Chemistry, Manufacturing, and Controls Flexibilities for Developing Human Cellular and Gene Therapy Products for a Biologics License Application

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Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). Submit one set of either electronic or written comments on this guidance at anytime. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with docket number FDA-2026-D-4692.

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For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes how FDA applies flexibility to the chemistry, manufacturing, and controls (CMC) requirements for human cellular and gene therapy (CGT)[1] products being developed for biologics license applications (BLAs) under Title 21 of the Code of Federal Regulations (CFR) Part 601 (21 CFR 601).[2] Consistent with the statutory and regulatory requirements for biological products, FDA uses a flexible approach to ensuring applicable CMC requirements are met for CGT products. FDA's flexible approach serves to help expedite development, review, and patient access to safe and effective CGT products to treat serious or life-threatening conditions that represent significant unmet medical needs.

FDA has issued several guidances that provide CMC recommendations to sponsors developing CGT products.[3] Sponsors developing CGT products should consider the CMC recommendations in this guidance in addition to those guidances for industry, as applicable. This guidance provides information on when CMC flexibilities may be appropriate for the development of CGT products and does not comprehensively address the CMC information and data necessary to support CGT product licensure under section 351 of the Public Health Service Act (42 U.S.C. 262).

[1] In this guidance, the term *cellular and gene therapy* (CGT) product refers collectively to cellular therapy and gene therapy products. These products meet the definition of "biological product" in section 351(i) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(i)).

[2] While this guidance specifically focuses on CMC flexibilities for a CGT product biologics license application, FDA may consider extending some of the flexibilities to manufacturing supplements submitted post-licensure.

[3] For guidances related to chemistry, manufacturing, and controls (CMC) for sponsors developing cellular and gene therapy products, check the FDA Cellular and Gene Therapy web page at https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances.

This guidance applies only to CGT products regulated by the Center for Biologics Evaluation and Research (CBER). This guidance does not apply to animal CGT products regulated by the Center for Veterinary Medicine or to other biological products.

Sponsors should discuss their approach for CMC development with the relevant review division prior to implementation.[4]

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Many CGT products are innovative biological products that show promise in providing treatments for a wide range of serious or life-threatening conditions in patients with significant unmet medical need such as cancers, genetic disorders, and chronic illnesses. As such, CGT products may be eligible for expedited programs[5] (e.g., fast track designation, breakthrough therapy designation, regenerative medicine advanced therapy designation,[6] priority review designation, accelerated approval[7], platform technology designation[8]) to facilitate the development and review of these products and to help ensure their readiness for licensure and availability to patients. However, FDA also recognizes that challenges still exist for sponsors developing safe, effective, and high-quality CGT products when using traditional product development strategies. Some of these challenges include product complexity, patient-specific manufacturing, sophisticated processes and advanced technologies, limited patient population

[4] For information on formal meetings between FDA and sponsors or applicants relating to the development and review of a CGT product, see the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023), available at https://www.fda.gov/media/172311/download. When final, this guidance will represent FDA's current thinking on this topic.

[5] For additional information regarding FDA's policies and procedures for programs intended to facilitate and expedite development and review of drugs, see the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014)(*"Expedited Programs 2014 Guidance"*), available at https://www.fda.gov/media/86377/download.

[6] For additional information regarding expedited programs for regenerative medicine therapies for serious conditions, see the draft guidance for industry *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions* (September 2025), available at https://www.fda.gov/media/188874/download. When final, this guidance will represent FDA's current thinking on this topic.

[7] For additional information regarding FDA's policies and procedures for accelerated approval, see the draft guidance for industry *Accelerated Approval – Expedited Program for Serious Conditions* (December 2024), available at https://www.fda.gov/media/184120/download. When final, this guidance will represent FDA's current thinking on this topic.

[8] For additional information regarding FDA's Platform Technology Designation Program, see the draft guidance for industry *Platform Technology Designation Program for Drug Development* (May 2024), available at https://www.fda.gov/media/178938/download. When final, this guidance will represent FDA's current thinking on this topic.

size, fewer manufacturing runs, product characterization and analytical testing, and short product shelf-life necessitating a narrow window of time from production to administration.

FDA has gained considerable experience with CGT products and has identified and implemented flexibilities within FDA's regulations[9] that accommodate the unique characteristics of these innovative therapies, while maintaining rigorous quality standards. FDA is issuing this guidance to help clarify FDA's use of CMC flexibilities, to inform sponsors, and to facilitate the development of safe, effective, and high-quality CGT products in preparation for a BLA submission.

III. FLEXIBLE APPROACHES FOR CMC DEVELOPMENT

FDA encourages sponsors of CGT products to consider the principles in this section when pursuing CMC development of products for potential licensure under a BLA. To meet the statutory requirement for licensure, sponsors must demonstrate that their CGT product meets the applicable requirements to ensure that it is safe, pure, and potent.[10] However, FDA recognizes that the unique nature of a CGT product and its development program may require a non-traditional approach to satisfy these requirements.

FDA considers the following CMC approaches to be appropriate for sponsors to support CGT product development.[11] The extent of the CMC data necessary and the suitability of a CMC flexibility may vary depending on the stage of development, the manufacturing process, and the product.[12] For sponsors considering pursuing a BLA, FDA may seek additional data and information on a case-by-case basis to ensure that the requirements for licensure can be met. Sponsors are strongly encouraged to engage with FDA early and throughout CGT product development.

A. Flexibilities During Clinical Development

Sponsors of CGT products should consider the following approaches for CGT product development during clinical investigations:

- **Implementing phase-appropriate current good manufacturing practice (CGMP).** In general, the production of an investigational drug[13] for use in a Phase 1 clinical trial is exempt from compliance with the regulations in 21 CFR Part 211.[14] This exemption generally applies to studies that are designed to establish basic safety, rather than the efficacy of the drug product.

[9] See 21 CFR Part 312 – Investigational New Drug Application, 21 CFR 610 – General Biological Product Standards, and 21 CFR Part 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals.
[10] See section 351(a)(2)(C) of the FD&C Act and 21 CFR 601.2(d).
[11] The flexible CMC development approaches provided in this section are not an exhaustive list of those that FDA may consider appropriate to support CGT product development.
[12] See the *Expedited Programs 2014 Guidance.*
[13] In this guidance, the term *drug* refers to human drug products and biological products.
[14] 21 CFR 210.2(c).

For example, FDA encourages the use of a phase-appropriate process control strategy and does not expect process validation for investigational products. However, we recommend that sponsors perform studies to characterize their manufacturing process throughout clinical development. This approach helps sponsors gain knowledge to implement an effective process control strategy, which will facilitate consistent performance of the commercial manufacturing process.

- **Developing release acceptance criteria that are consistent with the phase of the investigational studies.** FDA may accept relatively permissive criteria for the release of early-stage investigational CGT products if such criteria do not compromise safety. Sponsors should refine the product specification as additional experience is gained through clinical and product characterization studies. Prior to initiating Phase 2 or 3 clinical investigations on the CGT product, release tests must have predefined acceptance criteria.[15,16] FDA recommends sponsors to discuss with FDA the timeline for finalizing release expectations in the investigational process, and when to establish numerical release acceptance criteria in connection with clinical studies intended to provide substantial evidence of effectiveness to maintain product quality and to ensure that a consistently manufactured product is administered during all phases of clinical investigation.[17]

- **Using a risk-based approach to comparability studies.** The manufacturing and control of CGT products may present challenges due to limitations such as limited process knowledge, limited product quantities, and complex manufacturing processes, which pose a higher risk to product quality than conventional biological products. As such, FDA recommends performing a risk assessment for all manufacturing changes to determine the impact on product quality. For an investigational product, in circumstances where FDA considers a manufacturing change to be minor and with a low risk to product quality, FDA may accept limited comparability data if the CGT product quality attributes are met and the changes are submitted prior to administering the post-change product.[18]

- **Leveraging prior knowledge and experience to facilitate CMC development.** The amount of knowledge available to support multiple aspects of CGT product development

[15] For recommendations regarding CGT product release testing, see the draft guidance for industry *Frequently Asked Questions — Developing Potential Cellular and Gene Therapy Products* (November 2024), available at https://www.fda.gov/media/183631/download. When final, this guidance will represent FDA's current thinking on this topic.

[16] 21 CFR 211.165(d).

[17] For recommendations for phase appropriate acceptance criteria, see the guidance to industry *Chemistry, Manufacturing, and Control Information for Human Gene Therapy Investigational New Drug Applications* (January 2020), available at https://www.fda.gov/media/113760/download, and the draft guidance for industry *Potency Assurance for Cellular and Gene Therapy Products* (December 2023), available at https://www.fda.gov/media/175132/download. When final, this guidance will represent FDA's current thinking on this topic.

[18] For recommendations regarding product comparability and management of manufacturing changes for investigational and licensed CGT products, see the draft guidance for industry *Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products* (July 2023)("*Manufacturing Changes and Comparability for CGT Products Draft Guidance"*), available at https://www.fda.gov/media/170198/download. When final, this guidance will represent FDA's current thinking on this topic.

increases as more CGT products are developed. The Agency may consider proposals submitted to FDA with appropriate justification to leverage CMC knowledge across similar CGT products and, if applicable, critical components[19], such as analytical methods, method validation, lot release specifications[20], stability data, comparability data, and process development and process validation data.

For example, FDA may consider a sponsor's use of a platform analytical procedure to reduce the qualification and validation burden during clinical development.[21] A platform analytical method, as defined in the March 2024 guidance for industry entitled *Q2(R2) Validation of Analytical Procedures*, is a method suitable to test quality attributes of different products without significant change to its operational conditions, system suitability, and reporting structure.[22] The appropriateness of applying a platform qualification and validation may depend on the similarity between the test articles. FDA may request a product-specific verification to support the platform qualification and validation if differences are determined to potentially impact method performance.

- **Utilizing voluntary consensus standards for product development and assessment.** FDA has established the Standards Recognition Program for Regenerative Medicine Therapies to identify scientifically sound standards that do not conflict with FDA regulations or policy. Using standards can increase regulatory predictability and reduce the amount of documentation needed in a submission. A list of recognized standards and the terms of recognition are available on CBER's website.[23]

B. Process Validation Flexibilities

Sponsors of CGT products should consider the following CMC approaches for process validation:

- **Developing a process performance qualification (PPQ) strategy that scientifically**

[19] See the guidance for industry *Chemistry, Manufacturing, and Control Information for Human Gene Therapy Investigational New Drug Applications* (January 2020), available at https://www.fda.gov/media/113760/download.

[20] In this guidance, a *specification* is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product, or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. See also the guidance for industry *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999)(*"Q6B Specifications Guidance"*), available at https://www.fda.gov/media/71510/download.

[21] Assay qualification involves determining the assay's performance characteristics (e.g., accuracy, precision, specificity, and sensitivity). Assay validation should confirm the performance characteristics of the fully-optimized assay by comparing assay performance during the validation study to appropriate pre-specified acceptance criteria for accuracy, precision, specificity, and other relevant performance characteristics. See also 21 CFR 211.165(e) and 211.194(a)(2).

[22] This type of method would apply to molecules that are sufficiently alike with respect to the attributes that the platform method is intended to measure.

[23] See the FDA website on Standards Development for Regenerative Medicine Therapies at https://www.fda.gov/vaccines-blood-biologics/standards-development-regenerative-medicine-therapies, and see also the guidance for industry *Voluntary Consensus Standards Recognition Program for Regenerative Medicine Therapies* (October 2023), available at https://www.fda.gov/media/159237/download.

supports the number of PPQ batches submitted to the BLA. PPQ is a critical step in validating the performance of a commercial manufacturing process and sponsors are expected to include PPQ data in their BLA submission. FDA acknowledges that sponsors of CGT products may experience PPQ production limitations. FDA uses a flexible, scientific, and risk-based approach to help expedite CGT product development. FDA does not specify a minimum number of PPQ batches in the biologics licensing requirements[24] or CGMP regulations.[25] As such, FDA recommends that sponsors justify the appropriate number of PPQ batches based on context-specific factors, such as the overall level of understanding of the product and process, complexity of the manufacturing process, and levels of control in place.[26] Sponsors should document the studies performed during the design of the manufacturing process and the control strategy, and any relevant manufacturing experience from other sufficiently similar products and processes, in the BLA.

- **Releasing PPQ batches for clinical or commercial distribution.** When PPQ production limitations exist, FDA may consider a flexible approach for the completion of PPQ studies post-licensure. A PPQ protocol can be designed to release a PPQ batch for distribution before complete execution of the protocol steps and activities.[27] FDA may consider allowing concurrent release of PPQ batches for commercial use after BLA approval if the batches meet the commercial release specification and are within the commercial shelf life. In addition, any such batches that meet the phase-appropriate release criteria established under an IND may be used for a clinical investigation.

C. Commercial Specification Flexibilities

Sponsors of a CGT product should consider the following CMC approaches for establishing a commercial specification when pursuing submission of a BLA:

- **Developing product release strategies consistent with the nature of the product, the manufacturing process, and the number of lots available at the time of BLA submission.** FDA recognizes that there may be situations where only a small number of CGT product lots are available for analysis at the time of BLA submission, often due to the inherently small patient population. In these circumstances, when appropriate and while still ensuring product quality, FDA may consider flexible approaches for establishing product release specifications when it is not feasible to define statistically

[24] 21 CFR 601.20.

[25] See, e.g., 21 CFR 211.100 and 21 CFR 211.110.

[26] FDA encourages sponsors who are preparing to validate the manufacturing process of a CGT product to contact FDA to discuss their validation strategy before implementation. For more information regarding the general principles and approaches that FDA considers appropriate elements of process validation for the manufacture of biological products, see the guidance for industry *Process Validation: General Principles and Practices* (January 2011)(*"Process Validation Guidance"*), available at https://www.fda.gov/media/71021/download. See also the guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016), available at https://www.fda.gov/files/drugs/published/Q7-Good-Manufacturing-Practice-Guidance-for-Active-Pharmaceutical-Ingredients-Guidance-for-Industry.pdf.

[27] For more information and recommendations regarding concurrent release for process performance qualification (PPQ) batches, see Section V of the *Process Validation Guidance*.

robust commercial acceptance criteria at the time of initial approval.

- **Developing a scientifically supported analytical method validation strategy.** For validation of analytical methods used for release testing, FDA does not specify a minimum number of lots to be used in the validation study. FDA may consider analytical method validations using a single representative lot, when appropriate. FDA may consider such a strategy if it is scientifically supported and the relevant data submitted to FDA demonstrates the method to be sufficiently robust and suitable for its intended use.[28,29]

- **Leveraging post-approval manufacturing experience to ensure robust commercial acceptance criteria.** Consistent with FDA's policies regarding change management of analytical procedures, sponsors can consider discussing with FDA whether it may be appropriate to commit to post-approval reevaluation of product release acceptance criteria in certain circumstances (e.g., when only a small number of CGT product lots are available at the time of BLA submission, and when there are data generated from multiple commercial batches produced after the approval if the manufacture of the CGT product demonstrates consistent product quality).[30] This approach supports the development of more statistically sound acceptance criteria over time. Changes to specifications after approval must be submitted in a prior approval supplement.[31]

D. Additional Flexibilities

Sponsors of a CGT product should consider the following CMC approaches when pursuing submission of a BLA:

- **Leveraging stability data to support commercial expiration dating.** FDA generally recommends that sponsors submit real-time stability data from three lots manufactured at the commercial facility, with a minimum of six months of data. However, FDA may consider an alternative number of stability lots based on a risk evaluation. In addition, sponsors may use stability data from clinical lots if the lots are representative (e.g., manufactured with the commercial process, using the commercial formulation, and in the commercial container closure). In this case, sponsors should provide sufficient data from the clinical lots to support the product's shelf life. In addition, sponsors may submit stability data from similar products to be considered for use as supporting data for setting the initial stability period when a concurrent testing strategy is included in the stability testing protocol. For more information related to these recommendations, see the June

[28] For more information, see the guidance for industry *Q2(R2) Validation of Analytical Procedures* (March 2024), available at https://www.fda.gov/media/161201/download, and the guidance for industry *Q14 Analytical Procedure Development* (March 2024), available at https://www.fda.gov/media/161202/download.

[29] 21 CFR 211.194(a)(2).

[30] Under 21 CFR 211.180(e), sponsors must maintain written records to evaluate the quality standards of each drug product, at least annually, to determine the need for changes in the drug products specifications of manufacturing or control procedures. Further refinement of acceptance criteria may be warranted if supported by additional manufacturing experience and data obtained after approval. For more information, see the *Q6B Specifications Guidance*.

[31] 21 CFR 601.12. See also the *Manufacturing Changes and Comparability for CGT Products Draft Guidance*.

2025 draft guidance for industry entitled *Q1 Stability Testing of Drug Substances and Drug Products*[32]; when final, this guidance will represent FDA's current thinking on this topic.

- **Seeking an exception from FDA for retaining reserve samples.** Under most circumstances, a manufacturer of a biologic must retain sufficient material from each lot of product manufactured for six months after the expiration date.[33] However, FDA recognizes that meeting this requirement may not be feasible when CGT product lots are very small or manufactured for individual patients. In such circumstances, FDA may consider exceptions, as appropriate and consistent with 21 CFR 600.13.

- **Using alternative analytical methods in lieu of compendial methods to reduce sample volume or testing time for release of intermediates, drug substance, and drug product lots.** Compendial methods have historically been used for some lot release tests of biological products. However, alternative analytical methods with rapid detection capabilities, which often use proprietary and/or novel technologies, may provide more efficient microbiological control and assurance to allow for expedited release of CGT products. As such, FDA may consider the use of an alternative analytical method if sufficient information and data is available to demonstrate that the alternative analytical method meets the appropriate standards of accuracy, sensitivity, specificity, and reproducibility[34] and is validated to be suitable for its intended purpose.[35] For sterility testing, 21 CFR 610.12 allows for the use of different types of test methods, as they become available, to accommodate scientific and technological advancements, provided that they are appropriately validated and verified as provided in the regulation.[36]

[32] Available at https://www.fda.gov/media/187161/download.
[33] 21 CFR 600.13.
[34] For discussion about the use of noncompendial analytical procedures, see also the guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics* (July 2015)(*"Analytical Procedures and Methods Validation Guidance"*), available at https://www.fda.gov/files/drugs/published/Analytical-Procedures-and-Methods-Validation-for-Drugs-and-Biologics.pdf. As a holder of the BLA, you must: (1) submit the data used to establish that the analytical procedures used in testing meet proper standards of accuracy and reliability, and (2) notify the FDA about each change in each condition established in an approved application beyond the variations already provided for in the application, including changes to analytical procedures and other established controls. See 21 CFR 601.2(a), 601.2(c), and 601.12(a); see also 21 CFR 211.165(e). In addition, for a product licensed under a BLA, if the change is to a procedure prescribed in FDA regulations that change must be approved by FDA pursuant to 21 CFR 610.9(b).
[35] 21 CFR 211.194(a)(2). See also the *Analytical Procedures and Methods Validation Guidance*.
[36] *See* Amendments to Sterility Test Requirements for Biological Products, 77 Fed. Reg. 26162, at 26174 (May 3, 2012).