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Instituto de Salud Pública
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134 años

Regulating Advanced Therapy Medicinal Products (ATMPs) in Chile: Regulatory Foundations, Process Mapping, and Future Outlook

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01

ATMPs: Definition, Classification & Regulatory Challenges

ATMPs are **personalised medicines** that **rewrite, replace or regenerate** a patient's own cells or genes.

Batch of One

Each patient is simultaneously the donor and the recipient. No serial production — every unit is unique.

Ultra-Short Shelf Life

CAR-T cells must be infused within hours. Standard 14-day sterility testing simply does not apply.

Irreversible Action

Gene integration lasts a lifetime. Long-term follow-up monitoring required for 15+ years post-treatment.

These three properties make conventional pharmaceutical GMP structurally inadequate — risk-proportional frameworks are required.

Three Categories of ATMPs

Gene Therapy

Modifies, replaces or adds genetic material (DNA/RNA) via viral vectors (AAV, lentiviral, adenoviral)

≥15 yr post-treatment monitoring

APPROVED:

Luxturna · Zolgensma · Hemgenix

Somatic Cell Therapy

Patient (autologous) or donor (allogeneic) cells modified ex vivo · CAR-T targets tumour antigens · 1 unique batch per patient

Batch-of-one production

APPROVED:

Kymriah · Yescarta · Carvykti

Tissue-Engineered

Cells or tissues combined with scaffolds to regenerate tissue · may include genetic components (combined ATMPs)

Long-term structural integration

APPROVED:

Holoclar · Alofisel · MACI

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02

Global Regulatory Landscape — Eight Jurisdictions

The Global Hard Core of ATMP Regulation

Analysis of 8 jurisdictions (EU, US, Japan, South Korea, China, Brazil, Argentina, Colombia) identifies 5 convergent elements in all mature ATMP frameworks:

01

LEGAL TAXONOMY

Binding ATMP-specific definition, distinct from general biologics

02

SPECIALISED COMMITTEE

ATMP-competent evaluators: EMA/CAT · FDA/OTP · PMDA

03

ADAPTIVE APPROVAL

Conditional authorisation on incomplete evidence + confirmatory post-market requirements

04

RISK-PROPORTIONAL GMP

Standards determined by: vector type · autologous/allogeneic · development phase

05

EXTENDED PHARMACOVIGILANCE

LTFU ≥10–15 years · 30-year traceability (EU) · mandatory patient registries

Common denominator: risk-proportionality — not batch size, not institution type.

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Reference Frameworks: EU, US and Japan

- **EU European Union (EMA)**

- Regulation (EC) 1394/2007 — the world's first dedicated ATMP-specific framework
- CAT Committee: specialised evaluation + binding opinion to CHMP
- Pathways: CMA (conditional marketing authorisation) + PRIME (early support)
- Hospital Exemption (Art. 28): without central MA, for individual patients
- **2025 — Key developments:**
- 4 new MAs (Vyjuvek, Aucatzyl, Zemcelpro, Waskyra)
- Mandatory Joint Clinical Assessments (JCAs) for ATMPs from January 2025
- Revised investigational ATMP guideline effective July 2025

- **US United States (FDA/CBER)**

- IND–BLA framework: phase-appropriate GMP (lower bar for Phase I academic sponsors)
- RMAT designation (21st Century Cures Act): Breakthrough benefits + RWE for confirmatory evidence
- ≈370 RMAT designation requests; 184 granted; 13 products with final MA

- **2025 — 3 draft guidances (September):**
- Expedited programmes for regenerative medicine therapies
- Innovative clinical trial designs for CGT products
- Post-approval methods to capture safety and efficacy data

- **JP Japan (PMDA/MHLW)**

- PMD Act (2014): first framework globally to distinguish regenerative medicine from conventional biologics
- GCTP: GMP-equivalent standard with ATMP-specific adaptations (concurrent validation, management of human-origin starting material)
- Conditional and Time-Limited Approval (CTLA): approval based on Phase I/II safety data + ≤7 years to confirm efficacy

- *CTLA is the most permissive adaptive pathway globally, but creates tension between patient access and evidence robustness.*

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Emerging Frameworks: South Korea and Brazil

- **KR South Korea (MFDS)**

- ARMAB Act (2020): first dedicated advanced biopharmaceutical framework in Asia
- NHIS: formal MA–coverage linkage; reimbursement decision within weeks of MA
- 2025 reform: approval timeline cut from 420 to 295 days (−125 days)
- Rolling CMC Review: allows partial quality module submission before full dossier

- *The Korean model is the most complete in terms of MA–coverage integration: the funding decision follows the MA in days, not years.*

- **BR Brazil (ANVISA)**

- RDC 505/2021: first ATMP-specific framework in Latin America
- Expedited Review Route (ACR): for products with ≥5 years of MA at a recognised reference agency
- IN 270/2023: risk-proportional GMP + third-party manufacturing under hospital titular responsibility
- 6 CAR-T products authorised by early 2026

- *Brazil is the most direct regulatory reference for Chile: same Latin American context, comprehensive framework, and explicit hospital-titular third-party manufacturing.*

03

The Authorization–Access Paradox

THE PROBLEM

32%

ATMP withdrawal rate (EMA, 2009–2026)

vs. ~8% non-ATMP orphan drugs

Multi-causal withdrawal drivers:

- Reimbursement failure (USD 1–3M per treatment course)
- Manufacturing scale-up constraints
- Emergence of superior alternative therapies
- Failure to complete post-MA efficacy commitments

INSTITUTIONAL RESPONSES

EU

EU — Joint Clinical Assessments

JCA mandatory Jan 2025 · synchronises MA and reimbursement evidence · ~8 ATMPs projected 2025

KR

South Korea — NHIS Model

Formal parallel evaluation · coverage decision within weeks of MA · most complete integration globally

ES

Spain — AEMPS/SNS Plan 2025–2028

≥2,000 patients treated · academic CAR-T at 4× lower cost than commercial products

Without a formal MA–HTA link, regulatory approval does not guarantee real patient access.

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04

Chile: NT N°257 Enacted Foundation & Future Challenges

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Chile: NT N°257 — The First Enacted ATMP Framework

- On 29 January 2026, Minister of Health Ximena Aguilera Sanhueza signed Decreto Exento N°11, enacting Norma Técnica N°257 on Medicamentos de Terapia Avanzada — Chile's first legally binding, specific ATMP regulatory instrument (16 pages). It replaces case-by-case regulation under DS3/2010.

- **What NT N°257 already establishes:**

✓ Legal taxonomy: 4 ATMP categories (gene therapy, somatic cell therapy, tissue engineering, combined products) — aligned with EMA Regulation 1394/2007 and ANVISA RDC 505/2021.

✓ Hospital Exemption defined (Glosario item 13): occasional production within a hospital or clinic, by individual medical prescription, for a single patient — equivalent to EU Art. 28.

✓ Non-industrial manufacturing defined (item 14): small-scale production in hospitals, clinics or academic institutions for clinical studies, no commercial purpose.

✓ Provisional release for ultra-short shelf-life products (Art. 2.5–2.6): ISP may authorise release before all QC tests are complete — the critical gap from the Propuesta PTA is now closed.

✓ GMP requirements (Chapter 6): mandatory BPM aligned with NT N°127, WHO TRS 1025, and ANVISA IN 270/2023.

✓ Marketing registration required (Chapter 4): all ATMPs manufactured or imported must obtain registration from ISP before distribution.

- *Reference agencies explicitly cited: EMA, AEMPS, PMDA (Japan), ANVISA (Brazil). NT N°257 is the operative instrument; DS N°3/2010 applies subsidiarily for unregulated aspects.*

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NT N°257: What Remains as Future Regulatory Challenges

• Not yet in NT N°257

- No adaptive/conditional authorisation pathway: NT N°257 requires full registration under DS3/2010. No conditional 3-year MA, no Accelerated Review Route equivalent to ANVISA's ACR or EMA's CMA.
- No reliance-based extrapolation (Art. 54B equivalent): no fast-track pathway leveraging EMA, FDA or PMDA evaluations — every ATMP must undergo full national review.
- No specialised evaluation body: no Advanced Therapy Evaluation Commission equivalent to EMA's CAT or FDA's OTP — evaluation remains within ANAMED's general structure.
- No formal MA–FONASA linkage: NT N°257 addresses quality and registration only. There is no mechanism connecting ISP authorisation to public health system coverage — the access paradox remains structurally unresolved.
- GMP complementary guidelines pending: Chapter 6 establishes BPM as mandatory but defers technical specifics to NT N°127 and NT N°139. ATMP-specific guidance (concurrent validation, PoC release, third-party under hospital titular responsibility) is still to be developed.

• The Road Ahead for ANAMED

- Adaptive authorisation pathway: develop a conditional registration route with post-authorisation efficacy confirmation — modelled on EMA CMA or ANVISA ACR.
- Reliance framework: operationalise Art. 54B-equivalent reliance on EMA/FDA/PMDA/ANVISA evaluations to accelerate access to approved ATMPs.
- Specialised committee: establish a multidisciplinary ATMP Evaluation Commission within ANAMED with CAT-equivalent scientific competence.
- 5 complementary BPM guidelines: (1) third-party manufacturing under hospital titular responsibility; (2) concurrent validation for autologous products; (3) provisional release for ultra-short shelf life; (4) cleanroom classification by process type; (5) decentralised/PoC manufacturing (prospective, MHRA POCAR model).
- **ISP–FONASA–MINSAL intersectoral work stream: formal MA–coverage linkage mechanism must be built now — in parallel with regulatory development, not after.**

Conclusions: What Chile Has, and What Comes Next

01 NT N°257: Foundation Established

Chile's first enacted ATMP framework (29 Jan 2026) defines 4 categories, hospital exemption, non-industrial manufacturing, provisional release for short shelf-life products, and GMP requirements.

The hard core is in place. What remains is the architecture for access.

02 GMP Frontier: Point-of-Care

MHRA POCAR (July 2025): manufacturing at bedside, governed by a single Control Site. NT N°257's non-industrial and decentralised manufacturing definitions anticipate this model.

5 complementary BPM guidelines still to be developed by ANAMED.

03 The 32% Paradox — Unresolved

ATMP withdrawal rate (32%) vs non-ATMP orphan drugs (~8%). NT N°257 addresses quality and registration only. No adaptive pathway, no reliance route, no conditional MA.

EU JCAs (Jan 2025): the first structural mechanism to watch as outcome data accumulate.

04 The Critical Gap: MA–Coverage

NT N°257 grants no pathway to FONASA coverage. Registration without reimbursement = the same access paradox, now in Chile.

ISP–FONASA–MINSAL intersectoral work stream must begin now — in parallel, not after.

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Gracias

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