CELL & GENE THERAPY INSIGHTS

2020 VISION
TOOLS AND TECHNOLOGIES OF TOMORROW

SPOTLIGHT

INTERVIEW

Analyzing key ATMP talking points through IP and regulatory lenses

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Q Can you firstly give us some background on your involvement and activities in the life sciences area as

a whole, and in cell and gene therapy/regenerative medicine more specifically?

BSM: Ever since I was a child, I've been fascinated by how organisms and cells achieved complex behavior. I studied Natural Sciences at Cambridge University, specializing in cell and molecular biology and genetics, but it was after an 8-week stint in '94 in Professor David Ish-Horowicz's lab at what was then the Institute of Cancer Research Fund (ICRF) Unit in Oxford that I became a huge fan of developmental biology.

Having obtained my PhD, and after a short Post Doc, I retrained to become a lawyer and intellectual property specialist. Life sciences has been a key focus and passion for me in my legal career too, and I've advised numerous pharma, biotech and medical device companies on a range of issues including regarding cell and gene therapy applications. I've also been a member of the UK Bioindustry Association Cell and Gene Therapy Advisory Committee for over 7 years.

JM: I've always had a passion for science, but I knew I wanted to be a lawyer, and I converted to law after completing my Natural Sciences degree. I joined Arnold and Porter in 2005, and completed my training here, specifically because of the life sciences practice. I'm now a Partner in that group, focusing on regulatory advice to the innovative pharmaceutical industry and indeed, to the broader life sciences sector.

As part of this work, we provide advice to companies on a range of first-in-class products including, in more recent times, Advanced Therapy Medicinal Products (ATMP). This advice focuses on navigating the rather complex regulatory framework, ensuring these products meet safety/efficacy requirements and helping them reach and stay on the market.

Q As you both look at cell and gene therapy as a whole with its various component technologies and modalities, what particular areas stand out for you in terms of current/ongoing IP- and regulatory-related concerns that need to be addressed?

BSM: Patentability is always an issue! However, there are a number of challenges that particularly concern cell and gene therapy products.

In the EU we have the Biotech Directive, which came into force in 1998. Its purpose was to harmonize what was and wasn't patentable in the biotech field. There's a broad exemption in that Directive for inventions that are considered to be contrary to public policy or morality, but it also excludes

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a number of inventions from being patentable for ethical reasons. Specific exclusions relevant to the cell and gene therapy field include processes for modifying the germ line identity of a human being, and the use of human embryos for industrial and commercial purposes.

It is this latter exclusion that caused much controversy in the cell therapy field, culminating in the Court of Justice of the European Union (CJEU) decision on the International Stem Cell Corporation ("ISC") case (Case: C-364/13, ECLI:EU:C:2014:2451, which was preceded by the Brüstle decision [Case: C-34/10, ECLI:EU:C:2011:669]). This landmark ruling related to the question of which human cells are deemed to constitute a human embryo such that their use in an invention is not patentable under the Biotech Directive.

The European Patent Office (EPO) had previously ruled in the WARF case (Enlarged EPO Board of Appeal decision G2/06) that inventions that required the destruction of human embryos in order to put them into practice were not patentable, and that the only exception to that would be those that involved the use of pluripotent embryonic stem cells that could be derived from cell lines which were publicly available at the filing date.

However, the CJEU went one step further and extended this exclusion significantly, saying that an invention is not patentable if that invention required the destruction of human embryos, no matter when this may have occurred. Additionally, they adopted quite a strict interpretation of what a human embryo is, covering all of the early stages of human development, and all other similar cells capable of commencing the process of development of a human being.

In short, as long as a cell cannot form a viable human being and the invention hasn't required the destruction of human embryos, then it is possible to obtain a patent for it – that is of course as long as it meets all of the other patentability criteria.

It's 5 years since the ISC decision and, in practice, the concerns over the ramifications of these decisions from the CJEU and the EPO, and the subsequent revised guidelines from the EPO, were probably exaggerated at the time. I think the concerns did not materially hinder the industry partly due to the fact the field was, and is still to an extent, in its infancy. There is currently not enough competition to drive companies to contest the validity of these patents, beyond opposing them before the EPO and we have yet to see any litigation in the UK courts concerning this type of technology. Furthermore, patent attorneys have (as ever) found ways around the limitations posed by the decision.

All this said, I could anticipate there being litigation in the future relating to the current EPO guidelines, because they now accept inventions using human embryonic stem cells filed after February 2008. This is on the basis that, at that point, those cells could be obtained without destroying

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the embryos. However, I think that could ultimately be challenged before the courts because those embryos are frozen indefinitely, they are not re-implanted, and one would assume they would be ultimately destroyed.

Beyond these specific concerns on patentability that are particular to cell and gene therapy, there are also the usual general patentability hurdles. These include the fact that, under the European Patent Convention and the UK Patents Act, methods for the treatment of the human or animal body by surgery or therapy are excluded from patentability. Patent claims therefore have to be worded using a specific language – a legal fudge to avoid this exclusion. People refer to these types of claims as second (or further) medical use claims, and it's these that innovators are finding most challenging to obtain, enforce and successfully defend their validity. These challenges are relevant not just to the cell and gene therapy field but also, in particular, in relation to orphan drugs.

One way around patentability issues is for companies to rely on confidential information and trade secrets, rather than trying to obtain protection through the patent system. In the UK, we do have one of the most well-developed regimes for this, and the UK courts are quite used to maintaining information confidential. This is also something that is now possible across the EU thanks to the recent Trade Secrets Directive. And this could be an attractive option for certain technological aspects, because you could maintain exclusivity indefinitely, without having to invest in patent prosecution and maintenance fees.

But it is not without its own challenges. For example, if information can be reverse engineered, or is developed independently, you can't prevent the third party in question from doing so. The third party could then go ahead and patent similar or related technology that covers your confidential information, which would obviously make it difficult to expand your own commercial objectives. Moreover, if the confidential information becomes public through lawful means, there's no way you can protect it.

So, there are clearly costs associated with maintaining information confidential and it can be difficult to prove someone has misused that. As a result, companies do tend to use mixed strategies to balance the challenges in protecting these products and processes.

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JM: On the regulatory side, the areas that need to be addressed are more focused on the approval process, and then what happens when the product is on the market.

Everybody knows that the number of clinical trials involving ATMPs is booming – one statistic I saw recently is that there are currently over a thousand clinical trials ongoing around the world involving these products (ARM and BIA Report, Leading Innovation; The UK's ATMP Landscape, July 2019). This volume of activity clearly puts strain on the regulatory authorities. In addition, the EU framework for authorization of these products is now over 10 years old, having been implemented in 2007 (Regulation [EC] No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation [EC] No 726/2004), and while there have been amendments to try to update the legislation, the reality is that there are still relatively few products that are widely available on the market. And indeed, some of the products that have been approved have actually been withdrawn post-authorization due to difficulties with manufacture or reimbursement. I believe there are currently around 14 ATMPs on the market in the EU, which is not very many when you consider the number that are undergoing clinical investigation.

The reality is that most ATMPs have to go through the authorization process afresh each time, because of the unique aspects of the product, its manufacturing process, the starting materials, and the target disease. This all means there's pressure in terms of time and resources, both for the authorities and the companies. However, we have now reached a stage where a certain number of products have gone through this process; lessons and best practices have been learnt, difficult issues have been considered, and hopefully, there will be a more streamlined process going forward.

The other area that needs to be addressed from the regulatory side is that there are a lot of interlocking rules in this area that will impact the development and authorization of these products, not all of which relate to the medicine's authorization. For example, companies also have to consider rules on genetically modified organisms, and on blood, tissues and cells. These are areas of legislation that have been implemented differently across the EU, and member states take different views on these issues as part of the European Medicines Agency's (EMA) committees. For example, in relation to the interaction between the regulation on the collection and transfer of blood, tissues and cells, and the regulation on the authorization of ATMPs, we are aware that different EU countries take different approaches in terms of which regulatory regime applies at the various stages of the manufacturing process – at the beginning when you collect the starting material, and later, when you provide the final product to the patient. Despite the fact

these products are authorized at an EU level, there's a surprising amount of divergence at the national level, which leads to complications for both the regulators and the companies.

There are also additional requirements in relation to licensing of premises that handle tissues and cells, or receive imports of such products into the EU (for example, because part of the manufacturing process may be based in the USA), and for the quality testing that has to be carried out. All of these requirements are on top of the medicine authorization rules. This overlap and inconsistency has been identified as an area of concern, and discussions around how to streamline, or at least harmonize, these rules across the EU are underway in a bid to deliver some clarity in the future.

Q Beatriz, we are seeing – and will continue to see in the near future – the first examples of competition between marketed cell and gene therapy products. What are your expectations in terms of how robust patent protection will be in this space moving forward?

BSM: Before we even start to consider the robustness of patent protection, I would query the extent to which patent protection for specific applications may actually exclude competitors. This remark is due to the highly specific nature of the cell and gene therapy applications currently being developed.

For such specific applications, whilst robust patent protection is clearly preferable, it may well be that the scope of the protection – what is actually claimed in those patents – may not actually cover those competitor technologies. In other words, the patent system will not necessarily be relevant to provide exclusivity by asserting that a competitor product infringes an innovator's patent.

However, where I do think there will be more litigation, at least in the short-term, is with the platform technologies – that's where patent protection could certainly hinder competition.

The clearest current example is with the recently introduced genome editing techniques, such as CRISPR, which can and do have wide application. Valid patents in this arena are extremely powerful and lucrative. It's for this reason that we have seen hard-fought battles already over the first generation of CRISPR patents, particularly between the Broad Institute on the one hand and the University of California Berkeley (UCB) on the other in the US and Europe.

There is a crowded patent landscape developing around CRISPR technology. The Broad provided stats in July this year that the US Patent Office

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has apparently granted more than 80 patents with claims relating to CRISPR and/or Cas9 to more than 300 inventors from nearly 60 applicant organizations! In Europe, it's less: the EPO has issued more than 20 patents to 30 inventors from about 10 applicant institutions. But overall, globally, more than 1,500 patent applications have been filed but not yet granted.

Licensing activity in this arena has been fierce and well reported. The Broad Institute is very open about the approach that it's taking - its policy has been to make CRISPR tools readily available for academic and non-profit use, so no licenses are necessary for that work. Licenses are required, however, by research companies and companies wishing to sell tools and reagents – those licenses are non-exclusive – and then exclusive licenses may be obtained for human therapeutic use. Other organizations currently involved in licensing or sub-licensing deals in this space include UCB, the University of Vienna, Duke University, Massachusetts General Hospital, CRISPR Therapeutics, Editas, Caribou Biosciences… The list goes on.

So CRISPR is an example of where I do think that robust patents will be helpful. It will be interesting to see whether these first-generation patents are ultimately upheld and, if so, what their scope will be as well as what secondary patents will be the ones to stand the test of time.

Q Jackie, what are your expectations in terms of the impact of commercial competition upon future regulatory approval and market access environments for ATMPs?

JM: Market access continues to be very difficult for these products, given the high research and manufacturing costs – in particular, where the product is only used by a small patient population, and sometimes only a handful of patients across the entire world, leading to large costs per patient. It's no secret that the current economic environment across the EU means healthcare systems are struggling

"...companies also have to consider rules on genetically modified organisms, and on blood, tissues and cells. These are areas of legislation that have been implemented differently across the EU, and member states take different views on these issues..."

to fund these highly specialized medicines. When there are many patient groups with unmet needs, such high cost of treatment raises ethical and political issues; when should healthcare organizations divert finite resources to only a few patients, potentially leading to difficulties with being able to treat others? Finding ways to balance those difficult decisions is the reality for healthcare organizations, and for ATMP companies.

Authorities are also increasingly employing novel methods to procure cheaper access to products, and they are pushing the boundaries of the legislation in this regard. Again, companies have to contend with the resultant difficult market access conditions when trying to launch these products.

I think that new, tailored payment models will have to be developed to take into account the high upfront costs for ATMPs as compared to the often very dramatic long-term benefits of treatment. It may be necessary to spread the cost of treatment over time, or to agree some form of risk sharing payment scheme with healthcare organizations. However, that may require changes to healthcare accounting rules to properly account for the need to spread the cost of therapy over a number of years – that is not necessarily how these systems are currently set up. It will certainly also require collaboration between industry and the healthcare organizations to ensure that both sides are able to meet their obligations and patients are able to access these products.

The unfortunate reality is that if healthcare systems can't afford to pay for these products, and they're not commercially successful because reimbursement can't be obtained, then they may be withdrawn. Based on publicly available information, three ATMPs have been withdrawn for precisely this reason, one of which is reported to have only treated one patient while commercially available. After such long development and authorization processes, that's a real shame for patients.

Another issue is about the data necessary to support market access. These products often target rare diseases and/or may seek to be authorized through an accelerated review process, sometimes based on limited data sets, so these products can be placed on the market as quickly as possible. It's often difficult in such clinical trials to establish a proper control group, because it's not ethical to provide a placebo to half of the patients, meaning less robust or extensive data may be generated compared to, say, the data for more standard chemical products. This can lead to uncertainty of long-term outcomes. Apart from the difficulties this presents in terms of obtaining a marketing authorization, this uncertainty doesn't help in demonstrating to authorities that the product is cost-effective and should be reimbursed at a relatively high price.

All of these interlocking issues need to be addressed by companies moving forward if ATMPs are to flourish on the market.

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Q Given the increasing likelihood of commercial competition between multiple approved advanced therapies in some orphan disease indications, plus the recent ongoing discussion around orphan similarity involving regulators on both sides of the Atlantic, just how secure is Orphan Exclusivity (OE) moving forward, in your view?

JM: Some commentators believe that OE is currently too broad and covers too many products, which places undue strain on healthcare systems. The European Commission and the EU authorities are generally trying to reduce the scope of OE, narrowing which indications and products are covered. There have been a number of recent changes to the guidance (Commission notice on the application of Articles 3, 5 and 7 of Regulation [EC] No 141/2000 on orphan medicinal products, C/2016/7253) – and to a lesser extent, the legislation – that have impacted the interpretation of OE, such as when a follow-on product will be considered similar or clinically superior to a product that's already on the market. This has led to a number of disputes between industry and the EMA/European Commission about the interpretation of the legislation, some of which have resulted in cases before the European Court.

But actually, if you manage to retain orphan designation and receive OE when the product is authorized, it's relatively secure. A similar product for the same indication can only be placed on the market in quite limited circumstances, and that true monopoly right has been protected by the courts.

So, while there are legitimate concerns about the ability to obtain OE in the first place, once you have it, it should be relatively secure.

Q Can you each comment on the potential for the equivalent of biosimilars to impact cell and gene therapy in the near- to mid-terms?

BSM: I'm not a regulatory expert, but considering the length of time and the challenges that biosimilars have faced in reaching and becoming established on the market - and given that cell and gene therapy products are far more unique, patient-specific and technically complex than mAbs, for example - then I think it will be very difficult for the equivalent of biosimilars to be authorized any time soon or in the mid-term.

JM: I completely agree. It's very unclear to what extent manufacturers of follow-on products would be able to meet the requirements to enable

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them to prove comparability of their product with the reference product that is already on the market. And as Beatriz said, it took the authorities some time to get comfortable with the data necessary to approved biosimilars – it's likely there will be similar questions in terms of how the current guidelines should be applied to ATMPs. So, I don't think the launch of these products is at all imminent.

However, of greater concern currently is the issue of unlicensed follow-on products, and supply of unlicensed products under the various exemptions in the legislation continues to be controversial. There's an exemption in relation to advanced therapies in particular that allows for the supply of these products without a marketing authorization, providing certain conditions are met – for example, usage is within a hospital, within an individual member state, on a non-routine basis. We've seen in other circumstances that these exemptions are pushed to the limit by authorities, particularly where there may be perceived cost savings. These provisions have also been implemented quite differently in different member states – for instance, in terms of the definition of 'non-routine', and whether the exemption only applies if there is no authorized product on the market.

The potential for competition from such unlicensed products, which do not have to bear the heavy R&D costs and are not subject to the same stringent authorization regime, is seen as a real commercial risk by some companies.

Q Beatriz, what would be your advice for early-stage cell and gene therapy developers seeking to devise a patent protection strategy with likely future trends in mind?

BSM: I mentioned previously that companies in general, and certainly those that are early in development, need to consider a multi-pronged strategy covering patent protection, licensing deals, and the protection of confidential information or trade secrets. On top of that, besides protecting their own IP and portfolio, companies need

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to be aware of what their competitors and other third parties are doing to ensure that they have freedom to operate.

In the UK, over the past 2 years, there have been three Supreme Court decisions that impact this field in terms of what can and can't be patented. These decisions should be borne in mind by early-stage companies as they consider alternative or complementary strategies. They highlight three key aspects in particular:

1. Companies need to consider whether the product they are developing could be deemed to be equivalent to something that has been granted by a third party, and therefore be liable to patent infringement. Taking equivalence as an example: if part of your claim refers to DNA sequences, it may be that a nonidentical DNA sequence could fall within the scope of that claim and be deemed to be equivalent;

2. The amount of data required in patent applications is becoming more significant in this field – in particular, for inventions concerning second (or further) medical use. This presents the challenge for companies of whether they should seek patent protection early or wait until they have more data: if they file early, they could ultimately find their patent claims are invalid due to a lack of sufficient data; if they delay, they run the risk of a competitor filing an application first, or of a publication appearing that may make it difficult for them to have a subsequent application granted;

3. Some improvements made to a known product – to a cell line, for example – that are not necessarily obvious in advance of clinical testing may not be patentable. It is very important for early-stage companies to liaise with their legal counsel in order to find the best strategy for them in this regard. For example, companies might well seek patent protection over the actual product, the specific cell lines and the scaffolds used, but lab techniques and processes for making those cell lines may well be kept confidential.

Q Jackie, what would be your advice to early-stage cell and gene therapy developers seeking to devise a regulatory compliance and market access strategy – again, with likely future trends in mind?

JM: Naturally, we see many companies focusing on the data and expertise required to navigate the marketing authorization process. This is of course an important part of the company's strategy and it's not without its difficulties given the novel nature of these products. We are aware that opinions differ among competent authorities on the extent of data required for ATMP authorization and on the appropriate comparators to use in clinical trials, which are still being discussed and resolved.

It's important that companies seek appropriate advice from the regulatory authorities before submitting an application. In fact, there was a paper published just last month by some EMA regulators discussing a particular product and the advantages gained from the company seeking Scientific Advice during the development process and prior to submission (Schuessler-Lenz *et al.*, Regulators' Advice Can Make a Difference: European Medicines Agency Approval of Zynteglo for Beta Thalassemia, Clinical Pharmacology & Therapeutics, 08 November 2019). The product in question went through the approval process very quickly as a result.

Companies also need to focus on post-authorization issues. We discussed earlier that pricing and market access can be difficult, and it's important that these considerations are kept in mind early on in a product's development. As more and more ATMPs are launched, healthcare organizations are going to be seeking increasingly competitive prices, and companies need to make sure they collect the necessary data through their clinical trials to support these negotiations and avoid delays in launch of the product.

However, discussions with healthcare professionals and organizations before a product has obtained a marketing authorization are always difficult and raise compliance issues – this is also true for ATMPs, which raise particular questions in this area. For example, hospitals need to be trained on the collection and preparation procedure for the starting materials for the product, and on what information to give to patients as part of the consent process, but individual EU member states adopt very different views on how much of this can be done before marketing authorization. There may also be requirements relating to diagnostic testing, which again raise questions for reimbursement and how the company can support this type of testing as part of the product offering. Having a strategy in place as early as possible for how to approach these discussions, and when, will help ensure the early adoption of these products.

Finally, the scale-up of manufacture and batch-to-batch consistency are important, of course, and are things that some ATMP companies have struggled with following commercial launch. The practicalities of making these products commercially available when manufacturing sites are spread across the world have raised difficulties. This also links to broader compliance issues, such as how and when to provide information to healthcare professionals, and indeed, to patients, on any benefits that may be associated with the treatment. It may be necessary for a patient and their family to travel to a specific clinic and stay there during treatment – the degree to which companies are able to support such travel and associated costs is difficult to navigate. The Codes of Practice for the Pharmaceutical Industry (for example, the EFPIA Code of Practice, July 2019) don't deal with these issues – companies have to make decisions based more on first principles than any real guidance, and on a case-by-case basis with each product

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launch. Again, having a strategy in place relating to what the company will provide and on what basis is really important for getting these products to market as quickly as possible.

Q Standardization is a major talking point across the board for the cell and gene therapy field at present – in what particular areas would you like to see standardization initiatives pursued to the benefit of the sector?

BSM: I think minimum standards and standardization in general for tools, media, storage and transportation requirements in this sector would all be beneficial.

This does however come at a price from an IP perspective, as first mover companies gain patent protection for platform-related inventions. The aforementioned patent battles and extensive licensing deals in the CRISPR space are a good example of what can happen if the relevant standard is covered by patents.

In the future, we may well see developments in this arena to the extent that standards are formally adopted. Patents may be granted that are deemed essential for the application of these formal standards. In those circumstances, the owners of those standard-essential patents (SEPs) would need to disclose those patents during the development of the relevant standard, and they subsequently would be obliged to license those SEPs on fair, reasonable and non-discriminatory terms.

If standards were to be formally applied in this field, I would anticipate that patent disputes would follow – we've seen a significant number of disputes over SEPs in the telecoms field, for example. However, that said, I think there clearly is benefit and should be an objective to reasonably standardize, and also to continue to develop guidelines to assist in the commercialization of cell and gene therapy products.

JM: On the regulatory side, we've noted already that due to their unique attributes, at the moment, each ATMP has had to go through the authorization process afresh and more or less on a case-by-case basis. However, now that a measure of experience has been gained and there is increasing familiarity with these products, much-needed guidelines are beginning to emerge that will hopefully assist with the process moving forward.

For example, there was new manufacturing guidance published in 2017 (Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products, 22 November 2017) that adapted the general good

manufacturing practice requirements to the specific characteristics of ATMPs, such as decentralized manufacturing and complex supply chains – the aim being to ensure consistency of manufacturing despite variability in the starting materials and the complex global manufacturing chain. The guidelines very much take a risk-based approach, allowing manufacturers to be flexible as long as they have control systems in place, and proportionate to the level of risk.

Similarly, earlier this year, clinical guidance (Guidelines on Good Clinical Practice specific for Advanced Therapy Medicinal Products, 10 October 2019) was published that will greatly assist with the clinical development process and provide guidance for companies on how to structure their trials, including the number of patients necessary to demonstrate safety and efficacy, and appropriate comparators to use, which have been some of the major areas of concern.

These guidance documents have been drawn up based on the experience of the authorities in assessing the products that are already on the market. They provide much-needed detail for companies seeking to obtain an authorization and hopefully, over the coming years, we will see more guidance coming through covering a broad range of regulatory issues.

But it's also important that there are efforts to assist with standardization of the more practical aspects of treatment. At present, each product has its own collection protocol, its own storage process in a specific type of freezer (that the hospital has to procure), and its own booking and traceability protocol (each of which tends to involve different email- and web-based systems). While there are only a few products on the market, these differences are manageable for hospitals. But as the number of products increases, and if even a fraction of the thousand products that are currently in clinical trials reach the market, then these more practical aspects will also need to be standardized.

BSM: There's a balance to be found here. In some circumstances, guidelines will be sufficient – sometimes you require flexibility for new products and, if everything is standardized, you might actually limit innovation. But for other practical aspects, standardization would be a significant help.

JM: I agree. On the regulatory side, the authorities tend to develop guidance, which they can then adapt as necessary for specific products. This does cause difficulties as companies may not be able to understand or predict the authority's approach in a given situation. But more formal standards in relation to the practical aspects, such as refrigeration, traceability or booking, would help a great deal with the beginning and end of the supply chain.

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Q Finally, on the topic of the current challenges around market access of cell and gene therapy products, what for you are the key considerations and next steps for the community as a whole to ensure patients can benefit from ground-breaking new therapies in the decade to come?

BSM: I think the challenges are more heavily weighted on the regulatory compliance side but, as ever, strong IP protection – whether by way of patents, confidential information, or a mixture of the two – will always be an important part of the puzzle. It is vital for ensuring innovators can access sufficient investment to enable them to bring a product to the market (assuming that product also clears all the regulatory and compliance hurdles, of course). Investors want reliable exclusivity of products and processes and if that cannot be secured, investment won't follow.

On a more general level, to promote the sector, I think there should be more reliable protection for novel cell and gene therapies through the patent and the regulatory systems – particularly for second (or further) medical use products. I consider this to be a key challenge both at present and moving forward.

JM: Ensuring patients benefit from these therapies will require cooperation between the healthcare systems, the health technology assessment bodies, and industry. All these stakeholders now have experiences to draw on from ATMPs that have been authorized and are on the market. Important lessons have been learnt and best practices can be defined. It's now time for stakeholders to work together to resolve some of the complications we've mentioned during our discussion, and to help streamline the process for future products.

Early engagement by companies with the authorities, patients and healthcare professionals will be a crucial component of this effort. This will help to ensure increased familiarity with the technology and the manufacturing

processes – and indeed, will increase the community's understanding of what these products can achieve.

Companies should also engage with industry bodies to provide their views as part of industry-wide discussions and responses to consultations to help drive harmonization in some of these areas.

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