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RMAT Designations: Lessons Learned on the "Clinical Evidence" Requirement

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The 21st Century Cures Act (Cures Act), signed into law in December 2016, was designed to reduce regulatory obstacles for FDA approval of innovative medical therapies and accelerate the process of bringing innovative products to patients in need. Included in the Cures Act was a pathway to accelerate FDA approval and market entry of regenerative medical therapies, such as cell therapies or human tissue products, known as the Regenerative Medicine Advanced Therapies ("RMAT") designation. The RMAT designation carries all of benefits of Breakthrough and Fast Track therapy designations, including: intensive interaction with FDA on an efficient drug development program beginning as early as phase 1, organizational commitment involving senior FDA personnel, and rolling BLA review. RMAT designees are also eligible for *accelerated approval and priority review if relevant criteria are met.*

According to Section 3303 of the Cures Act, a drug is eligible for the RMAT designation if: (1) the drug is a regenerative medicine therapy; (2) the drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and (3) *preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition.*

The first two requirements are defined in the statute, but this final requirement – preliminary clinical evidence showing the potential to address unmet need – necessarily varies on a case-by-case basis. Understanding how FDA evaluates the preliminary clinical evidence is therefore crucial to successfully achieving the RMAT designation. Now, after nearly two years, a draft FDA Guidance, and nearly 21 total RMAT designations, there appear to be at least a few discernible trends in how FDA assesses the clinical evidence supporting successful RMAT candidates, particularly with regards to the relationship between (a) the rarity of the disease being treated and (b) the study design and the quantum of supporting data.

Draft FDA Guidance suggests that the rarity of the disease or condition being treated is a crucial element in assessing clinical study design and results.

A draft FDA Guidance Document on Expedited Programs for Regenerative Medicine Therapies for Serious Conditions ("Draft Guidance"), dated November 2017, lists several non-exhaustive factors that FDA intends to consider when assessing the preliminary clinical evidence: the rigor of data collection; the nature and meaningfulness of the outcomes; the number of patients or subjects, and the number of sites contributing to the data; and the severity, rarity, or prevalence of the condition. [1] [2]

FDA recognizes the tradeoff between the rarity of a disease or condition and the ability to achieve ideal clinical trial design, as the Draft Guidance states that the evidence need not always come from prospective trials with a concurrent control and that "in some cases clinical evidence obtained from studies with appropriately chosen historical controls, may provide sufficient preliminary clinical evidence of the potential to address an unmet need."[2] [3] The ability to use historical data as a control greatly facilitates designing studies and developing drugs for treating rare diseases and conditions. Patient enrollment is a major challenge in such cases, making it very difficult to meet the "gold standard" of study design (i.e., a double-blinded, placebo-controlled study).

As discussed below, the statements in the Draft Guidance seem to be playing out, as there appears to be an inverse correlation between (a) the rarity of the disease being treated and (b) the robustness of the trial design and the amount of supporting clinical data.

There appears to be a correlation between the rarity of the condition and the trial design.

True to the Draft Guidance, at least four RMAT designations appear to have been awarded based on clinical studies utilizing historical controls. These are:

• Abeona Therapeutics' EB-101 (for treating Recessive Dystrophic Epidermolysis Bullosa (RDEB), a genetic condition impacting wound healing ability);

• Kiadis Pharma's ATIR101 (for treating mortality from blood disorders following haploidentical hematopoietic stem cell transplantation);

• Asterias Biotherapeutics' AST-OPC1 (for treating loss of motor function following spinal cord injury); and

• NightStar Therapeutics' NSR-REP1 (for treating choroideremia, a rare, degenerative, genetic retinal disorder that leads to blindness**).**

The designees that successfully utilized historical controls are, as one might expect, intended to treat rare diseases (e.g. RDEB and choroideremia), or else are intended to treat conditions that are time-sensitive (e.g. spinal cord injuries, blood disorders following transplantation). These clinical studies necessarily had low enrollment (ranging from 7 to 35 subjects), thereby making it difficult to design a more robust study based on concurrent controls. Thus, at least in the early going, FDA appears receptive to the use of historic controls in these circumstances.

On the other hand, FDA seems to require a more robust study design for therapies intended to treat more common conditions. For example, FDA has granted the RMAT designation to several therapies that are intended to treat relatively common cardiovascular conditions, including:

• Athersys' MultiStem (for treating damaged blood vessels damaged from ischemic stroke);

• Caladrius' CD34+ cell therapy (for treating refractory angina);

• Vericel's Ixmyelocel-T (for treating advanced heart failure due to ischemic dilated cardiomyopathy); and

• Mesoblast's Mesenchymal Precursor Cell (MPC) Therapy (for heart failure).

The clinical trials used to support these RMAT designations were of the highest accepted standards. That is, they were randomized, double-blinded, placebo-controlled, and had high enrollment. Thus, there seems to be a general trend that more common conditions require more robust study design, whereas a small (but well-designed) study utilizing historic controls can suffice in the case of rare diseases.

Nevertheless, there appears to be one interesting outlier to this trend. MiMedx's AmnioFix for treating knee pain from osteoarthritis was granted RMAT designation based on results from 10 subjects, even though this is not an uncommon condition. Subjects in the ongoing phase 1/2 trial reported 65 percent improvement in pain levels —which suggests that especially promising early results may make up for small sample size. Another intriguing possibility is that FDA is prioritizing therapies that provide alternatives to opioid painkillers. It will therefore be interesting to see if FDA grants any further RMAT designations for pain treatment and to examine the supporting clinical evidence and trial design for any such designations.

There also appears to be a correlation between the rarity of the condition and the state of the clinical trial evidence.

Of the 21 total RMAT designations, it appears that at least half were based on clinical evidence derived from completed or ongoing phase 1/2 trials, or earlier, mostly for therapies intended to treat rare diseases. Moreover, three of the four above examples of RMAT designations for rare disease treatments were based on ongoing phase 1/2 data (i.e. the early stages of clinical testing). By contrast, the four above examples of designations for treatments for more common cardiovascular diseases were based on completed phase 2 studies. This suggests that the more rare the disease, the earlier FDA will grant the RMAT designation**—**perhaps reflecting a desire on FDA's part to expedite therapies for conditions that are in need of treatment attention.

Looking ahead

It will be interesting to see if these apparent trends of the last few years continue. And, in lieu of any further draft or final guidance on the RMAT designation, it will also be interesting to see whether FDA affirms certain other statements made in the November 2017 Draft Guidance. For example, FDA indicated that for cellular or tissue constructions intended to replace a human organ, long term assessment may not be feasible, and that short term performance to clinically meaningful endpoints might suffice.[3] [4] No such products have been designated as of the writing of this article, so the nature of clinical data that FDA accepts for any such products will therefore be instructive. Additionally, FDA states that it may rescind the RMAT designation if at any point the product fails to meet the qualifying criteria.[4] [5] Presumably this means that FDA will revoke RMAT status if at any point the therapy stops showing the ability to address unmet medical needs. It will be interesting to see if this becomes an issue for any of the designees – especially those for rare diseases where the quantum of clinical data supporting the designation appears to be relatively small (and in the early stages) – and also to track any disputes or litigation that may result from a revocation of the RMAT designation.

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References

[1] [7] Draft Guidance at 6.

[2] [8] Draft Guidance at 6.

[3] [9] Draft Guidance at 11.

[4] [10] Draft Guidance at 7-8.

Links:
[1] http://www.pharmexec.com/william-rose-and-suchira-ghosh
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