The Landscape of Clinical Approval

Due to an enhanced interest in the advancement of cell and gene therapy, it is essential to assess the current regulatory climate and how to accelerate drug approval.

Cell and gene therapies, and other advanced medicinal products, have generated substantial public health interest, and deservedly so. These living drugs have shown remarkable effectiveness against cancer and other life-threatening illnesses, including rare diseases with previously no treatment available. Recent approvals of cell- and gene-based therapies underscore the industry’s conviction that these drugs will have a strong, positive impact on patient health (1-2). At the same time, accelerated approval pathways are placing a heavy onus on drug developers to assure a consistently pure and efficacious product. Sourcing donor material and assuring efficacy are a lot more complicated when a drug comprises living cells and tissues rather than synthetic products. Accelerated approval also puts significant strain on starting material suppliers, especially in the cell therapy space.

In the last two years, both the FDA and EMA have rolled out strategies to expedite the advancement of cell therapies and regenerative medicines (see Figure 1). Under their new Regenerative Medicine Advanced Therapy (RMAT) designation, the FDA lists criteria for various accelerated approval pathways (3). Meanwhile, in Europe, the new Priority Medicines (PRIME) initiative is helping to expedite authorisation of advanced therapy medicinal products (4). Both RMAT and PRIME regulations allow for drugs that address unmet medical needs and meet specified clinical criteria to apply for an expedited regulatory process. The main goals of these new approval strategies are clear: to get potentially lifesaving treatments to patients as efficiently as possible. In practice, the process is not so straightforward. Pharmaceutical developers and starting material suppliers must intensify scrutiny of their starting material collection and processing methods to keep up with industrial and medical expectations.

**Single, Pivotal Approvals**

In both the US and Europe, there are four distinct pathways by which a medicine may be expedited.

---

**Standard FDA/EMA approval process**

1. Basic research
2. Design and discovery
3. Preclinical development
4. Clinical development phases
   - Clinical development phases 1
   - Clinical development phases 2
   - Clinical development phases 3
5. FDA filing and approval

**Accelerated FDA/EMA approval process**

1. Basic research
2. Design and discovery
3. Preclinical development
4. Clinical development phases
   - Clinical development phases 1
   - Clinical development phases 2
   - Clinical development phases 3
5. FDA Fast Track filing and approval

**Figure 1**: Advanced therapies meeting specific regulatory criteria can apply for expedited approval.
for approval, and the eligibility guidelines are different for each regulatory agency (see Figure 2). Last year, the FDA approved a record-breaking 59 novel drugs, 42% on the basis of a single pivotal clinical trial (5). Lumoxiti®, Astrazeneca's treatment for adult patients with a rare type of slow-growing leukemia, was studied in a single-arm, open-label clinical trial comprising only 80 patients and was fast-tracked on the basis of its orphan drug status (6).

Another cancer drug, Pfizer's Vizimpro®, was approved on the basis of a single clinical trial of 452 patients with advanced non-small cell lung cancer (7). Stemline Therapeutics won FDA approval for their blood cancer treatment, Elzonris®, after a single US-based clinical trial of 94 patients (8).

In Europe, the statistics are similar; 45% of EMA approvals from 2012 to 2016 were based on evidence from a single pivotal trial (9). Novartis' Kymriah® made headlines when it was approved in both the US and, shortly after, Europe. The drug is a first-in-class CAR T cell treatment for refractory B cell leukemia and was approved based on one multicentre clinical trial of 63 paediatric and young adult patients. The overall remission rate in that trial was an astonishing 83% (1).

These numbers are part of a strong trend over the past few years. Cell and gene therapy manufacturers have devoted a great deal of energy and resources towards solving problems of 'scale up' and 'scale out'. There is a good deal less discussion regarding how a burgeoning pipeline and accelerated approval pathways are affecting cell therapy starting material suppliers. Single-trial approvals, in particular, lend heightened importance to beginning the manufacturing process with biological materials of consistent purity and efficacy, with low variability. Using GMP-compliant materials as early as possible in the process saves time and resources later. It may well make sense to ‘redistribute’ initial manufacturing steps to the cell collection centre. This growing concern is exemplified by the fact that one of the largest cell collection centres has now incorporated their own GMP-qualified cleanroom environment (11).

In Europe, the statistics are similar; 45% of EMA approvals from 2012 to 2016 were based on evidence from a single pivotal trial (9). Novartis' Kymriah® made headlines when it was approved in both the US and, shortly after, Europe. The drug is a first-in-class CAR T cell treatment for refractory B cell leukemia and was approved based on one multicentre clinical trial of 63 paediatric and young adult patients. The overall remission rate in that trial was an astonishing 83% (1).

These numbers are part of a strong trend over the past few years. Cell and gene therapy manufacturers have devoted a great deal of energy and resources towards solving problems of ‘scale up’ and ‘scale out’. There is a good deal less discussion regarding how a burgeoning pipeline and accelerated approval pathways are affecting cell therapy starting material suppliers. Single-trial approvals, in particular, lend heightened importance to beginning the manufacturing process with biological materials of consistent purity and efficacy, with low variability. Using GMP-compliant materials as early as possible in the process saves time and resources later. It may well make sense to ‘redistribute’ initial manufacturing steps to the cell collection centre. This growing concern is exemplified by the fact that one of the largest cell collection centres has now incorporated their own GMP-qualified cleanroom environment (11).

Cell collection and isolation is a complex process, and the variability of cellular starting material is well documented. The FDA cites inherent variability and functional complexity as one of the main challenges facing the manufacture of cell and gene therapies (12). It is important to remember that the quality of starting material for cell and gene therapies will impact all downstream processes (see Figure 3). Human stem cell and immune cell-based therapies rely on donors. Cell collection varies not simply from donor to donor, but also from one collection centre to the next, or from the same donor. Expertise in donor management, particularly in the aspects of donor nurturing and consistent training and collection methods, are critically important in mitigating some of this variability.

There is ample evidence that disease states, notably cancer, affect the quality and number of various immune cell subtypes present in apheresis material (13). A study presented at last year’s American Association for Cancer Research conference noted that T cells from patient-donors

<table>
<thead>
<tr>
<th>FDA fast track</th>
<th>Expeditethe review of drugs that treat a serious condition and fulfil an unmet medical need</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA breakthrough therapy</td>
<td>Expeditereview of drugs that demonstrate improvement over available therapy</td>
</tr>
<tr>
<td>FDA accelerated approval</td>
<td>Allow the approval of drugs that fulfil an unmet need to be approved based on surrogate end point</td>
</tr>
<tr>
<td>FDA priority review</td>
<td>A process that directs resources to drugs that represent significant improvements in safety compared to standard applications</td>
</tr>
<tr>
<td>EMA conditional approval</td>
<td>Allow drugs for life-threatening diseases to be approved with limited clinical safety or efficacy data</td>
</tr>
<tr>
<td>EMA exceptional circumstances</td>
<td>Allow drugs for life-threatening diseases to be approved without comprehensive efficacy and safety data</td>
</tr>
<tr>
<td>EMA accelerated assessment</td>
<td>A process designed to expedite products of major interest in terms of public health and therapeutic innovation</td>
</tr>
<tr>
<td>EMA PRIME</td>
<td>To enhance support for the development of medicines that target an unmet medical need</td>
</tr>
</tbody>
</table>

Figure 2: FDA and EMA list distinct expedited approval pathways
previously exposed to chemotherapy showed a decline in the expansion capability, as opposed to healthy donor T cells (14). Another publication noted that the cytokines used in growth media can affect CAR T cell safety and efficacy profiles during clinical trials (15). Many factors can contribute to the variability of a final product. Starting material suppliers need to take what steps they can to reduce that variability.

The goal of process development is to achieve the greatest therapeutic benefit at the lowest risk of toxicity. Therefore, apheresis should aim not simply to maximise collection volumes, but the purity of the collection in terms of therapeutic cell types. This helps minimise cell isolation and processing steps, streamlining manufacturing and making it easier to scale up. A robust, consistent manufacturing process with strict quality oversight ensures consistent efficacy downstream. Pharma developers should begin cell therapy process development with the end goal in mind, and cell therapy starting material providers can have valuable input in that process.

**Accommodating Demand**

The rapid increase in emerging cell therapies is already putting hospitals and cell collection centres under strain, and efforts to boost donor recruitment and expand collection centre capacity are currently under way (16). Hospitals and cell collection centres would also benefit from additional staff, expanded workplace hours, and additional collection facility space.

Sourcing the cells that go into the cell therapy development process can be difficult; a large, well-managed donor network is a necessity. It is very expensive in both time and resources to have to search out new, compatible donors during late-stage development or clinical testing. Access to a wide pool of donors with varying characteristics helps avoid bottlenecks for allogeneic donor sourcing as well as for autologous therapy process development. Access to recallable donors is also very valuable. The ability to recall donors that are reliably responsive and available can help reduce variability and ensure that suitable materials can be obtained in a timely manner (see Figure 4).

Obtaining materials for autologous treatments like CAR T therapy is more difficult than sourcing material from healthy donors. Serious diseases often significantly impact the number of therapeutic cells present per collected unit (17). If a patient cannot donate sufficient cells for an effective dose, or if the collected material is heavily contaminated with other cell types, it impacts cell therapy production times and, worse, can negatively impact a patient waiting for lifesaving treatment. For this reason, many pharma companies are now leaning towards finding ways to mitigate immune response and transplant rejection.
issues and allocate their resources towards designing allogeneic products.

Working with living cells and tissues means there will always be some variability. It is essential that starting material suppliers have a good understanding of which parameters can and cannot be controlled and work towards standardising, where possible, and having strong quality-control systems in place to cover each step during collection, isolation, cryopreservation, and shipping.

**Keeping the End Goal in Mind**

Cell therapies pose unique manufacturing and commercialisation challenges. The evolving clinical landscape heightens the importance of high-quality cell therapy starting materials, and places pressure on suppliers to accommodate expedited approval pathways, single pivotal trial approvals, and a rapidly expanding pipeline.

The consistency of upstream starting material collection strongly impacts the consistency of downstream products. The translation of strong cell therapy pipelines into successful lifesaving medicines requires a shift in how cell therapy starting materials are viewed and leveraged. Both cell therapy suppliers and pharma manufacturers must take steps to mitigate risks in terms of variability, efficacy, consistency, and quality oversight of starting materials. To respond to the rapidly changing clinical approval landscape, manufacturers and suppliers will need to form close partnerships from the start and begin the process of cell therapy development with the end goal in mind: safe, effective, and innovative therapies.

**References**

9. Visit: www.raps.org/regulatory-focus%E2%84%A2/newsarticles/2017/11/nearly-half-of-recent-eeu-approvals-based-on-a-
12. Visit: https://www.fda.gov/media/73624/download
13. Knauss HA et al, Signatures of CDB+ T cell dysfunction in AML patients and their reversibility with response to chemotherapy, JCI Insight 3(21): 2018
15. Hoffman JM et al, Differences in expansion potential of naive chimeric antigen receptor T cells from healthy donors and untreated chronic lymphocytic leukemia patients, Front Immunol 8: pp1,556, 2018

**About the author**

Dominic Clarke PhD has 15-plus years of experience developing enabling solutions for cell therapy and bioprocessing applications. Dominic is the Global Head of Cell Therapy at HemaCare, the leading provider of donor starting material for development and commercial cell and gene therapies, where he is actively engaged with industry experts to ensure the highest quality materials are delivered. Previously, he has held roles as the Global Product Manager for Charter Medical’s cell therapy and bioprocessing disposables portfolio, focused on creating flexible closed-system solutions for early- and late-stage production, and as the Director of Research and Development at BioLife Solutions, developing novel biopreservation media and methods to support extended stability of cells and tissues.

**Email:** dclarke@hemacare.com

Brad N Taylor PhD is the Global Marketing Director at HemaCare. Brad has 13-plus years of experience in the biotech industry, addressing multiple aspects of drug discovery and preclinical development. Previously, he has held roles as Application Scientist and Product Manager in the In Vivo Imaging division of PerkinElmer, where he worked to bring innovative solutions to market to assist the research community in expediting and streamlining the process of preclinical drug discovery for cancer and other clinical applications in animal models of disease.

**Email:** btaylor@hemacare.com