Postapproval Methods to Capture Safety and Efficacy Data for Cell and Gene Therapy Products

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Draft Guidance for Industry

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Guidance for Industry[1]

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I. INTRODUCTION

The purpose of this guidance is to discuss methods and approaches for capturing postapproval safety and efficacy data for cell and gene therapy (CGT) products. Given the potential for long-lasting effects of CGT products, and the generally limited number of participants treated in clinical trials conducted to support approval of CGT products, postapproval monitoring is important for gathering data on product safety and effectiveness over time. This guidance does not address data collected for the purpose of expanding clinical indications.

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II. BACKGROUND

The FDA's Center for Biologics Evaluation and Research (CBER) Office of Therapeutic Products (OTP) hosted a virtual public listening meeting on April 27, 2023 [Ref. 1] and opened a docket (FDA-2023-N-0398) to solicit input on methods and approaches for capturing postapproval safety and efficacy data for CGT products. Stakeholders provided perspectives on multiple topics, including methods, approaches, logistics, and privacy concerns. The event was held to meet an FDA commitment that is part of the seventh authorization of the Prescription Drug User Fee Act (PDUFA), *PDUFA VII: Fiscal Years 2023 – 2027 FDA*.[2]

[1] This guidance has been prepared by the Office of Therapeutic Products and the Office of Biostatistics and Pharmacovigilance in the Center for Biologics Evaluation and Research at the Food and Drug Administration.
[2] See www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027.

The collection of postapproval study data for CGT products is important because during premarketing clinical development, the number of patients receiving CGT products is typically limited. Additional postapproval efficacy and safety data increases understanding of the long-term safety and effectiveness of CGT products, can help guide safe clinical use of CGT products, and help inform subsequent regulatory decision-making. FDA has previously recommended long-term follow-up (LTFU) observation studies for some CGT products [Ref. 2] noting that long-term observations can be an important tool to monitor long term safety. Postapproval efficacy considerations include treatment durability, while safety considerations include monitoring for long-term effects, unknown side effects, and mortality due to the underlying disease or its treatment. In certain populations, particularly pediatric patients, the lifecycle of CGT products may be a factor in accurately capturing postapproval data. For example, additional considerations, especially those intended for pediatric patients, include the potential for lifetime monitoring, the transition from pediatric to adult care, and the need for consenting the adult patient. Because the period of LFTU for CGTs can be long (e.g., 15 years), pediatric patients will often be followed into adulthood. Therefore, obtaining informed consent must be addressed in accordance with 21 CFR 50 Subpart D and B, respectively, to allow participation for the duration of data collection, research interventions, and/or procedures. Additionally, sponsors should provide a plan for follow-up, including funding, in the event the sponsor ceases to operate the study before completion of LTFU observations [Ref. 2].[3]

Postapproval methods that capture safety and efficacy data can help balance premarket and postmarket data, including for CGT products approved under accelerated pathways. The postapproval collection of real-world evidence (RWE) can add additional data to studies with small sample sizes, lack of comparators, and low completion rates. The postapproval methods discussed here may facilitate identification of subgroup differences and adverse events.

III. METHODS AND APPROACHES FOR CAPTURING POSTAPPROVAL DATA

A. Use of Real-World Data and Real-World Evidence

FDA's real-world evidence (RWE) program [Ref. 3] addresses the use of real-world data (RWD) sources to derive RWE. For the purposes of this guidance, CBER employs the definitions of RWD and RWE described in previous FDA guidances [Refs. 4, 5]. Sponsors are encouraged to consult CBER early when selecting RWD sources to support RWE-containing submissions for CGT products. CBER also accepts proposals under the FDA's Advancing Real-World Evidence Program [Ref. 6], which seeks to improve the quality and acceptability of RWE-based approaches in support of submissions with RWD.

When using RWE, sponsors should safeguard patient data, by establishing robust data governance structures that ensure the integrity and confidentiality of RWD. This

[3] A list of relevant guidances can be found at https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances.

includes implementing measures such as data quality control, anonymization, and cybersecurity controls; maintaining transparent and auditable processes that comply with relevant laws and regulations (e.g., the Health Insurance Portability and Accountability Act); and reporting demographic and clinical data in a de-identified manner to protect patient privacy. Digital health technologies may be used to support collection of postapproval data. Software programs used to produce and process postapproval data are subject to 21 CFR part 11 [Ref. 7]. Sponsors should consult relevant FDA guidance documents [Refs. 4, 5, 8] to inform and update their data governance practices.

B. Use of Electronic Health Records, Medical Claims, and Vital Statistics Data

Administrative medical claims, vital statistics, and electronic health records (EHRs) are not typically designed to collect data for evaluation of safety or effectiveness of medical products. Therefore, sponsors should consider several important constraints when assessing fitness for use of these RWD sources for approved CGTs, especially in rare disease settings where patient numbers are limited, diagnosis is delayed, and clinical presentations are heterogeneous. These constraints include:

- Lack of data in the RWD source on pertinent patient and rare disease variables.
- Inadequate or lagging medical coding terminology, resulting in a lack of structured data and challenges ensuring data reliability and validity.
- Fragmented data due to medical insurance or healthcare provider switching that restricts long-term studies.
- Limitations in analyzing rare outcomes due to small study sizes and inadequate statistical power, even in data derived from large EHR and claims databases.

Nonetheless, with adequate strategies for study sample selection, data validation, and ascertainment of exposures, outcomes, and covariates [Ref. 4], sponsors can consider using these RWD sources for one or more of the following purposes:

- Utilization studies to assess CGT exposure and characteristics of patients and prescribers.
- Assessment of rates of clinical outcomes in CGT-treated patients.
- Determination of background rates of malignancies or cardiovascular complications, or other outcomes of interest, occurring in the absence of CGT exposure.
- Observation of CGT outcomes in multiple patient populations.
- Training of Artificial Intelligence (AI) and Natural Language Processing (NLP) machine-learning models to develop computable phenotypes for CGT safety or effectiveness outcomes.

When proposing RWD for analysis of approved CGTs, sponsors should consider the following methodological approaches to data source selection, verification, and assurance

of data quality, and share information with FDA about their choices for a proposed evaluation [Ref. 9]:

- A feasibility assessment can be conducted to ensure that selected data are representative of the target disease population. In rare diseases, diagnosis may be delayed and/or recorded through variable codes in claims databases, so sponsors should consider developing algorithms with varied scenarios for comprehensive study sample construction and relevant data capture. If computable phenotypes are used, their definitions, algorithms, and data elements should be included in the study protocol.
- RWD collection coincides with clinical care provided over time, and there may be additional time between data collection and availability of data for analysis. Sponsors should consider changes in clinical practice and guidelines (e.g., criteria for disease diagnosis, cancer staging, and the introduction of new treatments), so that a proposed RWD analysis reflects the current clinical environment.
- Assurance of uninterrupted data selected for the study is an important aspect of data quality, particularly, when long-term outcome assessment is needed for CGT products. Sponsors should consider follow-up using RWD from the index date of CGT use until either the end of the pre-planned follow-up time or the last time a CGT patient is identified within the RWD source. The study end date should be set on a day when data checks and audits can assure that the underlying data are of sufficient quality for use in postapproval studies.
- When CGT data in rare disease populations are available primarily as unstructured EHR or patient-generated data, instead of standardized values or codes in structured database fields, sponsors should develop and operationalize methods to extract usable information. Data analysis proposals should outline the technology, algorithmic assumptions, and validation procedures, including any applicable NLP or AI-training methods and sources used.
- Data completeness and the ability to reliably pull data from varied RWD sources are essential for the validity of postapproval evaluation of CGTs. When working with fragmented data, sponsors should outline the study protocol methods used for missing data, including data not collected in a selected RWD source and data intended for collection but missing. To reduce the study uncertainty and minimize data extraction gaps, techniques such as data linking, or use of proxies may be employed [Refs. 4, 9].

C. Use of Registries

For the purposes of this guidance, a registry is an organized system that collects clinical and other data in a standardized format for a population defined by a particular disease, condition, or drug exposure. The Coordinated Registry Network (CRN) is a type of registry established by clinical professional societies. CRNs are highly curated RWE resources that may be able to overcome common RWD limitations. By leveraging professional networks, CRNs may provide granular data that may inform regulatory

decisions among other uses. Sponsors can partner with clinical society registries to access existing CRN data and develop new resources as needed [Ref. 10].

We recommend keeping the following considerations in mind regarding registries:

- Registries, in addition to patient-level clinical and laboratory data, can include repositories of genetic data, histopathology specimens, diagnostic medical device imaging data, and patient-generated data with input from in-home use of digital health technologies.
- Registries offer advantages over other RWD sources because they allow collection of longitudinal, curated data with predefined data elements in a defined population of patients exposed to an approved product, particularly the course of the disease and its complications.
- Registries have the potential to overcome the limitations of other datasets such as medical claims datasets or EHR datasets because they can also collect information on patient-reported outcomes, treatment adherence, and measures of disease severity.
- Registries may not be representative of the target population of interest due to challenges related to patient recruitment and retention. For example, patients with more severe disease may be more likely to be enrolled in a registry compared to patients with milder disease, or vice versa. FDA therefore encourages sponsors to be mindful of the requirements for registry participation and encourage all patients to participate in the registry, if feasible.
- In the postapproval setting, where patient registries can be used to collect both safety [Ref. 5] and efficacy data for CGTs, registry data may be particularly relevant in the following situations:
  - Assessment of long-term durability of response after exposure to CGTs, including evaluation of biomarkers (e.g., changes in laboratory or imaging tests) indicative of changes in one or more clinically meaningful outcomes.
  - Growth and developmental milestone data for pediatric recipients of CGT products.
  - Surveillance for malignancies after receiving CGT products.
  - Fertility and pregnancy outcomes-related data in recipients of CGT products who are exposed to conditioning treatments.

D. Decentralized Data Collection

A decentralized clinical trial (DCT) refers to a clinical trial where some or all of the trial-related activities are conducted at locations other than the traditional clinical site [Ref. 11]. Use of a decentralized model of data collection, similar to those used in DCTs, can play a critical role in capturing and assessing postapproval efficacy and safety data for CGT products, because it provides a new paradigm of data collection that is more accessible and less burdensome. Benefits of using a decentralized model for data collection include increased enrollment and data on study populations, which improves

the generalizability of study results. The reduction or elimination of travel time to the clinical study sites can optimize efficiency and improve patient convenience and retention.

The following strategies should be considered when using a decentralized model for the collection of postapproval data for CGT products [Ref. 1]:

- Identify data elements that need to be collected for safety or efficacy in the postmarketing setting [Ref. 2].
- Ensure robust data collection methods to substantiate accuracy and reliability of the results.
- Incorporate flexibility in the study design to tailor to the therapeutic area, the type of treatment, and the patient journey.
- Use of local healthcare professionals (HCPs) and facilities and telemedicine visits:
  - Assessments performed by local HCPs may vary, therefore the protocol should describe how investigators or HCPs will track and document postapproval study activities, including how effectiveness outcomes (e.g., durability of response) or adverse events (e.g., secondary malignancy) will be captured and assessed.
  - Remote visits can occur at locations such as participants' homes or local health care facilities, and telehealth visits can be considered. Therefore, the protocol should specify where the study participants can seek local medical assistance when necessary and where to receive follow-up care (e.g., following treatment with a CGT, where will a patient receive the routine follow-up and where will they be assessed if a secondary malignancy occurs). In addition, the protocol should describe how care will be provided for adverse events that require urgent or in-person care or events that require further evaluation (e.g., collection of tissue samples for insertion site analysis in case of secondary malignancies).

Please note that the regulatory requirements for institutional review boards[4] and obtaining informed consent[5], [Ref. 12] apply to collecting data in a postapproval setting.

[4] 21 CFR Part 56
[5] 21 CFR Part 50

IV. REFERENCES

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