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Review Article

Regulatory Pathways and Ethical Oversight of Advanced Therapy Medicinal Products in Europe

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Abstract

Background: Regulation (EC) No 1394/2007 made advanced therapy medicinal products medicines, routed them through a compulsory centralised procedure, and created a dedicated committee to assess them.

Objective: To judge the framework on its authorisations, withdrawals and hospital exemption.

Methods: Narrative review of legal instruments, authorisation-timeline analyses and comparative regulatory literature.

Findings: Twenty-seven products held authorisation as of 30 November 2024, with median time to Commission decision of 441 days. Under Article 28, 110 products were approved between 2008 and 2025 and 62 remained available, on data reflecting January 2025, with national review durations from 14 to 210 days.

Conclusions: The record supports centralised assessment as effective gatekeeping, but not earlier access as the binding constraint; the exemption lacks a common floor.

Keywords: Advanced therapy medicinal products; Marketing authorisation; Hospital exemption; Conditional approval; European Union regulation

Introduction

Advanced therapy medicinal products occupy an awkward position in European medicines law. They are manufactured from living cells, tissues or nucleic acids, they are frequently made for one patient at a time, and they were regulated for a decade by whatever national rules a member state happened to apply to tissues, transplants or medicines. Regulation (EC) No 1394/2007 ended that patchwork by defining gene therapy, somatic cell therapy, tissue-engineered and combined products as medicines, routing them through a single compulsory centralised procedure, and creating the Committee for Advanced Therapies to assess them [1]. The stated purpose was to raise and harmonise standards while giving developers one door into a market of the whole Union.

Nearly two decades later the framework can be judged on its outputs rather than its intentions. Those outputs are a small authorised portfolio, a meaningful rate of withdrawal that is largely commercial rather than safety-driven, and an exemption clause written for occasional in-house preparation that has become a parallel system operating on radically different terms in different member states. This review sets out what the framework governs, what it has authorised and how quickly, what has left the market and why, what the Commission's 2025 study reveals about Article 28, and how the European position compares with Japan's conditional and time-limited route and with the United States. It closes on the enforcement gap that no authorisation statistic captures.

Two framing decisions follow from the evidence rather than from preference. Counts of authorised products are quoted here with the date on which they were true, because a regulatory count without a date decays within months and invites false comparison between figures compiled on different bases. And the comparison with

other jurisdictions is made on named qualitative criteria, because the published European figures have no verified counterparts in the Japanese and United States literature reviewed here, and filling those cells from recollection would be worse than leaving them empty.

The centralised framework and its instruments

The Regulation does not stand alone. Commission Directive 2009/120/EC supplies the operative definitions that decide whether a product is a gene therapy, a somatic cell therapy or a tissue-engineered product, and therefore which guidance and which quality expectations apply [2]. Commission Regulation (EC) No 507/2006 provides the legal basis for conditional marketing authorisation, the principal early-access route within the centralised system [3]. Regulation (EU) No 536/2014 governs the clinical trials that generate the evidence, including the written consent and prior-interview requirements that matter disproportionately for first-in-human cell and gene therapy [4]. The Committee for Advanced Therapies guideline EMEA/149995/2008, adopted on 21 November 2008 and effective from 1 January 2009, sets the post-authorisation expectations for safety and efficacy follow-up and risk management that distinguish these products from conventional medicines [5].

Together these instruments form a coherent design: a single scientific assessment, class-specific quality requirements, an early-access valve, and long-term follow-up obligations to compensate for the thin evidence base at the moment of approval [6,7]. The design has been described in detail from both the regulatory and the hospital-pharmacy side, and the practical difficulty is consistently located in the same place, namely the distance between what a centralised dossier demands and what an academic or hospital developer can assemble [8].

The authorised portfolio and the pace of assessment

The portfolio is small. Twenty-seven advanced therapy

medicinal products held an EU marketing authorisation as of 30 November 2024, the cut-off stated by the most recent peer-reviewed analysis of authorisation timelines, of which twenty-six entered that study's timeline analysis [9]. The Committee for Advanced Therapies reported a figure of thirty-one as of 2 December 2025; that figure is cumulative rather than a count of products currently on the market, and the two numbers answer different questions [10]. Neither should be treated as a live inventory: the agency's public register of authorised products is the authoritative current source, and aggregate counts extracted from committee reports are not a substitute for it.

Table 1: Principal European instruments governing advanced therapy medicinal products, with the year of adoption and the matter each governs [1,3,2,4,5]; instruments in force as described as of 30 November 2024.		
Instrument	Year	What it governs
Regulation (EC) No 1394/2007	2007	Compulsory centralised authorisation; Committee for Advanced Therapies; Article 28 hospital exemption
Commission Regulation (EC) No 507/2006	2006	Legal basis for conditional marketing authorisation
Commission Directive 2009/120/EC	2009	Definitions of gene therapy, somatic cell therapy and tissue-engineered products
Regulation (EU) No 536/2014	2014	Clinical trials, including written consent and prior interview
Guideline EMEA/149995/2008	2008	Post-authorisation safety and efficacy follow-up and risk management

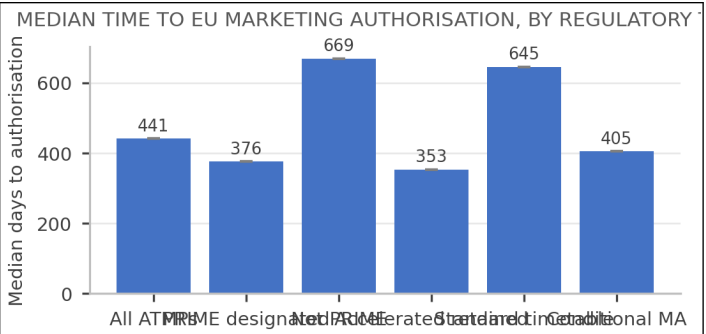


Figure 1: Median time from start of procedure to European Commission decision for EU-authorised advanced therapy medicinal products, by regulatory tool; n = 26, data as of 30 November 2024 [9].

Within that cohort of twenty-six, gene therapies dominate, at nineteen products or 73 per cent, against four somatic cell therapies, two tissue-engineered products and one combined product, as of 30 November 2024 [9]. Median time from the start of the procedure to the European Commission decision was 441 days, with an interquartile range of 370 to 645 days and a range of 237 to 1,656 days; active evaluation time to the opinion of the Committee for Medicinal Products for Human Use was 214 days, and the interval from opinion to Commission decision 60 days [9].

The regulatory tools work unevenly. Fourteen of twenty-six products had held PRIME designation, associated with a 42.7 per cent reduction in time to authorisation, 376 days against 669 days without it [9]. Nineteen of twenty-six held orphan designation, associated with a 32.8 per cent reduction [9]. Eleven of twenty-six were authorised conditionally, at a median 405 days, but the conditional route did not differ significantly from the standard route in regression [9]. Accelerated assessment performs worst of all as an instrument: half of all procedures started under it and 69 per cent of those were switched back to the standard timetable during review [9]. Class matters more than any designation. Median time to authorisation was 385 days for gene therapies, 660 days for somatic cell therapies and 1,174 days for tissue-engineered products, as of 30 November 2024 [9]. All twenty-six products had sought scientific advice, at a median of 3.5 consultations each [9].

Withdrawal, commercial exit and the limits of the framework

A framework that authorises few products and then loses some of them has a different problem from one that simply authorises few. Products have left the European market at a rate that would be unremarkable for a mature therapeutic class and is striking for one this small, and the exits have overwhelmingly been commercial decisions by marketing authorisation holders rather than regulatory

action on safety grounds. Reimbursement negotiations across twenty-seven national payers, manufacturing at a scale that never materialised, and the withdrawal of products whose clinical value was never disputed have all featured. The pattern is the strongest available evidence that centralised authorisation solves the scientific gatekeeping problem and leaves the access problem untouched, a disjunction visible in comparisons of gene therapy availability across major jurisdictions [11].

The distinction between a commercial withdrawal and a safety withdrawal is not merely presentational. A safety withdrawal is the framework working: post-authorisation obligations generate data, the data change the benefit-risk assessment, and the product goes. A commercial withdrawal is the framework being overtaken by conditions it does not control, principally national pricing and reimbursement, which Regulation (EC) No 1394/2007 deliberately left to member states. Patients enrolled in follow-up when a holder exits are left in an ill-defined position, since the risk management obligations attach to an authorisation that no longer exists.

Two points follow. First, the withdrawal record undermines the assumption embedded in the adaptive-licensing literature that earlier access is the binding constraint [12]. Conditional authorisation delivered no timeline advantage in the European cohort, and products that reached the market still failed to stay on it. Second, exhaustive product-by-product tabulation of authorisations and withdrawals is unreliable at any given moment, because the aggregates published in committee documents do not always reconcile with the underlying product lists. Counts should be quoted with their as-of dates and checked against the individual assessment reports, and the register treated as the live source of record.

Article 28 and the divergent hospital exemption

Article 28 of Regulation (EC) No 1394/2007 permits an

advanced therapy prepared on a non-routine basis, to a specific quality standard, and used in a hospital under the professional responsibility of a named practitioner for an individual patient, to be supplied without a centralised authorisation [1]. It was drafted as a narrow carve-out. It has functioned as something considerably larger, and the mismatch has been documented for more than a decade, first as a matter of principle and stakeholder concern [13,14], then through partial national surveys [15], and more recently in terms of patient access and its ethical consequences [16].

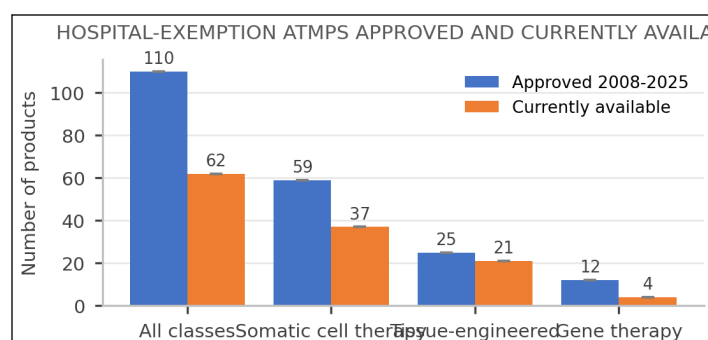


Figure 2: Hospital-exemption advanced therapy medicinal products approved between 2008 and 2025 against those currently available, in total and by class; 110 approved and 62 available, on data reflecting the position to January 2025 [17].

The Commission's 2025 study on the hospital exemption replaces that extrapolation with the first EU-wide picture. It records 110 hospital-exemption products approved between 2008 and 2025, targeting at least twenty-eight therapeutic indications, of which 62 were currently available, with the data reflecting the position to January 2025 [17]. Nineteen of the twenty-seven member states had adopted national rules providing a framework for the exemption, three of them with a framework but no products available, as of January 2025 [17]. National review durations for a single application ranged from 14 days in Denmark to 210 days in Spain [17], a spread that no single-country account, including the detailed Spanish one, could have exposed [18].

The class distribution inverts the centralised route.

Somatic cell therapies account for 59 approvals and 37 currently available products, tissue-engineered products for 25 and 21, and gene therapies for only 12 and 4, as of January 2025 [17]. Where the centralised procedure is dominated by gene therapy, Article 28 carries the cell and tissue work that cannot support a centralised dossier. The approval holders are also not exclusively academic: of 51 holders mapped, 26 were public or academic hospitals, 10 non-profit institutions, 14 private companies and one a private hospital, as of January 2025 [17]. Fourteen private companies operating under a hospital exemption is not what the drafting contemplated, and it complicates the standard defence of Article 28 as the route by which academic centres serve patients that industry will not. The study drew on 119 stakeholder responses collected to April 2025, which is a substantial base for a policy exercise and still leaves the underlying national records uneven in what they record and in whether they record it at all.

The study's own caveats deserve reproduction rather than smoothing. Poland's 24 available products are recorded as assumed available and Italy's 21 comprise single-patient approvals, so the two largest national totals do not count the same kind of object; the position in eight member states could not be determined; and patient-treatment figures carry an explicit warning that some predate the Regulation. There is consequently still no comparable EU-wide count of patients treated under Article 28, and the honest statement is that the denominator is unknown.

Japan, the United States and the European position

The comparison that matters is not who approves more products but what each system requires at the moment of first approval and what it can do afterwards. Japan's conditional and time-limited route for regenerative medical products makes the bargain explicit in statute: approval on suggestive evidence, a fixed period in which confirmatory data must be produced, and a defined decision point at which the product converts to full

approval or leaves the market [19]. The scheme was criticised at its inception as lowering the evidentiary bar and pricing products beyond their demonstrated value [20,21], and the subsequent history of the first conditionally approved cellular product has been read both as evidence that the review machinery eventually worked and as evidence that the scheme failed [22,23]. Broader analyses of conditional pathways in regenerative medicine treat the time limitation itself as the distinguishing feature [24].

Table 2: Qualitative comparison of the European, Japanese and United States routes for advanced therapies on named criteria; numeric cells are omitted deliberately because no verified counterpart figures were available for Japan and the United States [3,5,19,22,26,25].			
Criterion	European Union	Japan	United States
Early-access route	Conditional marketing authorisation	Conditional and time-limited approval	Designations accelerating review
Evidence standard at first approval	Comprehensive benefit-risk, with defined obligations outstanding	Suggestive efficacy with confirmed safety	Substantive licensing standard unchanged by designation
Time limitation in law	Renewable, no statutory terminal date	Fixed period ending in conversion or exit	No terminal date attached to designation
Post-authorisation obligation	Risk management plan and long-term follow-up	Confirmatory data for the second review	Post-marketing requirements on the licence
In-house or hospital exemption	Article 28 hospital exemption	Not directly comparable in this review	Not directly comparable in this review

Europe's conditional marketing authorisation is annual renewable rather than terminal, and its post-authorisation obligations are delivered through risk management and follow-up requirements rather than a statutory sunset [3,5]. The United States, by contrast, combines a biologics licensing route with designations that accelerate review without altering the substantive standard, and the comparative literature has repeatedly found that the three

jurisdictions reach different decisions on overlapping evidence [25,26]. The European system is the most demanding at entry and the least equipped to force an exit.

The enforcement gap and what is not counted

None of the above touches the clinics that sell cell-based interventions outside any of these routes. The global business landscape was mapped a decade ago [27], adverse events from unproven stem-cell interventions have been reviewed systematically [28], and the argument that regulation should sell help rather than hope has been made forcefully [29]. What does not exist is a current EU-wide survey of providers. The published counts are United States-focused [30], including the pandemic-era marketing of unproven treatments [31], and the best European case material is national and interpretive, notably the analysis of how EU advanced-therapy law has been exploited in Poland [32]. The appropriate statement is that no current EU-wide survey of unproven-cell-intervention providers has been published, and that the Polish and Italian material serves as illustration rather than as a count.

This is an enforcement problem, not a measurement problem to be solved by inventing a number: Article 28 and the national frameworks around it are administered unevenly, and the same national divergence that produces a 14-day review in one state and a 210-day review in another produces uneven appetite for pursuing providers who claim the exemption without meeting it.

Conclusion

The centralised framework has done what it was designed to do and little more. Twenty-seven products held authorisation as of 30 November 2024, gene therapy dominates them, tissue-engineered products take three times as long to authorise, and the accelerated route is abandoned mid-procedure in most cases where it is attempted. Meanwhile 110 products have been approved

under a clause meant for exceptional in-house preparation, 62 remain available, and only nineteen member states have a framework at all, on data reflecting January 2025. The reform question is therefore not whether to loosen the central standard but whether the exemption can be given a common floor and a common register without extinguishing the academic work it now carries.

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