American Society of Gene + Cell Therapy

March 6, 2025

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Comments for Docket No. FDA-2024-D-2033
Expedited Programs for Serious Conditions—Accelerated Approval of Drugs and Biologics; Draft Guidance for Industry

Dear Sir/Madam,

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to provide comments on the Draft Guidance for Industry: Expedited Programs for Serious Conditions—Accelerated Approval of Drugs and Biologics. ASGCT is a nonprofit professional membership organization that represents more than 6,400 scientists, physicians, clinicians, and other professionals working in cell and gene therapy (CGT) across academic, hospital, independent research, and biotechnology settings.

ASGCT commends FDA's ongoing commitment to refining the Accelerated Approval (AA) pathway and ensuring that patients with serious conditions and high unmet medical needs have timely access to transformative therapies. Given the unique attributes of CGTs, ASGCT urges FDA to ensure that AA remains a predictable, flexible, and fit-for-purpose regulatory pathway for these therapies.

General Comments

ASGCT strongly supports the AA pathway as a viable option for CGTs and emphasizes the importance of ensuring that it remains adaptable to the realities of CGT development. Given the mechanisms of action, durability of effect, and reliance on surrogate endpoints that characterize CGTs differ from the products traditionally utilizing the pathway, it is critical that FDA explicitly recognize the suitability of AA for CGTs.

To enhance the AA pathway for CGTs, ASGCT recommends that FDA leverage platform-based regulatory efficiencies to support AA determinations—particularly in the validation of surrogate endpoints and cross-program data utilization. While the draft guidance does not explicitly address platform technologies, CGTs increasingly rely on standardized development and manufacturing approaches that could improve regulatory consistency. Given that FDA has established the Agency to consider applying similar efficiencies when evaluating the evidentiary requirements for AA.

III. Overview of Accelerated Approval (Lines 87-170)

The draft guidance highlights that AA is primarily intended for serious conditions where clinical endpoints require long-term follow-up or are difficult to measure. While this framework has been appropriate in the past, CGTs often provide rapid clinical benefit with strong biological plausibility, making them well-suited for AA. ASGCT urges FDA to explicitly acknowledge in the guidance that CGTs should not be excluded from AA simply because they do not fit past precedent (lines 100-110).

ASGCT appreciates FDA's efforts to enhance transparency in regulatory decision-making and recognizes that recent initiatives, including updated guidance and public discussions, demonstrate a commitment to improving clarity around Accelerated Approval pathways. However, despite these efforts, many CGT sponsors report challenges in obtaining early, actionable feedback on the feasibility of AA, particularly regarding surrogate endpoints, confirmatory trial expectations, and overall program alignment with AA requirements. While the draft guidance encourages early engagement (lines 154-162), it does not establish clear criteria or structured timelines for these discussions. Many CGT sponsors find that initial interactions yield limited actionable feedback, with key decisions deferred to later-stage reviews. ASGCT requests FDA to provide publicly available criteria on how sponsors can align their development plans with the AA framework from the outset. Enhancing early-stage transparency will improve predictability and efficiency, ultimately benefiting both patients and the advancement of CGT therapies.

IV. Granting of Accelerated Approval (Lines 173-487)

A. Accelerated Approval Endpoints

Scientific advancements in CGT development justify an expanded and more flexible approach to AA, particularly as many CGTs demonstrate rapid and significant clinical benefit. The traditional framework for AA has primarily been applied to conditions with long disease courses or infrequent clinical events, but this should not be a limiting factor for CGTs. ASGCT requests that FDA clarify that CGTs should not be held to additional evidentiary standards beyond those applied to other modalities under AA, particularly regarding reliance on surrogate endpoints to support approval.

1. Surrogate Endpoints

The draft guidance outlines FDA's approach to surrogate endpoints (lines 193-226), but ASGCT requests explicit clarification on how existing regulatory flexibility applies specifically to CGTs. Given that many CGTs rely on novel biomarkers or mechanisms of action that may lack prior validation in other therapeutic areas, FDA should ensure that these surrogate endpoints are not constrained by precedent from other therapeutic modalities. Additionally, ASGCT requests FDA to clarify that the time lag between a surrogate and clinical endpoint should not preclude a CGT's eligibility for AA, provided that the surrogate is reasonably likely to predict clinical benefit. Since many CGT surrogate endpoints may not have long-term validation at the time of approval, FDA should provide guidance on how sponsors can demonstrate their reliability for regulatory decision-making.

B. Evidentiary Criteria for Accelerated Approval

Footnote 36 of the draft guidance acknowledges that clinical data may not always be needed for AA when strong evidence supports a surrogate endpoint, particularly for gene therapies targeting genetic disorders. ASGCT strongly supports this policy direction and urges FDA to provide further clarification on how this principle applies specifically to CGTs, including how sponsors can justify reliance on compelling nonclinical data for surrogate endpoints in AA decisions.

C. Confirmatory Trials

2. Other Aspects of Confirmatory Trial Design

FDA's recognition of alternative study designs for confirmatory trials, such as adaptive designs, enrichment strategies, and decentralized trials (lines 447-449), is a critical step forward. Given the challenges specific to CGTs, ASGCT encourages FDA to clarify how such trial design methodologies may be applied to CGT confirmatory trials. Sponsors would benefit from further guidance on the feasibility, regulatory acceptability, and implementation of these trial designs for CGTs under AA.

In addition to innovative trial designs, alternative confirmatory evidence sources—such as real-world evidence (RWE) and natural history studies—may be necessary for CGTs when traditional confirmatory trials are infeasible. FDA recognizes that confirmatory trial enrollment may become challenging post-AA due to commercial availability (lines 417-421) and that limited exceptions exist to the general requirement that trials be underway before AA approval (lines 396-399). ASGCT requests that FDA explicitly outline the criteria under which alternative data sources may be used to fulfill post-approval requirements.

Furthermore, ASGCT requests FDA to consider CGT-specific feasibility challenges when making AA determinations, particularly for conditions where no alternative treatments exist. If a CGT represents the only potential therapy for a serious condition, the inability to conduct a confirmatory trial should not result in undue delays or withdrawal of AA, provided that a totality-of-evidence approach—including RWE and natural history data—supports approval. Given FDA's acknowledgment of alternative confirmatory trial designs (lines 447-459), ASGCT requests that FDA clarify whether RWE and natural history data may be integrated within these approaches when traditional confirmatory trials are impractical.

V. Withdrawal of Accelerated Approval (Lines 490-825)

ASGCT strongly urges FDA to ensure that the withdrawal of Accelerated Approval (AA) remains a fair, case-specific, and evidence-driven process that fully accounts for the unique challenges faced by cell and gene therapy (CGT) developers. Given the complexities of CGT development, particularly in rare diseases where conducting traditional confirmatory trials may be impractical, FDA should explicitly recognize the scientific and ethical constraints that may limit trial feasibility. ASGCT further emphasizes the critical role of alternative data sources, such as real-world evidence (RWE) and natural history data, in verifying clinical benefit and fulfilling post-approval commitments. Without a clear and predictable approach to incorporating these data

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sources, the potential for unnecessary withdrawals may discourage innovation and delay patient access to transformative therapies.

ASGCT appreciates FDA's commitment to refining the Accelerated Approval framework to ensure that patients with serious conditions have timely access to transformative therapies. The continued advancement of CGTs presents an opportunity to strengthen this pathway by maintaining predictability, flexibility, and alignment with the realities of CGT development.

The Society would welcome the opportunity to work with the Agency on this guidance. Thank you for the consideration of these comments. If you have any questions, please do not hesitate to contact Margarita Valdez Martínez, Chief Advocacy Officer, at mvaldez@asgct.org.

Sincerely,

David Barrett, J.D.
Chief Executive Officer