

Title: Innovator cell therapies present barriers to the entry of copy versions regardless of patent protection

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Introduction

Concerns are expressed about the commercial viability of cell therapies that lack patent protection. These concerns originate from the perception that unpatented cell therapies do not present high enough barriers to entry of copy versions; below we discuss defence mechanisms that apply, regardless of patent protection, to those cell therapies which are licensed “Advanced Therapy Medicinal Products” (ATMPs). Cell therapies which are not ATMPs and have not achieved marketing authorisation do not have the methods of protection described in this article.

Due to lengthy development timelines, by the time the typical small molecule or biologic launches, a substantial part of its patents’ life has already been exhausted; furthermore generic drug manufacturers may enter the market with their copies few years before patents expire. The combination of these factors can result in generic versions launching as early as 5 years post-innovator launch. Therefore pharmaceuticals are renowned for having fewer effective years of patent protection than other products (Focus on Innovation, PHRMA, 2004).

Data exclusivity, market exclusivity and supplementary protection certificates (SPC) may provide additional time. Beyond these exclusivity and SPC periods, anti-generics defence strategies are employed by the manufacturer of the innovator product to minimise price and volume erosion for the remaining of its product’s lifecycle. In this article we discuss how such strategies can be leveraged in the cell therapy arena and emphasize that licensed ATMPs present higher barriers to copy entrants than small molecules and biologics.

The defense strategies presented here are clustered in two groups i.e. A. those that leverage regulatory frameworks and B. commercial strategies that utilise product lifecycle management mechanisms to help minimise volume erosion.

Strategies leveraging regulatory framework and legislation

1. **Biosimilarity:** Unlike molecule-based therapies, cell therapies face significantly greater challenges in substantiating claims of biosimilarity. The reality of achieving biosimilarity for a complex ATMP remains untested; some senior EU regulators have said publically that this may not be possible. However, according to the biosimilarity legislation, it is conceivably possible based on the core principle of comparability between the biosimilar and reference medicinal product but requires demonstration of comparability in quality, pre-clinical and clinical studies. Therefore those competitors considering launching copy versions would need to invest in extensive developmental activities to be able to demonstrate biosimilarity with respect to the quality, pre-clinical and clinical categories.
2. **Data exclusivity:** For licensed Advanced Therapy Medicinal Products (ATMPs) the data exclusivity period in Europe is 8 years dating from the EMA authorisation decision: before that, no generic applications may be filed; two further years will be required before the generic can be marketed (market protection period) and 1 year more if the authorisation holder successfully

files for a new additional indication. In the US the legislation favours advanced therapies as the data exclusivity of 7 years that applies to small molecules is increased to 12 years for the biotech category.

3. **Market exclusivity:** Licensed ATMPs for orphan indications in particular present even higher barriers for copy entrants through the market exclusivity period, which means that subsequent “me-too” ATMPs will not be granted authorisation for that period: in the EU, this is 10 years from market authorisation (extended up to 12 years for paediatric orphans), and in the US it is 7 years.

Commercial strategies to raise barriers to competitive entry

1. **Secrecy of know-how:** For a cell-therapy production process without patent protection, it is important that know-how is kept secret both during development and post-launch periods. This way, replication of the process by competitors and demonstration of biosimilarity would be much more difficult to achieve.
2. **Gathering of post-launch real world evidence/long-term data to support favourable market access for the therapy:** Payers put a strong emphasis on the availability of data on long-term outcomes to favourably differentiate amongst treatments and proceed with decisions about a therapy’s endorsement, funding and inclusion in formularies, clinical protocols and guidelines. More so than small molecules and biologics, cell therapies have the potential to deliver long-term benefits. Due to time constraints these can be challenging to demonstrate during pre-clinical development. Therefore timely generation of post-launch data for the innovator cell therapy will provide differential advantage over subsequent copy launches that have not been long enough in the market to substantiate claims of long-term benefits.
3. **Communicate the impact of cellular variability between innovator and copy cell therapies:** Such variability could result in differences in clinical and cost effectiveness. There are multiple options to communicate impact e.g.
 - a. Model the clinical and/or economic consequences of these differences in order to support, if possible, the innovator therapy.
 - b. Employ KOL engagement and advocacy development programmes.
 - c. Leverage physician and patient forums to communicate level of cell-therapy differentiation and present concerns and/or risks.
 - d. Utilize media and conferences to highlight and communicate therapy differentiation.
4. **Therapy inclusion in formularies/clinical guidelines:** Incorporation of the therapy in national, regional and local level treatment protocols, clinical guidelines and formularies is driven by clinical and economic considerations and has a favourable impact on uptake. Revisions of these documents take a long time to materialise hence inclusion of the innovator therapy becomes a barrier for subsequent entrants.
5. **Patient access schemes/risk-sharing agreements/innovative contracts:** These arrangements between the manufacturer and the payers can facilitate innovative therapy uptake especially when data at launch are not considered robust enough. These often involve some degree of administrative burden for payers; therefore strategies for absorption of such burden by manufacturer can increase likelihood of implementation and consequently therapy uptake.
6. **Provide added-value services for the healthcare system and the patient** e.g. Total disease management schemes are increasingly popular strategies for partnerships between healthcare providers and manufacturers and can support therapy uptake through the provision of associated services (e.g. diagnostic, home-care, patient lifestyle adjustment, counselling); in

these schemes, patients receive more intensive education, assistance, and monitoring in following a treatment plan tailored to their needs.

7. **Ongoing awareness & training initiatives** to engage and build long-term relationships with healthcare providers and treating physicians.
8. **Technology improvements/development of associated proprietary devices and diagnostics**
 - a. A typical pharmaceutical anti-generics strategy is to switch patients to next-generation drugs to balance existing brand erosion, a practice known as “*Evergreening*”
 - i. For example the manufacturer of OxyContin for pain relief (Purdue Pharma), reformulated the medication using proprietary drug-delivery technology to minimise risk of abuse; the safer newer version resulted in FDA banning the launches of all generic versions of the original.
 - b. Furthermore as discussed earlier, if the authorisation holder successfully files for a new additional indication, the data exclusivity period increases by 1 year (EMA).
9. **Size of target population:** high cost cell-therapies are considered more commercially viable in diseases of high unmet need and small number of patients where comparative clinical and cost-effectiveness claims can be substantiated and budget impact concerns can be minimised; therefore many cell therapies are being developed for rare diseases or niche high unmet need subpopulations within larger therapy areas; as a result the size of the target population can be too small to encourage subsequent market entrants with the exact same value proposition; demonstration of incremental benefit rather than a “me-too” status would be a more commercially viable strategy for subsequent market entrants to pursue.
10. **Avoid voluntary price reduction:** High manufacturing costs (coupled with high developmental costs required to bring a copy to market) would limit potential for copy versions being competitively priced. Furthermore reducing innovator therapy price as a response to me-too entries may trigger a price war, which can erode and destroy profitability.
11. **Ongoing manufacturing and supply chain optimisation** to maximize competitive advantage and overcome challenges of forced by payers price reduction over time e.g. resulting from the inclusion of a therapy into a capped DRG (Diagnosis Related Group) tariff (as exemplified by the case of Dermagraft in the US).
12. **Campaign against competitive tendering of cell therapies:** For cell therapies, the concept of therapeutic equivalence cannot be applied. It is important to engage with procurement functions of healthcare providers and clarify the need to recognise and distinguish all the qualities and features of individual cell therapies so that their grouping for competitive tendering and saving purposes is avoided.
13. **Explore deal-making with emerging competition** to reduce sales erosion, a strategy known amongst pharmaceuticals as “*Flanking*” can be employed
 - a. Under this strategy, brand-name drug companies sign licensing agreements with their generic competitors to establish manufacturer-distributor relationships.

Conclusions

To conclude, weak or inexistent patent protection should not be perceived as a barrier to the successful commercialisation of a licensed ATMP; the key defensibility strategies discussed in this article can help maintain competitive advantage and minimise erosion of the commercial opportunity. However where the opportunity for patent protection arises, it should be pursued in order to maximize competitive advantage. IP protection would be particularly valuable in those cases where a licensed ATMP faces



unlicensed competition e.g. by hospital produced unlicensed alternatives under the hospital exemption scheme.

Ultimately parameters such as disease burden and unmet need, the therapy's incremental benefits vs current and emerging competition, the robustness of its supporting clinical and economic data and their impact on pricing, reimbursement and uptake, as well as its manufacturing and supply chain cost-efficiency will be the key drivers for commercial success.

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