NISKANEN CENTER

LIFE EXTENSION ADVOCACY FOUNDATION

Regulatory Comment

Comments submitted to the Food and Drug Administration in the Matter of:

EXPEDITED PROGRAMS FOR REGENERATIVE MEDICINE THERAPIES FOR SERIOUS CONDITIONS

Ryan Hagemann
Director of Technology Policy
Niskanen Center

Keith Comito
President
Life Extension Advocacy Foundation

Elena Milova
Director of the Board
Life Extension Advocacy Foundation

Submitted: February 15, 2018
Docket Number: FDA-2017-D-6159

The **Niskanen Center** is a 501(c)3 issue advocacy organization that works to change public policy through direct engagement in the policymaking process; The **Life Extension Advocacy Foundation** is a 501(c)(3) non-profit organization dedicated to promoting increased healthy human lifespan through fiscally sponsoring longevity research projects, and raising awareness regarding the societal benefits of life extension.

INTRODUCTION

With the advent of precision medicine treatments, advanced drugs and biologics manufacturing, the emerging application of advanced artificial intelligence analytics, and the coming age of genetic modification, the Food and Drug Administration's (FDA) "regenerative medicine advanced therapy" (RMAT) designation guidance is a timely and welcome addition to the agency's regulatory toolkit. Emerging technologies and advancements in the life sciences portend substantial changes to how we identify, research and ultimately treat a wide array of diseases and debilitating conditions. Thus, we welcome the FDA's RMAT guidance, and hope its new expedited approval process helps usher in an age of revolutionary regenerative treatments for many of the ailments that plague humanity.

While we are exceptionally supportive of the FDA's guidance, there are a number of areas we believe could be improved, including broader reforms to the standards by which new drugs and biologics are approved. We begin by pointing out a number of areas that could benefit from greater clarity, followed by two general recommendations that can help improve the RMAT designation in particular, and the FDA regulatory approval process more generally.

PART I: CLARIFYING UNCERTAINTIES

Gene Therapies under the Regenerative Medicine Framework

Under section 3033 of the 21st Century Cures Act, a "regenerative medicine therapy" is unclearly defined, though it mentions that such therapies include, "cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products,"[1] with exceptions for select products regulated under the qualifying provisions of 21 C.F.R. 1271.10[2] and the regulations to control communicable diseases under the Public Health Service Act.[3] However, we are happy to see that the agency's RMAT guidance document clearly defines regenerative medicine therapies to include gene therapies:

> As FDA interprets section 506(g), gene therapies, including genetically modified cells, that lead to a durable modification of cells or tissues may meet the definition of a regenerative medicine therapy. Additionally, a combination product (biologic-device, biologic-drug, or biologic-device-drug) can be eligible for RMAT designation when the biological product component provides the greatest contribution to the overall intended therapeutic effects of the combination product.[4]

---

[1] 21 U.S. Code § 356(g)(8).
[2] 21 C.F.R. § 1271.10, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=1271.10.
[3] 42 U.S.C. § 264, Regulations to control communicable diseases, https://www.law.cornell.edu/uscode/text/42/264.
[4] *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions*, Food and Drug Administration, Center for Biologics Evaluation and Research, Draft Guidance for Industry, November 2017, p. 2, https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585414.pdf. (hereafter *Regenerative Medicine Therapies Guidance*)

As we interpret it, this definition suggests the agency would be supportive of most any drug, biologic, or cell therapy technique being designated as a "regenerative medicine therapy," so long as it meets the other two prongs of the criteria as laid out under 506(g) of the FD&C Act.[5] As it stands, the first criteria under 21 U.S. Code § 356(g)(2) seems almost entirely superfluous, since any drug, biologic, or cell therapy would qualify, so long as it met the second and third criteria. Such a broad definition may lend to uncertainty and confusion, and while it is commendable that the agency makes itself available to new applicants wishing to inquire about specifics, the FDA could help ameliorate considerable uncertainty by providing greater clarity.

That having been said, we are wholly supportive of the explicit inclusion of gene therapies as qualifying for RMAT designation and commend the FDA for its foresight in such a decision. However, in the interest of assuaging concerns for market certainty, we would ask for additional specificity and clarity on this matter.

Standards of Clinical Evidence and Regulatory Reform

We are supportive of the FDA's language that suggests a RMAT designation, unlike a Breakthrough Therapy Designation, "does not require evidence to indicate that the drug may offer a substantial improvement over available therapies."[6] Liberalizing the qualifying criteria in this way is a positive improvement over Breakthrough Therapy Designation standards, and we commend the agency for embracing such an approach.

Regarding the clinical evidence used to support a RMAT designation, the FDA's guidance notes its intention "to consider factors" that include "the nature and meaningfulness of the outcomes."[7] This factor suggests a reference to the agency's long-standing commitment to using standards such as "clinical utility" and "life outcomes" in making its determinations regarding the "safety and effectiveness" of new drugs, biologics, and cell therapies. Despite such considerations being slightly outside the scope of these comments, we mention them because in order to better capture the real benefit of RMATs beyond the expedited designation stage, the FDA needs to begin rethinking how it interprets these various standards and approval mechanisms.[8]

One option, recently proposed by Commissioner Scott Gottlieb, is capitalizing on advanced technologies and artificial intelligence to collect and process data in real-time for pre-market approval analysis and post-market oversight and surveillance.[9] Another solution is to embrace a tiered categories of approval

[5] Those criteria stipulate that, "[a] drug is eligible for designation as a regenerative advanced therapy" if it: (1) meets the broad definition of a "regenerative advanced therapy" under 21 U.S. Code § 356(g)(8); (2) "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 a disease or condition." 21 U.S. Code §§ 356(g)(2)(B), (C).

[6] *Regenerative Medicine Therapies Guidance*, p. 6. ("As opposed to breakthrough designation, the RMAT designation does not require evidence to indicate that the drug may offer a substantial improvement over available therapies.")

[7] *Regenerative Medicine Therapies Guidance*, p. 6.

[8] For more information, see Ryan Hagemann, *Comments submitted to the Food and Drug Administration in the Matter of: Benefit-Risk Assessments in Drug Regulatory Decision-Making*, Docket No. FDA-2017-N-4076-0001, submitted October 19, 2017, https://niskanencenter.org/wp-content/uploads/2017/10/Comments-Benefit-Risk-Assessments-FDA.pdf.

[9] "Expanding the FDA's capacity to utilize real-world evidence to evaluate the pre- and post-market safety and effectiveness of medical products would generate processes that could improve the efficiency of the regulatory process, better inform patients and providers about pre-and post-market safety, reduce some of the burdens that drive up the time and cost required to bring beneficial innovations to the market and address barriers that can make certain

process, by which new drug applications are reviewed based on the nature of evidence tied to support of a sponsor's claims of effectiveness.[10] A more "adaptive approval" system of approval like this could offer significant cost-savings for companies, while benefiting the FDA's overall mission of safeguarding public health by allowing the agency to focus scarce time and resources on those approvals that clearly require a higher approval threshold.[11] A similar initiative, also proposed by Commissioner Gottlieb, aims:

> to establish a new paradigm for digital health technologies under which a company could market lower-risk products without FDA premarket review and market higher-risk products following a streamlined FDA premarket review if the company receives prior third-party certification for engaging in high-quality software design and testing (validation) and ongoing maintenance. This regulatory model would be fully proven and expanded from its current pilot status to a broader program. For low-risk products, rather than evaluate each individual digital health product before the product comes to market, the FDA would instead focus its resources on validating the quality of a firm's software design and the firm's methods for certifying the quality and reliability of its underlying software performance. The agency would further reduce the time and cost of market entry of digital health technologies while assuring appropriate patient safeguards by relying on post-market collection of real-world data to support new and evolving product functions.[12]

Given the commitment to a pilot study that mirrors certain features of an adaptive approval system for digital health technologies, a similar framework for a pilot program focused on drugs, biologics, and gene therapies should be considered as a means of improving other avenues of the agency's regulatory approval process.

Endpoints and Clinical Trial Designs

The guidance explicitly notes that one criteria that may qualify RMATs for accelerated approvals is consideration of "previously agreed-upon surrogate or intermediate endpoints that are reasonably likely to

---

important safety and effectiveness information around the real-world use of products hard to collect and evaluate." *Statement from FDA Commissioner Scott Gottlieb, M.D., on Administration's request for new FDA funding to promote innovation and broaden patient access through competition*, FDA Statement, Feb. 13, 2018, https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm596554.htm.

[10] *Tiered Order of FDA Approval Based on Evidence and of Effectiveness*, Fairleigh Dickinson University Initiative for Patient-Centered Innovation, Report #10, Nov. 2016, http://www.josephgulfo.com/wp-content/uploads/2016/11/161120-Categories-of-approval-MI3.pdf.

[11] Such an approach "would involve a series of approval stages that would iteratively expand the market for a drug based on the evidence generated about the drug's risks and benefits. Adaptive approval contrasts with the binary approach to drug approval that predominates today, whereby a drug is approved or rejected based on a given data package at a single moment in time; the binary approach fails to adequately acknowledge and signal evolving knowledge about risks and benefits." *Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation,* Executive Office of the President, President's Council of Advisors on Science and Technology, Sep. 2017, p. 66, https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf.

[12] *Statement from FDA Commissioner Scott Gottlieb.*

predict long-term clinical benefit."[13] The guidance notes a particular example of how novel endpoints *could* be considered in establishing clinical "meaningfulness":

> For regenerative medicine therapies that are cellular or tissue constructs intended to replace a tissue or organ, CBER recognizes that assessment of the long-term effectiveness of the construct might not be feasible prior to marketing approval. For these products, CBER could consider short-term performance to be novel, clinically meaningful efficacy endpoints. For example, in some rare diseases, there will likely be a limited number of affected individuals eligible to enroll in clinical trials. Innovative trial designs, such as trials that compare several different investigational agents to each other and a common control, may be particularly useful in studies of regenerative medicine therapies to treat rare diseases.[14]

Unfortunately, by focusing solely on shorter-term endpoints in establishing clinical utility (which, as indicated *supra*, is itself a notoriously unclear standard of evaluation), the RMAT guidance completely disregards the potential for longer-term endpoints to serve as useful indicators of effectiveness in longevity studies aimed at the extension of healthy lifespans. Indeed, in healthy lifespan extension studies the endpoint should be the moment of death. This is the only robust way to measure if a therapy can extend life or not. In the case of human studies, such evaluations take too long.[15]

However, we also know how certain biomarkers are related to disease progression and amelioration, and in the future we may be able to find ways to connect biomarkers to the estimated lifespan (there are some attempts in medical mobile applications to do that already), in which case such drug trials could use certain biomarkers and a corresponding lifespan as an endpoint. The FDA should consider these potential future scenarios, given one of the values of RMAT designations will undoubtedly be healthy lifespan extension drugs, biologics, and gene therapies.

Similarly, in designing clinical trials for RMATs, we would suggest easing the burdens on including elderly populations in such trials. Given that many regenerative medicines have rejuvenation as a functional aim, it only makes sense to include older populations in trials. The FDA should consider examining the potential for greater proportional representation of elderly populations in RMAT clinical trial designs, with a specific eye towards accommodating their mobility limitations. Therefore, we would recommend the inclusion of these recognitions under section IV of the RMAT guidance ("Considerations in Clinical Trial Designs").

PART II: RECOMMENDATIONS

Overall, the RMAT guidance is an immensely positive step forward and wholly support its provisions. However, we believe there are a number of areas that could benefit from additional clarification, as well as broader changes to the FDA's approval process that would better accommodate drug, biologic, and gene

[13] *Regenerative Medicine Therapies Guidance*, p. 9.
[14] *Regenerative Medicine Therapies Guidance*, p. 11.
[15] To clarify, we are not suggesting that such longer-term endpoints be the default standard, but rather wish to point out that in clinical trials specifically designed to determine the effectiveness of "lifespan extension" treatments, such endpoints have significant value for researchers. Given the particular relevance of regenerative medicine therapies to the healthy lifespan extension field, it is notable that such a mention was left out of the RMAT guidance.

therapy approvals, especially in the context of anti-aging and healthy lifespace extension research and development.

1. Refrain from predicating a RMAT designation approval on a showing of "clinical utility" or "improved life outcomes."

The inclusion of gene therapies in the FDA's interpretation of section 506(g) is an excellent decision, and one we support. However, the broad nature of considering "the nature and meaningfulness of the outcomes" for RMAT designations is a cause for concern—as is the explicit mention of potentially predicating accelerated approval for RMATs on "surrogate or intermediate endpoints that are reasonably likely to predict long-term clinical benefit."[16] Under its organic statute,[17] the FDA is granted immense flexibility in determining standards for what constitutes a "safe" and "effective" drug, but the current approach focusing on "clinical utility" outcomes premised on an "average patient" standard in pre-market approvals fails to appropriately narrow the scope of analysis, resulting in a less-than permissive approach that obfuscates the standard(s) for establishing a drug's effectiveness.[18] As such, we would recommend the FDA refrain from tying ultimate approval of an RMAT-designated product to these standards.

2. Consider broader reforms to the agency's approval standards by convening a multistakeholder process.

Although the agency has taken important steps towards easing the approval pathway for regenerative therapies, the benefits of such treatments may be far more pronounced when coupled with non-RMAT designated drugs and biologics. In order to maximize the benefits from this guidance, the FDA needs to begin considering reforms to its "safe" and "effective" standards for drug approvals, preferably by convening a multistakeholder process or other collaborative discussion forum to consider potential improvements to the current system. Such an approach would provide the agency with a low-cost method of effectively and transparently engaging with members from the patient advocacy community, civil society, and other interested stakeholders.

---

[16] *Id*., 9.

[17] 21 U.S.C. § 314.125(b).

[18] Joseph V. Gulfo and Jason Briggeman, *Fostering Resilience in the Medical Marketplace: A Plan for Reform of Pharmaceutical Regulation*, Farleigh Dickinson University Initiative for Patient-Centered Innovation, (*forthcoming*), p. 8. ("Clinical utility is an elusive standard—it is tantamount to proving that there are, in some overall and ultimate sense, benefits to patient health from a product. Generally, even the best science cannot produce conclusive evidence on such a question, as attested by the many conflicting studies of the health effects of aspirin, for example. Aspirin is a safe and effective product, when used in accordance with its labeling—it generally delivers the promised effect to alleviate pain—but scientists continue even today to investigate whether taking aspirin is ultimately 'good' with regard to different health risks, for different types of patients, over the long run, and so forth. … If we do not have the answers on ultimate patient outcomes from taking aspirin … there is little chance of correctly identifying ultimate health outcomes from any given new drug.")

CONCLUSION

Overall, we consider the RMAT guidance to be a stellar improvement over other expedited programs, especially in its qualifying criteria. However, greater clarity is needed in order to capture the benefits of more advanced cell therapies that can help contribute to the healthy aging and well-being of American citizens. As FDA Commissioner Scott Gottlieb recently noted:

> The benefits of [gene therapy] science—and the products that become available—are likely to accelerate. How we define the modern framework for safely advancing these opportunities will determine whether we're able to fully realize the benefits that these new technologies can offer.[19]

We agree wholeheartedly. Developing a regulatory framework that accommodates safety and innovation will be a key determinant of how quickly the benefits of regenerative medicine, gene therapy, and anti-aging research revolutionize the lives of Americans. This guidance is an important and promising step in the right direction. With the right modifications, it can help usher in a new age of healthcare improvement for individuals from all walks of life.

We would like to thank the FDA for the opportunity to comment on this issue and look forward to continued engagement on this and other topics.

[19] *Remarks by Dr. Scott Gottlieb on FDA's Role in Advancing a Modern Framework for Gene Therapy*, Dec. 19, 2017, https://www.fda.gov/NewsEvents/Speeches/ucm589740.htm.