A Reflection On BTD And RMAT Designations

The continuing interest in cell and gene therapies is reflected by the 800+ active investigational new drug (IND) applications within the field that are on file with the US Food and Drug Administration (FDA).[1] This trend is only set to increase, with the FDA foreseeing the approval of 10–20 cell and gene therapy (CGT) products per year by 2025.[2]

To increase the number of therapeutic options for treatment of conditions for which there is currently no cure, there are two FDA expedited pathways: the Regenerative Medicine Advanced Therapy (RMAT) designation and the Breakthrough Therapy designation (BTD). Both are well suited to the development of cell and gene therapies. This article reflects on the usage of these designations and, throughout, Keith Webber, Vice President, Biotechnology at Lachman Consultant Services, Inc., provides insights and advice regarding the two accelerated pathways for cell and gene therapies.

BTD Versus RMAT

Being the earlier of the two designations (2012), BTD holds the majority of product approvals. This pathway was followed in 2017 by the RMAT, which has a particular focus on cell and gene therapies, tissue engineering products, and human cell or tissue products. This differentiates it from the BTD, which is also applicable to other types of therapies if they address serious or life-threatening conditions. Table 1 provides an overview of the number of requests for each designation, as well as the success rate across 2019.

Despite the number of BTD requests exceeding quadruple the number of RMAT applications, the success rates are comparable, at around 35–40%. This has also been the case for cumulative data that show all submissions since each designation was introduced (refer to **this** 2018 *Pink Sheet* guide for cumulative information, plus further trends including therapy areas and sponsor types). However, there are certain differences in evidentiary criteria for applying for both pathways that may affect decision-making regarding which designation to apply for. With the BTD, sponsors must provide evidence that the treatment is likely to be a substantial safety or efficacy improvement over existing therapies, which is not the case for RMAT.[5] As

a result, if a product candidate is eligible, Webber notes that it could be beneficial to gain both designations as, "if you can apply for both, you can choose the most advantageous if you receive both, so it opens up more opportunities."

Inevitably, there are certain challenges associated with applying for either designation. According to Webber, one factor to be mindful of: "Often the clinical development is more advanced than the chemistry, manufacturing and controls (CMC) development. The CMC and product development can be a rate-limiting component for a Biologics License Application (BLA) submission or approval. So that is something to keep in mind. You don't want this to hold you back as you move through development." Ensuring all elements of the research and development process are aligned is therefore an important factor for boosting chances of rapid product approval.

Post-Approval Safety And Efficacy Studies

Post-approval requirements can be another consideration when determining which pathway is most suitable. For an accelerated approval under BTD, there is a requirement to perform a post-approval confirmatory study when the approval has been based on a smaller data set or surrogate endpoints. The post-approval requirements for the RMAT are not as rigid; Webber notes that "the accelerated approval may allow the use of historical controls, retrospective studies, monitoring data or real-world evidence – there are more opportunities for that confirmatory evaluation. This may be because the BTD is for all products, including traditional pharmaceuticals, whereas RMAT is only for the more complex biological products. As such, RMAT products are often times more challenging to design clinical studies for."

The topic of post-approval and surrogate endpoints can raise concern around treatments being ineffective, or possibly toxic, upon being marketed.[6] In terms of advice, Webber said, "Communicate with the FDA early and often when designing your trials or planning approval." There is an FDA guidance document, called "Interacting with the FDA on Complex and Innovative Trial Designs," which provides sound advice for developing successful clinical protocols. The recommendation is to get both FDA input and acceptance as early as possible on trial design. To support these critical interactions, the FDA has set a goal of recruiting 50 new clinical reviewers for CGT products.[7]

FDA Submissions – What To Look Out For

The recent development of Medicaid expanding coverage for products receiving accelerated approvals signifies the interest and investment in cell and gene therapies.[8] This is in tandem with a growing trend of larger companies being increasingly keen to own gene therapy technologies rather than partnering. Historically, gene therapies have been spearheaded by small biotechnology companies (typically in partnership with larger pharmaceutical firms). In fact, 90% of gene therapy development is by companies with fewer than 500 employees.[9] From his experience in carrying out due diligence for larger organizations interested in investing or acquiring smaller biotechnology companies, Webber noted: "Be vigilant in your due diligence assessments when considering buying or investing into a company. You should watch out for gaps in product development. For example, there may be deficiencies in the establishment of the master cell bank or working cell banks."

Look out for poorly characterized components in the product and qualification of materials. In addition, watch out for any lack of standardization, which can create issues further on in the process. Webber explains that "There may be a lot of variability in how the manufacturing processes are performed during development and that can be a challenge in terms of establishing what is the consistent product that's coming out of that manufacturing process. In many

TABLE 1. 2019 COMPARISON OF BTD[3] AND RMAT[4] FDA DESIGNATIONS

Designation	Total Requests Received	Granted	Denied	Withdrawn	Success Rate (%)
BTD	157*	54	63	18	34%
RMAT	37*	15	18	2	41%

*Requests that are still pending a decision are included in the total requests received column. Numbers are for US federal fiscal year 2019, ended 30 September 2019.

cases, the product is the process. So if the processes are changing continually, and the product is difficult to fully characterize (as often the RMAT products are), you can have considerable uncertainty with regard to the interpretation of any preliminary clinical data."

Data integrity can also be an issue, for which Webber suggests paying close attention to the ALCOA principles (Attributable, Legible, Contemporaneous, Original and Accurate). "Those principles should be in place, and if they aren't it can be challenging to be reliant on that data for presentation to the FDA during inspection."

Webber indicates that manufacturing is a final area of the process that can come under scrutiny: "Sometimes there are manufacturing changes during development that have not been qualified. So, the company makes changes where they haven't really evaluated the impact (of those changes) during development of the manufacturing process."

What Will The Future Look Like?

The direction of growth in cell and gene therapies is moving further toward personalized medicines. At this point, it is difficult to predict how the regulatory landscape will accommodate these advancements. One of the largest challenges to anticipate may be in assessing clinical outcomes, where variances could be due to patient-to-patient differences or product-to-product differences. "It might be necessary to develop methods to assess the *in vivo* product performance, for example, gene incorporation and gene expression, in addition to the assessment of clinical outcome, to further understand the relationship between clinical performance and product performance *in vivo*." Webber continued, explaining that the FDA's Center for Biologics Evaluation and Research (CBER) has released many new guidances regarding CGT, covering everything from certain therapeutic areas such as hemophilia to evaluations of devices used in regenerative medicine.

Given that the cell and gene therapy accelerated pathways are relatively new, and with the stance of Medicaid reimbursing such products, applications for accelerated approval pathways are set to skyrocket. The possibilities that cell and gene therapies may unveil could be truly profound. That being said, approval for CGT is undoubtedly going to become more complex with the advancement of personalized medicine, and this could create further complications when conducting studies and assessing clinical outcomes (due to individual variance).

A closing remark from Webber: "The FDA has a great interest in bringing new and effective treatments to patients, so I encourage sponsors to take advantage of this willingness, to meet with the FDA early and during product and clinical development phases. Also, work with consultants as needed to get guidance on preparing submissions and product development as you move forward."

SOURCES

1. https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/fdas-efforts-advance-development-gene-therapy
2. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics
3. https://www.fda.gov/media/95286/download
4. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/cumulative-cber-regenerative-medicine-advanced-therapy-rmat-designation-requests-received-fiscal
5. https://pink.pharmaintelligence.informa.com/PS124820/Gene-Therapies-Make-A-Mark-In-US-FDA-Expedited-Review-Programs
6. https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/gene-therapy-coming-of-age-opportunities-and-challenges-to-getting-ahead
7. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics
8. https://www.medicaidandthelaw.com/tag/gene-therapies/
9. https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/gene-therapy-coming-of-age-opportunities-and-challenges-to-getting-ahead

Lachman CONSULTANTS™

Experience. Excellence.™