT landscape continues to evolve and so too do regulatory pathways. It can, therefore, be difficult for parties negotiating CGT licences to anticipate and cater for every eventuality in their financial terms. However, there are still several points that we have explored above that parties can and should consider addressing when drafting financial milestones triggered by clinical or regulatory events relating to CGT products.

From the outset, parties should consider what clinical trials are likely to be relevant for the CGT in question. The divergence from the traditional clinical regulatory pathway for CGT products may also require considered divergence from traditional milestone payment triggers. To mitigate the risk of a product skipping a clinical milestone, licensors should seek to include a milestone sweeper provision, so that earlier regulatory milestones still become payable later (such as on first commercial sale), even if not all of the clinical milestones were technically achieved.

Where a CGT IP licence includes milestone payments triggered upon obtaining a regulatory approval, the parties should also consider the type of approvals that may be granted and whether or not those approvals are likely to be captured by the milestone trigger definitions, and if yes, whether they should be excluded.

Finally, given the possibility of disputes arising as to whether certain milestone events have been triggered in respect of a CGT product, parties to CGT IP licences may also be minded to consider including provisions that allow for the appointment of an expert in the event of a dispute to determine whether specific milestone events have, in fact, been triggered.

Conclusion

In many respects, IP licences for CGTs are very similar to IP licences for more traditional medicines, but there are some

important differences that parties should consider. In particular, care must be taken to ensure that the financial milestones are tailored to reflect the likely clinical and regulatory pathways. As more CGTs are developed, we expect there will continue to be discussion and disagreements about the interpretation of milestone triggers (particularly for IP licences that were drafted many years earlier) and the drafting of licence agreements for this sector will naturally adapt over time.