Post-Approval Safety Regulation of FDA-Approved Cell and Gene Therapies: A Longitudinal Regulatory Cohort Study

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Article

Post-Approval Safety Regulation of FDA-Approved Cell and Gene Therapies: A Longitudinal Regulatory Cohort Study

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Abstract

Background: Cell and gene therapies (CGTs) can require prolonged post-approval surveillance because pre-approval exposure is often limited and some biological effects and toxicities may emerge over long follow-up. Existing studies have characterized CGT approval evidence, pharmacovigilance, and postmarketing obligations, but the longitudinal structure of subsequent U.S. Food and Drug Administration (FDA) safety-regulatory actions has been less clearly described. **Methods:** We conducted a retrospective longitudinal regulatory cohort study of FDA-approved CGTs initially approved through December 31, 2025, with follow-up through August 23, 2026. FDA primary regulatory sources were manually adjudicated using a predefined action taxonomy and linked action-to-episode structure. The primary outcome was the first definitive major post-approval safety regulatory escalation (Category A). Product-time and observed action rates were summarized descriptively. Prespecified sensitivity analysis removed a shared class-wide CAR-T T-cell-malignancy episode as an event-generating mechanism; a post hoc approval-era analysis examined the potential influence of cohort composition and historical source granularity. **Results:** The cohort comprised 39 products. Nine products (23.1%) experienced a first Category A action during 167.16 product-years, corresponding to an observed product-level rate of 5.38 per 100 product-years. Median time to first major action among affected products was 2.82 years (range, 1.81-6.39). Five of the nine first events were generated by one shared class-wide CAR-T regulatory episode; excluding that episode, 4 of 39 products retained product-specific first events (2.22 per 100 product-years). Across the broader lifecycle taxonomy, 14 products had at least one qualifying regulatory action, resolving into 16 underlying episodes that included both escalation and de-escalation. **Conclusions:** Major post-approval FDA safety actions affected a minority of CGTs but were highly clustered by regulatory episode. An episode-aware structure distinguishes the number of products affected from the underlying FDA decisions that generated those actions and provides a more transparent representation of dynamic lifecycle risk management.

Keywords: cell and gene therapy; regulatory science; postmarketing safety; FDA; lifecycle regulation; boxed warning; REMS

Introduction

Cell and gene therapies (CGTs) have expanded from a small group of specialized products into a diverse therapeutic class spanning oncology, rare genetic diseases, tissue repair, immune disorders, and other indications. Their clinical promise is accompanied by regulatory challenges that can differ from those of many conventional medicines. Some products produce biological effects that persist for years, permanently alter or introduce genetic material, or carry risks whose frequency or clinical significance may become clearer only after broader use and longer observation. These characteristics make post-approval evidence generation and long-term safety surveillance integral to CGT regulation [6,8,9].

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This lifecycle perspective is increasingly explicit in FDA policy. In 2025, FDA issued draft guidance specifically addressing methods to capture post-approval safety and efficacy data for CGTs, citing both the possibility of long-lasting effects and the limited numbers of participants typically treated before approval [2]. FDA has also continued to update broader post-approval safety-data standards [11]. Postmarketing trials, long-term follow-up, spontaneous reporting, registries, and other evidence streams can therefore alter the regulatory assessment of an approved therapy over time.

Recent empirical work has characterized important features of CGT approval and postmarketing oversight. Shahzad and colleagues examined 38 FDA-approved CGTs through December 2025 and described expedited pathways, pivotal evidence, and postmarketing requirements or commitments [3]. Their 38-product denominator reflected an additional investigational-new-drug-based exclusion used for development-time analyses; because the present study begins follow-up at marketing approval, that exclusion was not applied, yielding 39 eligible products under the otherwise aligned approval cutoff. Cai and colleagues compared CGT postmarketing-surveillance frameworks across major jurisdictions [5], while recent reviews and pharmacovigilance studies have examined delayed toxicities, long-term follow-up, and safety-reporting patterns [6–8]. These studies establish that continuing evidence generation is a central feature of the CGT lifecycle. However, an approval-time obligation, a safety signal, and a subsequent FDA regulatory intervention are different endpoints.

Safety-related regulatory actions have been studied longitudinally in broader therapeutic cohorts. Bulatao and colleagues evaluated postmarketing actions among therapeutic biologics [4], and more recent studies examined time to first postmarket safety action among hundreds of novel therapeutics and among oncology drugs granted accelerated approval [22,23]. Those studies provide important methodological context but do not specifically reconstruct the regulatory histories of the full FDA CGT cohort or distinguish product-level impact from shared class-level FDA decisions.

For CGTs, this distinction is particularly relevant. One safety concern may produce several linked actions over time, including a public communication, a binding labeling notification, an indication restriction, or a change in a risk-management program. Conversely, one class-wide FDA decision may affect several products simultaneously and can be mistaken for several independent safety discoveries if the analysis is conducted only at the product level. Regulatory oversight can also move in the opposite direction: accumulated experience may support de-escalation of risk-management burden while long-term monitoring continues, as illustrated by FDA's elimination of REMS for six autologous CAR-T therapies in 2025 [10].

We therefore conducted a longitudinal regulatory cohort study to reconstruct major post-approval FDA safety-related actions for eligible approved CGTs, determine when they occurred, and represent how individual actions clustered into product-specific or class-wide regulatory episodes. A secondary objective was to characterize meaningful non-major safety actions and regulatory de-escalation. To our knowledge, no prior study has combined full-cohort CGT regulatory-history reconstruction from FDA primary sources with an explicit action-level, product-episode, and class-episode structure. We did not test whether limited evidence at approval caused later intervention; the study was designed as a descriptive analysis of regulatory lifecycle decisions.

Methods

Study Design and Objective

We conducted a retrospective longitudinal regulatory cohort study of CGT products approved by the FDA. The primary objective was to characterize definitive major post-approval safety-related regulatory actions, their timing after initial approval, and the regulatory sequences through which product risk management evolved. The endpoint was an FDA regulatory action rather than an adverse-event report. A pharmacovigilance signal may not lead to regulatory intervention, whereas

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a regulatory action represents an agency decision to alter risk communication, indicated use, risk-management requirements, access, distribution, or licensure.

Cohort Definition

The sampling frame was the FDA Center for Biologics Evaluation and Research, Office of Therapeutic Products list of approved cellular and gene therapy products [1]. Products were eligible if initially approved on or before December 31, 2025 under the standard biologics licensing framework represented in that sampling frame. Nine minimally manipulated hematopoietic progenitor cell cord-blood products were excluded as a distinct regulatory category. Products first approved after December 31, 2025 were excluded to avoid introducing products with only very short opportunity for post-approval observation before the study cutoff.

The unit of analysis was the product at initial FDA approval. Supplemental indications and indication expansions remained within the same product lifecycle and were not separate observations. Shahzad et al. reported 38 CGTs through the same calendar cutoff because their development-time analysis additionally excluded one product without U.S. investigational new drug development [3]. U.S. investigational new drug status was not an eligibility criterion here because the risk set began at FDA marketing approval.

Data Sources and Product-Level Clearance

Regulatory history was reconstructed from publicly available FDA and official U.S. regulatory sources. Sources included FDA product and approval-history pages, original and supplemental biologics license application letters, section 505(o)(4) Safety Labeling Change Notifications, prescribing-information histories, CBER Safety and Availability Communications, REMS records, relevant postmarketing requirements or commitments, and FDA clinical or regulatory reviews. FDA primary sources were required to establish Category A events. Official U.S. labeling history was used as supplementary verification when older FDA supplement records were not readily retrievable.

Positive and negative outcome ascertainment were both documented. For each of the 30 products without a Category A event, a structured negative-clearance registry records the review date, product-specific approval/supporting-document source, a falsifiable summary of postapproval supplement or labeling records reviewed, an explicit product-name search result for the CBER Safety and Availability communications index, REMS consideration where applicable, and the conclusion that no qualifying Category A action was identified through August 23, 2026. A negative clearance means that no action meeting the prespecified Category A threshold was identified; it does not imply absence of safety risk or lower-intensity regulatory activity. For the nine Category A-positive products, a separate baseline risk-management registry records whether a boxed warning and REMS were present at initial approval and summarizes the basis for classifying the later action as new or materially strengthened.

Outcome Taxonomy

The primary outcome was time from initial FDA approval to the first **Category A definitive major post-approval safety regulatory escalation**. Category A included: a new boxed warning based on post-approval or newly available safety information; material strengthening of an existing boxed warning; safety-related restriction or removal of an approved indication or population; a new or materially strengthened post-approval REMS or elements to assure safe use; FDA suspension; safety-driven withdrawal or revocation; or another binding FDA safety action of comparable regulatory consequence.

A formal FDA section 505(o)(4) Safety Labeling Change Notification was dated at the notification date when it directed a change meeting Category A severity criteria. Later implementation of the same required change was retained as a linked action, not a new episode. For TECARTUS, FDA's January 23, 2024 revised notification explicitly superseded a January 19 letter [29]; consistent with the

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earliest-binding-action rule, January 19 was used as the primary event date and the January 23 revision was retained as a linked stage. During the sentinel pilot, the SKYSONA implementation date of August 7, 2025 was initially used; source reconciliation before final analysis applied the same earliest-binding-action rule and corrected the event date to the April 3, 2025 505(o)(4) notification documented in the later approval letter [30]. Neither correction changed whether the event met Category A criteria.

Secondary categories captured other lifecycle actions. **Category B** comprised formal FDA safety communications or investigations identifying a serious safety issue before or without a definitive Category A action. **Category C** comprised material safety-regulatory de-escalation, such as REMS modification/elimination or clinically meaningful reduction in monitoring/access burden. **Category D** comprised definitive safety-related labeling or monitoring actions below Category A severity. Because Category D can arise from different evidence types, an additional evidence_nature field distinguishes realized postmarketing clinical events, long-term trial observations, theoretical/nonclinical risks, and monitoring/risk-characterization changes. Administrative, editorial, manufacturing, handling, efficacy-only, commercial, and routine non-safety changes were excluded.

Action, Episode, and Class-Episode Adjudication

Each dated regulatory record was stored as an action. Actions addressing the same product, underlying safety issue, and linked FDA regulatory sequence were grouped into one regulatory episode. Thus, a safety communication, binding notification, distribution action, and later label implementation could be multiple action records within one episode. Class-wide decisions affecting several products were represented both by product-level action records and a shared class-episode identifier, preserving the distinction between the number of products affected and the number of underlying FDA decisions.

The taxonomy was developed and refined during sentinel-case piloting, then fixed before final full-cohort clearance and statistical analysis. Subsequent source reconciliation was permitted to correct dates, source links, or episode relationships when required by the already-defined rules, with changes recorded in the audit trail; it was not used to broaden the Category A threshold in response to observed event counts. Adjudication was performed by a single author, so no claim of independent dual review is made. Quality control included explicit inclusion/exclusion rules, structured product-level negative clearance, a second-pass source reconciliation, foreign-key checks between product and episode registries, and programmatic numerical reconciliation.

Follow-Up and Statistical Analysis

Follow-up began on the date of initial FDA approval and continued to the first Category A event or administrative censoring on August 23, 2026. Commercial discontinuation alone did not terminate regulatory observation because FDA oversight and long-term obligations may continue to affect previously treated recipients after new commercial use stops.

We report the observed number and proportion of products with a first Category A action, product-time from approval to event or censoring, the observed product-level action rate per 100 product-years, and the median/range of time to first action among affected products. These quantities describe the complete eligible FDA cohort through the study cutoff. Product-level actions are not statistically independent when one class-wide decision affects multiple products; therefore inferential confidence intervals are not emphasized in the main text. Unadjusted exact intervals are retained in the reproducibility package only as descriptive supplementary calculations and do not account for class dependence.

A prespecified sensitivity analysis removed the shared CAR-T T-cell-malignancy episode as an event-generating mechanism and recalculated product-level event frequency, product-time, and the observed rate. Following independent audit of the public-source reconstruction, we also added a descriptive approval-era sensitivity analysis (2010-2019 vs 2020-2025 approvals) to quantify how observed rates varied with cohort era; this was explicitly post hoc and was not interpreted as a causal

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or biological temporal trend. A product-level Kaplan-Meier curve was retained only as Supplementary Figure S1 because a shared calendar-time class decision maps to different times-since-approval across products and can otherwise suggest more independent hazard information than the data contain. No multivariable Cox model was used because the number and dependence structure of major regulatory episodes could not support stable multivariable etiologic inference.

Secondary analyses summarized products with any Category A-D action, unique underlying regulatory episodes, maximum episode category, class-wide versus product-specific scope, evidence nature, and selected escalation/de-escalation trajectories.

Analyses were performed in Python. The released script recomputes follow-up directly from approval and event dates, verifies episode foreign keys and negative-clearance coverage, regenerates headline statistics and sensitivities, and outputs supplementary Kaplan-Meier estimates. All main manuscript numbers were reconciled against generated outputs. Generative AI assistance used during code drafting, literature-search query development, language editing, and quality-control review is disclosed in the Declarations; all regulatory-source verification, adjudication, analysis acceptance, and final interpretation were performed under author responsibility.

Use of AI-Assisted Technology

Generative AI tools, including ChatGPT (OpenAI) and Claude (Anthropic), were used as assistive tools for literature-search query development, Python code drafting, data-structure organization, manuscript language editing, and adversarial quality-control review. Regulatory claims were grounded in source documents verified by the author. The author independently verified the regulatory sources, adjudication decisions, analyses, and final manuscript content and takes full responsibility for the work. AI tools are not authors.

Ethics and Data Availability

The study used publicly available product-level regulatory records and did not collect identifiable private or patient-level data. There was no participant recruitment or interaction. The Supplementary Reproducibility Package includes the cleaned cohort, positive-event baseline registry, negative-clearance registry, action and episode registries, source registry, data dictionary, analysis script, environment specification, output tables, figures, and quality-assurance records.

Results

Cohort Construction and Follow-Up

The FDA sampling frame contained 53 approved cellular and gene therapy products. Excluding nine minimally manipulated HPC cord-blood products and five products first approved after December 31, 2025 yielded a primary cohort of **39 products** (Figure 1). Initial approval dates ranged from April 29, 2010 to December 9, 2025. All **30 products without a first Category A event** had a product-level negative-clearance record documenting the source review performed through the August 23, 2026 cutoff. Total follow-up to first Category A action or administrative censoring was **167.16 product-years**.

Major Post-Approval Safety Regulatory Actions

Nine of 39 products (**23.1%**) experienced a first Category A major post-approval safety regulatory action. The observed product-level rate was **5.38 per 100 product-years**. Among affected products, median time from initial approval to first Category A action was **2.82 years** (range, **1.81-6.39**).

The nine products were ZOLGENSMA, CARVYKTI, ABECMA, BREYANZI, KYMRIAH, YESCARTA, TECARTUS, SKYSONA, and ELEVIDYS (Table 2). FDA primary documents supported all first-event dates. For ZOLGENSMA, initial 2019 labeling already contained a hepatic boxed

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warning; the October 22, 2021 action was classified as material strengthening based on postmarketing safety information [15]. CARVYKTI had a product-specific December 21, 2023 boxed-warning action based on longer-term study information before the subsequent class-wide CAR-T action [16]. For the CAR-T class action, FDA first communicated the signal in November 2023 and subsequently required class-wide boxed-warning changes [12–14]. January 19, 2024 was used as the first binding date for affected products; TECARTUS had a revised January 23 notification that explicitly superseded its January 19 letter [24–29]. SKYSONA's April 3, 2025 binding date and ELEVIDYS's June 20, 2025 binding date were documented in later FDA supplement approval letters [30,31], with subsequent public implementation communications [17,18].

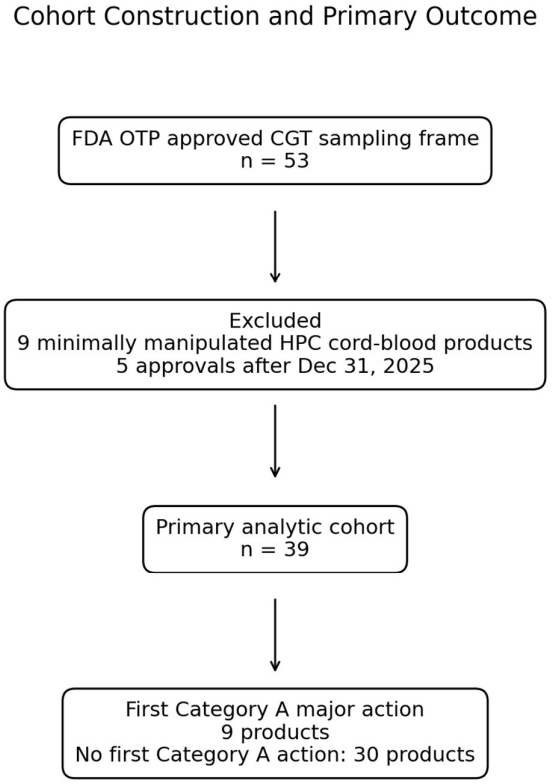

Figure 1. Cohort construction and primary outcome.

Table 1. Cohort construction, follow-up, and primary regulatory outcomes.

Measure	Value	Additional detail
FDA OTP approved-product sampling frame	53	
Excluded minimally manipulated HPC cord-blood products	9	
Excluded products first approved after 2025-12-31	5	
Primary analytic cohort	39	
Initial approval-date range		2010-04-29 to 2025-12-09

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Measure	Value	Additional detail
Median observed time to first Category A action or censoring, years	2.82	IQR 1.90-4.44
Total product-years to first Category A action or censoring	167.16	
Products with >=1 first Category A action	9	23.1% of cohort
Observed Category A actions per 100 product-years	5.38	Product-level descriptive rate; class-wide dependence is addressed in sensitivity analysis
Median time to first Category A action among event products, years	2.82	range 1.81-6.39
Products with any qualifying A/B/C/D lifecycle action	14	35.9%
Unique underlying qualifying lifecycle episodes	16	6 A, 8 D, 2 C by maximum category

Table 2. First Category A major post-approval safety regulatory action by product.

Product	Initial FDA approval	First Category A date	Scope	Years to action	Regulatory basis	Source
ZOLGENSMA	2019-05-24	2021-10-22	product-specific	2.41	FDA supplement updating Boxed Warning and multiple safety sections based on postmarketing safety information	[15]
CARVYKTI	2022-02-28	2023-12-21	product-specific	1.81	Boxed Warning revision based on protocol-specified end-of-study analysis	[16]
KYMRIAH	2017-08-30	2024-01-19	class-wide	6.39	505(o)(4) class safety-labeling action for T-cell malignancies	[27]
YESCARTA	2017-10-18	2024-01-19	class-wide	6.25	505(o)(4) class safety-labeling action for T-cell malignancies	[28]
TECARTUS	2020-07-24	2024-01-19	class-wide	3.49	505(o)(4) class safety-labeling action for T-cell malignancies	[29]

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Product	Initial FDA approval	First Category A date	Scope	Years to action	Regulatory basis	Source
BREYANZI	2021-02-05	2024-01-19	class-wide	2.95	505(o)(4) class safety-labeling action for T-cell malignancies	[25]
ABECMA	2021-03-26	2024-01-19	class-wide	2.82	505(o)(4) class safety-labeling action for T-cell malignancies	[24]
SKYSONA	2022-09-16	2025-04-03	product-specific	2.55	505(o)(4) safety-labeling notification for increased hematologic malignancy risk	[30]
ELEVIDYS	2023-06-22	2025-06-20	product-specific	2.00	505(o)(4) safety-labeling notification for fatal/serious liver injury	[31]

Class-Wide Clustering and Sensitivity Analyses

Five of the nine products received their first Category A action through one shared CAR-T T-cell-malignancy episode. CARVYKTI was also affected by that class decision but had already experienced a qualifying product-specific first event in December 2023. Thus, the nine affected products did not represent nine independent safety-regulatory discoveries.

When the class-wide CAR-T malignancy episode was removed as an event-generating mechanism, **4 of 39 products (10.3%)** retained product-specific first Category A events during **180.12 product-years**, corresponding to an observed rate of **2.22 per 100 product-years**. This sensitivity analysis quantifies dependence on one shared regulatory decision rather than estimating a counterfactual risk for CAR-T therapies.

Because historical source granularity, accumulated market exposure, regulatory practice, and follow-up opportunity differ by approval era, we also examined observed rates descriptively by approval period. Products approved in **2010-2019** contributed 90.19 product-years with three first Category A actions (**3.33 per 100 product-years**), whereas products approved in **2020-2025** contributed 76.97 product-years with six events (**7.80 per 100 product-years**). The comparison was based on only three and six first events, respectively, and **five of the nine events arose from one shared class-wide CAR-T decision distributed across both eras**. After removing that shared class episode as an event-generating mechanism, the corresponding observed rates were **1.05** and **3.54 per 100 product-years**, based on one and three events. These post hoc contrasts were not interpreted as evidence of a temporal or biological trend and were used only to expose sensitivity to cohort era and the regulatory data-generating context.

Regulatory Lifecycle Episodes Beyond the Primary Endpoint

Fourteen of 39 products (**35.9%**) had at least one qualifying Category A, B, C, or D action; recurrent later actions included the 2025 CARVYKTI enterocolitis boxed-warning episode [19]. After linked actions addressing the same underlying issue were deduplicated, **16 regulatory lifecycle episodes** remained: 14 product-specific episodes and two class-wide episodes. By maximum category reached, six were Category A escalation episodes, eight were Category D non-major safety episodes, and two were Category C de-escalation episodes (Table 3; Figures 2-3). Category B communications

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often appeared as intermediate stages within episodes that later reached Category A and were not counted again as separate underlying episodes.

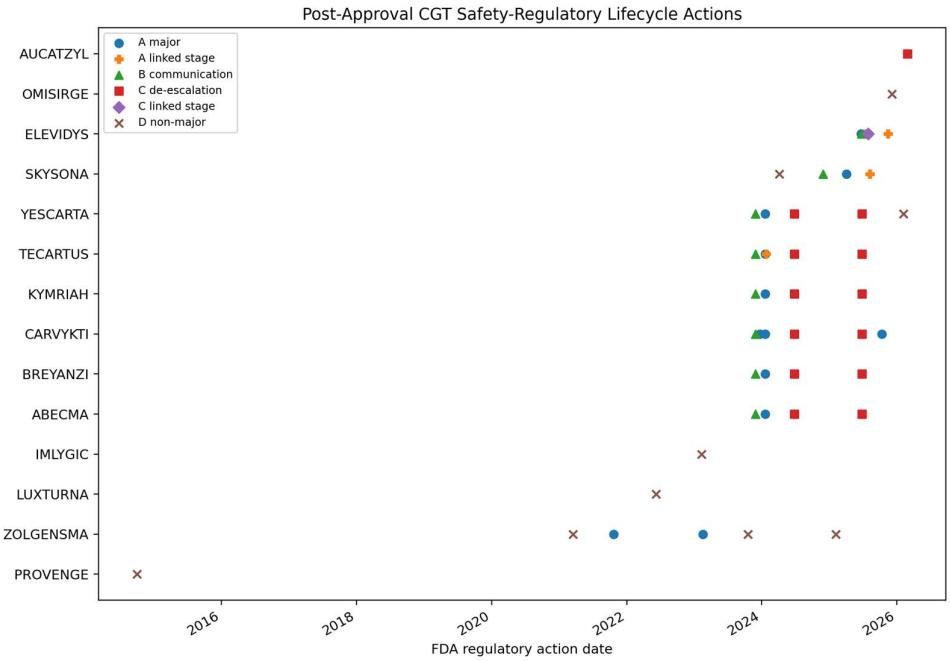

Figure 2. Post-approval CGT safety-regulatory lifecycle actions.

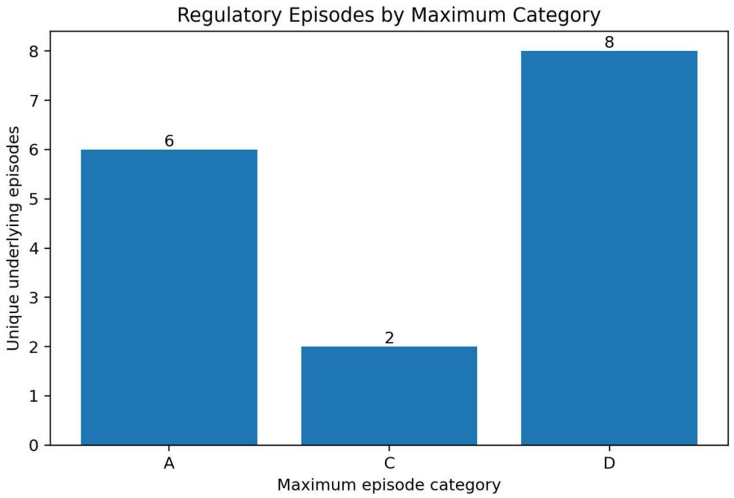

Figure 3. Regulatory episodes by maximum category.

Table 3. Underlying post-approval safety-regulatory lifecycle episodes.

Episode ID	Scope	Affected product(s)	Max category	First date	Final-stage date	Regulatory trajectory	Evidence nature
PROV_VASCULAR_2014	product	PROVENGE	D	2014-10-01		label update	realized_clinical_risk_label_evolution

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Episode ID	Scope	Affected product(s)	Max category	First date	Final-stage date	Regulatory trajectory	Evidence nature
ZOL_TMA_2021	product	ZOLGENSMA	D	2021-03-16		label update	realized_postmarketing_clinical_event
ZOL_HEPATIC_2021_2023	product	ZOLGENSMA	A	2021-10-22	2023-02-16	major boxed-warning update → later fatal-liver-failure strengthening	realized_postmarketing_clinical_event
LUX_CHORIORETINAL_2022	product	LUXTURNA	D	2022-06-08		postmarketing-experience label update	realized_postmarketing_clinical_event
IML_HERPES_2023	product	IMLYGIC	D	2023-02-10		warnings/postmarketing label update	realized_postmarketing_clinical_event
ZOL_TUMOR_2023	product	ZOLGENSMA	D	2023-10-17		warnings/patient-counseling update	theoretical_or_nonclinical_risk
CART_TCELL_2024	class	ABECMA; BREYANZI; CARVYKTI; KYMRIAH; TECARTUS; YESCARTA	A	2023-11-28	2024-01-19	public investigation → binding 505(o)(4) boxed-warning action	class_wide_clinical_and_postmarketing_signal
CARV_HEM_2023	product	CARVYKTI	A	2023-12-21	2023-12-21	boxed-warning revision	long_term_trial_observation
SKY_HEM_LIFECYCLE_2024_2025	product	SKYSONA	A	2024-04-05	2025-04-03	monitoring/counseling update → FDA investigation → binding major action → implementation	long_term_trial_observation
ZOL_INFUSION_2025	product	ZOLGENSMA	D	2025-02-05		warnings/administration/counseling update	realized_postmarketing_clinical_event
ELE_LIVER_2025	product	ELEVIDYS	A	2025-06-20	2025-11-14	binding 505(o)(4) action -> public communication -> shipment-suspension request/clinical holds -> voluntary distribution suspension -> partial removal of ambulatory hold -> final boxed-warning/indication implementation	realized_postmarketing_clinical_event

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Episode ID	Scope	Affected product(s)	Max category	First date	Final-stage date	Regulatory trajectory	Evidence nature
CART_REMS_DEESCALATION	class	ABECMA; BREYANZI; CARVYKTI; KYMRIAH; TECARTUS; YESCARTA	C	2024-06-26	2025-06-26	REMS burden reduction → REMS elimination	class_wide_regulatory_risk_management_reassessment
CARV_IEC_2025	product	CARVYKTI	A	2025-10-10	2025-10-10	boxed-warning update	realized_postmarketing_and_trial_clinical_event
OMI_AUTOCYTOPENIA_2025	product	OMISIRGE	D	2025-12-05		safety-label update + new safety-driven postmarketing study	long_term_trial_observation
YES_NEURO_2026	product	YESCARTA	D	2026-02-05		warnings/precautions update	long_term_trial_observation
AUC_DEESCALATION_2026	product	AUCATZYL	C	2026-02-26	2026-02-26	label alignment reducing monitoring/proximity restrictions	class_wide_regulatory_risk_management_reassessment

The episode architecture captured multi-stage regulatory histories. The ZOLGENSMA hepatic episode included material strengthening of an existing hepatic boxed warning in 2021 and further strengthening after fatal acute liver failure reports in 2023. SKYSONA's hematologic-malignancy episode evolved from monitoring/counseling changes and an FDA investigation to a binding April 2025 action and later implementation with stronger boxed-warning language and a restricted indicated population. ELEVIDYS progressed from a June 20 binding labeling action and June 24 public communication to FDA's July 18 request to suspend distribution and place related AAVrh74 trials on clinical hold, a July 25 voluntary distribution suspension, **FDA's July 28 recommendation to remove the voluntary hold for ambulatory patients while retaining it for non-ambulatory patients**, and November implementation of a new boxed warning and revised indication [31–34].

Regulatory learning also produced de-escalation. FDA reduced the class REMS burden for six autologous CAR-T products in 2024 and eliminated those REMS in 2025 while continuing long-term safety follow-up [10]. AUCATZYL was not subject to that REMS at initial approval; its later product-specific label-alignment action was therefore retained as a separate downstream episode linked to the broader class de-escalation rather than merged into the class REMS episode [35].

Category D captured genuine but lower-intensity safety actions and was further characterized by evidence nature. Examples included realized postmarketing events incorporated into labeling, longer-term trial observations, and theoretical/nonclinical risks. One Category D OMISIRGE episode involving autoimmune cytopenia was also linked to a new section 505(o) prospective postmarketing observational study; the study requirement was retained as regulatory-consequence metadata and did not become Category A solely because it was legally required [20]. The PROVENGE 2014

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Category D action was the only included action for which the public labeling history provided month-level rather than day-level date precision [21].

Discussion

Principal Findings

In this full eligible cohort of 39 FDA-approved CGT products, nine products experienced a predefined major post-approval FDA safety-regulatory action through August 23, 2026. The observed product-level rate was 5.38 per 100 product-years, and major actions occurred from approximately 1.8 to 6.4 years after initial approval among affected products. These findings demonstrate that material regulatory change can occur well beyond the approval date, but they should not be interpreted as nine independent safety discoveries. Five products received their first major action through one shared class-wide CAR-T decision, and removing that episode reduced the affected-product count to four and the observed rate to 2.22 per 100 product-years.

The broader lifecycle reconstruction also showed that a binary major-event indicator is incomplete. Fourteen products had at least one qualifying safety-regulatory action, and those actions resolved into 16 underlying episodes spanning major escalation, lower-intensity safety labeling, and de-escalation. In other words, post-approval CGT regulation behaved as a dynamic decision process rather than a one-way sequence from approval toward progressively stronger warnings.

Regulatory Action Is Not Adverse-Event Incidence

A Category A action is an FDA regulatory response, not a direct measure of biological adverse-event incidence or product safety. Products without a Category A action cannot be considered free of important risks, and products with an action are not necessarily intrinsically less safe than those without one. Regulatory intervention reflects the nature and credibility of evidence, background risk, disease severity, available alternatives, pre-existing warnings, feasibility of mitigation, class effects, surveillance intensity, and FDA benefit-risk judgment. Conversely, a safety signal may remain under evaluation without crossing the threshold for a major action.

This distinction is especially relevant to CGTs because long-term follow-up is intended to detect delayed outcomes that may be incompletely characterized before approval [6,8]. FDA's 2025 postapproval-data guidance specifically links the need for continuing evidence generation to long-lasting product effects and limited pre-approval exposure [2]. The present study therefore describes what happened when accumulated evidence crossed a regulatory-action threshold, not the underlying adverse-event burden.

Product Counts and Underlying Regulatory Decisions Answer Different Questions

The CAR-T T-cell-malignancy episode illustrates why dependence must be preserved in regulatory datasets. Counting six affected products is useful when the question is how many marketed products had their labeling changed. Counting that same event as six independent safety discoveries is not useful when the question is how many distinct regulatory processes occurred. The action -> product episode -> class episode structure preserves both views.

The prespecified class-episode sensitivity was more informative than adding a regression model. The data contain relatively few independent major episodes, and a multivariable Cox model treating product actions as independent would imply more information than the regulatory data-generating process contains. The same concern applies to conventional product-level confidence intervals. For transparency, unadjusted exact intervals remain in the reproducibility package, but the main manuscript emphasizes observed cohort quantities rather than inferential precision that does not account for class dependence.

This recording structure may be transferable beyond CGTs. Regulators often act across therapeutic or technological classes, and database studies that preserve only product rows can

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obscure whether several products changed because of independent evidence streams or one shared agency decision. We view the present architecture as a useful and auditable representation convention rather than as a claim of a new statistical method.

Relationship to Broader Postmarket-Safety Literature

The present findings sit within a growing literature on postmarket regulatory actions. Bulatao et al. previously evaluated time to safety-related action among therapeutic biologics [4]. Doernberg et al. subsequently studied 560 novel therapeutics approved from 2001 through 2019 and reported that 130 (23.2%) experienced a postmarket safety-related action during a median 12.1 years of follow-up [22]. The superficial similarity between their 23.2% product proportion and the 23.1% observed here should not be interpreted as evidence of equivalent safety profiles: the therapeutic populations, follow-up duration, regulatory endpoint definitions, market exposure, and dependence structure differ substantially. Our cohort had much shorter average observation and a prominent class-wide event that altered several products simultaneously.

Mooghali et al. also reported frequent postmarket safety actions among oncology drugs granted accelerated approval, with actions commonly occurring within a few years after approval [23]. Together with Bulatao and Doernberg, that work establishes the methodological lineage for studying FDA safety actions as postmarket endpoints. The incremental contribution of the present study is narrower: CGT-specific full-cohort reconstruction from FDA primary regulatory documents and explicit separation of product impact from product- and class-level episode structure.

This study is also complementary to CGT-specific work on approval evidence and surveillance architecture. Shahzad et al. characterized the evidentiary basis and postmarketing obligations of 38 CGTs [3], Cai et al. compared postmarketing-surveillance frameworks across jurisdictions [5], and Youssef et al. and Irinyi et al. emphasized pharmacovigilance and long-term follow-up [6,8]. Those studies describe what evidence was available and how surveillance is organized. We examine the downstream regulatory response when accumulated safety information resulted in a material FDA action.

Escalation and De-Escalation Can Coexist

Post-approval regulation was not uniformly escalating. Major episodes included new or strengthened boxed warnings, binding labeling actions, distribution intervention, and restriction of an indicated population. Yet accumulated experience also supported reduced regulatory burden. In 2025 FDA eliminated the REMS for six autologous CAR-T therapies after determining that labeling and clinical experience could adequately manage CRS and neurologic toxicity while long-term observational safety follow-up continued [10].

This is important conceptually and operationally. Removing a REMS does not imply that the underlying toxicities disappeared; it indicates that FDA judged a less burdensome risk-management mechanism sufficient. For developers and treatment systems, lifecycle decisions can affect eligible populations, site requirements, monitoring, distribution, and treatment logistics, linking regulatory strategy to clinical implementation and commercialization without making commercial outcomes an endpoint of this study.

Approval Era, Market Exposure, and Historical Ascertainment

The post hoc approval-era analysis showed different observed major-action rates among 2010-2019 and 2020-2025 approvals (3.33 vs 7.80 per 100 product-years), but the contrast was based on only three versus six first events and was materially shaped by a single class-wide CAR-T decision spanning both eras. When that shared episode was removed as an event-generating mechanism, only one versus three product-specific first events remained (1.05 vs 3.54 per 100 product-years). These comparisons are therefore not evidence of a temporal or biological trend. Older products did not simply lack reconstructable lower-intensity history: **2010-2019 approvals contributed seven**

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Category D action records across five of nine products, compared with two Category D records across two of 30 products approved in 2020-2025. This does not prove equal historical ascertainment, but it argues against treating sparse major-action counts in older products as synonymous with an absence of historical source review. Products still differed substantially in patient exposure, commercial uptake, indication, disease severity, and regulatory environment. Because the analysis uses product-time rather than patient-exposure time, a long-marketed but sparsely used product can contribute regulatory observation time without contributing an equivalent opportunity to generate safety signals.

We therefore retain the full 39-product approval-defined cohort as the primary denominator rather than excluding products post hoc based on commercial success or inferred exposure. The era sensitivity is presented to make denominator composition visible, not to select a preferred rate. Future work incorporating treated-patient exposure or standardized market-exposure estimates could better distinguish surveillance opportunity from calendar time under regulation.

Strengths

The study has several strengths. The 39-product denominator was reconciled to the current FDA OTP sampling frame and prespecified eligibility rules. All nine primary events were traceable to FDA primary documents, and baseline boxed-warning/REMS status was separately recorded for affected products to support new-versus-strengthened adjudication. The public package contains product-level negative-clearance records for all 30 non-event products rather than leaving absence of an action indistinguishable from absence of review. The analysis separates action records from product-specific and class-wide episodes, records exclusions, captures both escalation and de-escalation, and programmatically verifies episode foreign keys and manuscript numbers.

The study also deliberately avoids high-dimensional etiologic modeling. Given the small number of independent major regulatory processes, methodological restraint provides a more credible description than an unstable predictor model.

Limitations

Several limitations remain. First, the cohort is small and heterogeneous. CGTs span different modalities, indications, patient populations, and mechanisms of risk, so the observed product-level rate summarizes a regulatory portfolio rather than a biologically homogeneous therapeutic class.

Second, follow-up differs by approval date, and the 2020-2025 products have had less opportunity to accumulate delayed safety information. Product-years address unequal calendar follow-up but not patient exposure. The approval-era sensitivity confirms that the observed rate depends on cohort composition and regulatory era; it does not establish a temporal change in biological safety.

Third, product-level events are not independent under class-wide FDA action. We address this explicitly with class identifiers and sensitivity analysis, but no single product-level confidence interval can fully represent that dependence. The observed rate should not be interpreted as a stable future hazard.

Fourth, regulatory action is an imperfect proxy for safety burden. We do not have patient-level exposure denominators and cannot estimate adverse-event incidence or compare biological safety across products. FDA action thresholds and available regulatory tools can also change over time.

Fifth, historical reconstruction remains dependent on public-source completeness. Structured negative-clearance records improve auditability and now identify the product-specific records reviewed and the Safety & Availability name-search result, but older FDA histories are sometimes less granular than contemporary records. Omission of historical lower-intensity actions is more plausible for Category D than for the major Category A endpoint. PROVENGE also required month-level dating from official U.S. labeling history for one Category D action.

Sixth, adjudication was performed by a single author. No independent-reviewer agreement is claimed. The study mitigates this limitation through explicit rules, source-linked registries,

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documented source reconciliation, product-level negative clearances, baseline risk-management comparison for primary events, and machine-checkable joins and analysis outputs. Independent replication remains valuable.

Finally, the study did not test whether limited evidence at approval caused later regulatory intervention. The cohort and number of independent episodes are insufficient for credible multivariable etiologic modeling. Associations between approval characteristics and later regulatory action should be revisited when more CGTs and longer follow-up become available.

Future Research

The registry can be extended prospectively as additional CGTs are approved and existing products accrue longer observation. Larger episode counts could support analyses of prespecified approval characteristics while explicitly modeling class dependence and incorporating market exposure. Cross-jurisdictional comparison is another natural extension because the same underlying safety concern may lead to different timing or intensity of regulatory action across agencies [5]. Linking regulatory episodes to registries, postmarketing studies, long-term clinical follow-up, and treated-patient denominators may clarify which evidence streams most often trigger, strengthen, or resolve regulatory uncertainty.

Conclusion

Post-approval safety regulation of FDA-approved cell and gene therapies was dynamic but concentrated. Major FDA safety-related actions affected nine of 39 products in the observed cohort, but much of the product-level event burden arose from one shared class-wide CAR-T regulatory episode rather than multiple independent safety discoveries. Broader lifecycle reconstruction identified both escalation and de-escalation. An action- and episode-aware regulatory dataset therefore provides a clearer account of how FDA risk management changed after approval while keeping the number of products affected distinct from the number of underlying agency decisions. These results do not establish that CGTs are intrinsically unsafe, that absence of a major action means absence of risk, or that limited approval evidence causes later intervention.

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