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Classified, Authorised, Provided, Prescribed: A Global Regulatory Comparison of Regenerative Medicine in the United States, European Union, Japan and Brazil-and the Legitimate Space of the Curious Physician

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Abstract

Background: Regenerative medicine is governed not by a single permission but by at least four: classification of the intervention, authorisation to place a product on the market, authorisation to investigate or provide it, and professional authority to perform the medical act. A fifth practical permission — reimbursement — can operate independently. Conflation of these layers produces both unjustified therapeutic timidity and unjustified therapeutic adventurism.

Purpose: This perspective compares the United States Food and Drug Administration (FDA), the European Medicines Agency and European Union national-authority interface (EMA/EU), Japan's Pharmaceuticals and Medical Devices Agency and Ministry of Health, Labour and Welfare (PMDA/MHLW), Brazil's Agência Nacional de Vigilância Sanitária (ANVISA), and the Conselho Federal de Medicina (CFM). It proposes a clinically usable framework for lawful, evidence-generating innovation.

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Principal argument: The jurisdictions regulate different objects. FDA and EMA primarily regulate products; ANVISA expressly disclaims competence to recognise clinical indications; CFM regulates the medical act; and Japan separates product approval under the PMD Act from provision of regenerative medicine, including self-pay practice, under the Act on the Safety of Regenerative Medicine (ASRM). The EU hospital exemption likewise permits non-routine custom-made hospital provision without creating a marketable product. Adaptive pathways can work: Holoclar converted from conditional to standard EU authorisation after additional evidence, while Alofisel and Japan's HeartSheet exited when confirmation failed. They can also expose patients and payers to uncertainty: HeartSheet entered reimbursed practice after an uncontrolled seven-patient study. In fiscal year 2024, 95,168 patients received ASRM treatment in Japan versus 823 in research. A five-class evidence audit further shows that PRP has indication-specific and conflicting human evidence; BMA/BMAC and microfragmented adipose tissue have not demonstrated structural regeneration or consistent superiority over less invasive comparators; experimental peptides lack adequate human efficacy evidence; and exosome preparations remain poorly characterised and unsupported for routine injection.

Conclusion: Regenerative medicine does not need regulatory exceptionalism; it needs regulatory literacy and enforceable evidence loops. The defensible middle path is to classify correctly; obtain market, research/provision and professional permissions independently; begin confirmatory studies before adaptive access; pre-specify withdrawal rules; obtain explicit informed consent; register every outcome; publish negative results; and never advertise or commercially sell the unrecognised. That is what separates the good and curious physician from the entrepreneur of hope.

Keywords

Regenerative medicine; Regulatory science; Therapeutic peptides; Platelet-rich plasma; Bone marrow aspirate concentrate; Nanofat; Microfragmented adipose tissue; Extracellular vesicles; Exosomes; Advanced therapy medicinal products; Conditional approval; Medical ethics; FDA; EMA; PMDA; ANVISA.

Introduction

One patient, at least four permissions

A patient with symptomatic knee osteoarthritis sits in front of a physician in Santa Catarina, Brazil. The centrifuge in the next room holds a clearance from ANVISA. The autologous product it will produce is not a registered medicine anywhere. The evidence base for that product in that indication is positive but heterogeneous. The professional council has an opinion on the matter, and that opinion changed twice in eleven years. The question the physician must answer is not “does this work?” in the abstract. It is a narrower and much harder question: am I permitted to do this, by whom, under what conditions, and what exactly must I document?

That question is hard because it is not one question. Comparative law reveals at least four: what is the intervention; may the product enter the market; may it be investigated or provided at this site; and may this physician perform the act? FDA and EMA primarily classify and authorise products. ANVISA authorises market entry and quality systems. CFM authorises the medical act. Japan divides product commercialisation under the PMD Act from clinical provision under ASRM. In the EU, central marketing authorisation coexists with national trial, compassionate-use, named-patient and hospital-exemption routes. A cleared or CE-marked device does not authorise every procedure. A provision plan does not prove efficacy.

The conflation of these permissions produces two symmetrical errors, both of which damage patients and both of which damage regenerative medicine as a field. The first error is adventurism: reading a device clearance or a product registration as if it were a licence to treat, marketing cell-based interventions direct to consumers, charging patients to be subjects of an experiment that will never be published. The second

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error is timidity: reading the absence of an approved indication as an absolute prohibition, abandoning patients for whom approved options are inadequate, and declining to generate the very data that would move the norm. This article argues that both errors are avoidable, that the space between them is real, legally describable and ethically defensible, and that occupying it competently is the professional obligation of anyone who claims regenerative medicine as a field of work.

Section 2 defines the four-permission model. Sections 3 to 7 examine FDA, EMA/EU, PMDA/MHLW, ANVISA and CFM. Section 8 audits five intervention classes against human evidence; Section 9 documents cross-border divergences; Section 10 tests adaptive regulation against Brazilian, European and Japanese case histories; Section 11 converts the comparison into a clinical decision framework; and Section 12 states the ethical conditions that distinguish legitimate curiosity from commercial exploitation.

Four permissions, five authorities

The expanded comparison changes the core doctrine. The law can independently grant or withhold classification permission, market-authorisation permission, research/provision permission, and professional medical-act permission. Reimbursement is an empirically distinct fifth layer, because Japan has publicly reimbursed products while their efficacy remained conditional. Table 1 maps the principal authorities onto these objects.

Authority	Primary regulated object	Principal legal test / route	Independent permission not supplied
FDA (United States)	Products: biologics, drugs, devices, human cells, tissues and cellular and tissue-based products (HCT/Ps)	Licensure (BLA), approval (NDA/PMA), clearance (510(k)), or self-qualification under section 361 of the PHS Act	
EMA / European Union	Medicinal product placed on the market; ATMP categories: gene therapy, somatic cell therapy, tissue-engineered and combined products	Substantial manipulation or non-homologous use; CAT draft opinion, CHMP opinion and European Commission decision [67-71]	The medical act. EU law regulates placing products on the market, not how they are ultimately used; trial and hospital-exemption permissions remain national [73,80]
PMDA / MHLW (Japan)	Two objects: commercial regenerative medical products under the PMD Act and provision of regenerative medicine under ASRM	Product approval, including conditional/time-limited approval; separately, an ASRM provision plan, committee opinion and risk-class controls [96-98,104,107,108]	Product approval does not authorise off-label provision; an ASRM plan does not establish efficacy or permit general market entry

ANVISA (Brazil)	Market entry and quality systems: medicines, advanced therapy products (PTAs), medical devices, good practices in human cells	Registration, notification, clinical trial authorisation (DDCM), good-practice certification	Clinical use and therapeutic indications. ANVISA states in Nota Técnica 29/2024 that it “não possui competência legal para reconhecer o uso clínico e as indicações de terapias” and assigns that responsibility to the Ministry of Health and the professional councils [30]
CFM (Brazil)	The medical act and the physician performing it	Resolutions authorising, restricting or classifying procedures as experimental; ethical discipline under the Code of Medical Ethics	Whether a product may be manufactured, imported or sold. The CFM has no sanitary competence; Res. 2.464/2026 accordingly incorporates ANVISA's own instrument by reference for processing standards [41]

Table 1: Five authorities and the independent permissions they govern.

Three consequences follow immediately. First, a physician in Brazil needs both an ANVISA-lawful product and a CFM-lawful act; satisfying one is not a defence to failing the other. Second, a physician in Japan may have a lawfully submitted ASRM plan without a PMDA-authorised commercial product and without an individual governmental determination of efficacy. Third, a physician in the United States needs a lawfully marketed product and must accept that the practice-of-medicine shield in 21 U.S.C. §396 covers devices, not biologics, and expressly does not disturb the prohibition on promoting unapproved uses or the conditions attached to an approval [4]. The shield is real but narrow, and it has been tested in court twice in five years with results that every practitioner should know.

The FDA grammar: classification decides everything

The 361 / 351 divide

In the American system the decisive question is never “is it autologous?” but “which section of the Public Health Service Act does it fall under?” An HCT/P is regulated solely under section 361, that is, without licensure, only if it satisfies all of the criteria in 21 CFR 1271.10(a): the HCT/P is minimally manipulated; it is intended for homologous use only, as reflected in the labelling, advertising and other indications of the manufacturer's objective intent; its manufacture does not involve combination with another article except water, crystalloids or a sterilising, preserving or storage agent; and either it has no systemic effect and does not depend on the metabolic activity of living cells for its primary function, or, if it does, it is for autologous use, or allogeneic use in a first- or second-degree blood relative, or reproductive use [1]. Fail any one criterion and the product becomes a drug, device or biological product requiring premarket authorisation under section 351 [5,6].

Three definitional details in 21 CFR 1271.3 matter disproportionately in practice. Minimal manipulation is defined separately for structural tissue (processing that does not alter the original relevant characteristics

relating to utility for reconstruction, repair or replacement) and for cells or non-structural tissue (processing that does not alter the relevant biological characteristics). Homologous use means repair, reconstruction, replacement or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor. And critically, the same regulation excludes from the HCT/P definition both blood components, at §1271.3(d)(2), and minimally manipulated bone marrow for homologous use, at §1271.3(d)(4) [2]. This is why PRP and marrow aspirate are not analysed as HCT/Ps at all, while adipose-derived stromal vascular fraction is.

A limited additional carve-out exists at 21 CFR 1271.15(b) for an establishment that removes an HCT/P from an individual and implants it into the same individual during the same surgical procedure [3]. The scope of “same surgical procedure” has been the central battleground, and it is narrower than practitioners generally assume. Where classification is uncertain, the Tissue Reference Group provides a formal mechanism for obtaining FDA's view before, rather than after, clinical deployment [8] — a resource that is under-used and that a prudent innovator should use.

The end of enforcement discretion, and what the courts held

FDA's period of enforcement discretion for certain HCT/P manufacturers ended on 31 May 2021. The agency's own question-and-answer document from that period contains the sentence that has since become the most important single line in the field: an investigational new drug application is not marketing authorisation [7]. Filing an IND does not make a product approved; it makes it lawfully investigational, which is a different and much more constrained status.

Two appellate decisions then settled the practice-of-medicine argument for cell-based products. In *United States v. US Stem Cell Clinic, LLC*, the Eleventh Circuit affirmed on 2 June 2021 that the stromal vascular fraction product at issue was a drug requiring approval [23]. In *United States v. California Stem Cell Treatment Center, Inc.*, the Ninth Circuit reversed the district court on 27 September 2024, holding likewise that the SVF product was a drug and rejecting the same-surgical-procedure and practice-of-medicine defences as advanced [24]. A petition for certiorari was filed on 19 May 2025 [25]; its disposition is not established here and practitioners should verify the current docket status before relying on any prediction about it. The doctrinal lesson is nonetheless stable: characterising an intervention as the practice of medicine does not immunise it once the product itself fails 21 CFR 1271.10(a).

The affirmative pathways, and their scale

It is a serious misreading of the American system to describe it as merely prohibitive. The Regenerative Medicine Advanced Therapy (RMAT) designation, created by section 3033 of the 21st Century Cures Act and codified at section 506(g) of the Federal Food, Drug, and Cosmetic Act, provides intensive early interaction, potential priority review and eligibility for accelerated approval for regenerative therapies intended to treat serious conditions where preliminary clinical evidence indicates the potential to address an unmet medical need [9]. Through fiscal year 2025 the Center for Biologics Evaluation and Research had received 388 RMAT designation requests and granted 193 [10], and FDA lists 53 approved cellular and gene therapy products [11]. Expanded access categories for individual patients, intermediate-size populations and treatment protocols exist for patients who cannot enrol in trials [17], and the federal

Right to Try Act of 30 May 2018 adds a further, narrower route [18]. A physician who says “there is no lawful way to give this patient an investigational cell therapy” has usually not looked.

PRP, exosomes and energy devices: three different American answers

PRP. There is no dedicated FDA policy for PRP as a therapy. The lawful commercial route is a Class II clearance for the separator device — product code ORG, platelet and plasma separator for bone graft handling, 21 CFR 864.9245 [14]. The consequence is stated with unusual candour in the 510(k) summary for BK241083, which records that the PRP produced by the device “has not been evaluated for any clinical indications” [13]. A cleared instrument, therefore, with no cleared therapeutic claim. Everything downstream of the centrifuge sits in the practice-of-medicine space, which is precisely why professional norms, not sanitary ones, are the operative constraint.

Exosomes. The answer is categorically different. In its public safety notification of 6 December 2019 FDA stated that there are no FDA-approved exosome products and that such products are regulated as drugs and biological products requiring premarket authorisation [12]. Marketing autologous or allogeneic exosome preparations as therapies in the United States is not a grey zone; it is an unapproved-drug problem.

Energy-based devices. Here the constraint is indication-specific rather than product-specific. FDA's safety communication of 30 July 2018 warned against the use of energy-based devices for vaginal “rejuvenation” or vaginal cosmetic procedures, noting that no such device had been cleared or approved for those uses [15], and letters were sent to individual manufacturers. More recently, on 15 October 2025, FDA issued a safety communication on potential risks with certain uses of radiofrequency microneedling [16]. A cleared device used for an uncleared indication is a recurring pattern in aesthetic and regenerative practice, and the American answer to it is not prohibition of the act but prohibition of the claim.

The counter-signal: 2025 was not a year of tightening

Any argument that regulation moves only in the direction of greater stringency is falsified by the American record of 2025. On 27 June 2025 FDA eliminated the Risk Evaluation and Mitigation Strategy requirement for autologous CAR T-cell immunotherapies, while retaining boxed warnings, medication guides, adverse-event reporting under 21 CFR 600.80 and long-term follow-up [19,20]. The laboratory-developed test rule was vacated on 31 March 2025 and the regulatory text was subsequently reverted [21]. On 12 November 2025 the agency announced a “plausible mechanism” pathway for rare fatal genetic disorders, with senior officials describing existing requirements as burdensome and excessively strict [22]. Within a single period, therefore, the boundary moved in FDA's favour in cell therapy and against it in diagnostics. Regulation is a moving frontier in both directions, and that is an argument for engagement rather than for either despair or defiance.

The EMA/EU Grammar: a Centralized Product, a National Medical Act

ATMP classification and the centralised route

The European Union defines advanced therapy medicinal products (ATMPs) by legal category. Regulation (EC) No 1394/2007 covers gene therapy medicinal products, somatic cell therapy medicinal products, tissue-engineered products and combined ATMPs [67]. The two decisive triggers for cell and tissue

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preparations are substantial manipulation and use for a function that is not the same essential function in donor and recipient [68]. A somatic cell therapy medicinal product contains cells or tissues that meet either trigger and acts through pharmacological, immunological or metabolic action; a tissue-engineered product contains engineered cells or tissues and is presented for regeneration, repair or replacement [67,68]. The architecture resembles FDA's 361/351 boundary but is not textually identical, and a practitioner must resist transplanting American labels into European law.

The Committee for Advanced Therapies (CAT) prepares the draft opinion on each ATMP application; the Committee for Medicinal Products for Human Use (CHMP) adopts the final scientific opinion, and the European Commission issues the legally binding marketing-authorisation decision [67,69]. Developers may request an optional CAT scientific-classification recommendation, ordinarily delivered after consultation with the Commission within 60 days, and small and medium-sized enterprises may seek certification of quality and available non-clinical data [67,70]. By June 2026 CAT reported 727 classification recommendations adopted from 737 requests, a quantitative measure of how often the apparently preliminary question, “what is this?”, requires formal regulatory adjudication [71].

The same CAT report listed 33 authorised ATMPs and 9 withdrawn or non-renewed products, along with 184 PRIME requests discussed and 78 granted [71]. Those figures are important not because they prove regulatory success, but because they display both output and attrition. An adaptive system must be able to admit promising products, demand additional evidence and remove products whose scientific or commercial case does not survive.

Four lawful routes, not one

In a joint statement of 12 March 2025, EMA and the Heads of Medicines Agencies reduced lawful ATMP access to three principal routes: a central marketing authorisation, an authorised clinical trial or a national hospital exemption [72]. The complete legal map also contains compassionate-use programmes, coordinated and implemented by Member States under their own rules; named-patient supply in response to a bona fide unsolicited order for an individual patient under the direct responsibility of an authorised professional; and magistral or officinal pharmacy preparations [73,74]. None of these routes should be misdescribed as “EMA approval.” Clinical trials are authorised and supervised by Member States under Regulation (EU) No 536/2014 through the Clinical Trials Information System, and trial authorisation is permission to investigate, not permission to market [75].

The hospital exemption is the European provision that most clearly changes the doctrine of this article. Article 3(7) of Directive 2001/83/EC covers an ATMP prepared on a non-routine basis according to specific quality standards, used in the same Member State in a hospital, under the exclusive professional responsibility of a physician, pursuant to an individual prescription, for a custom-made product for an individual patient. Manufacturing must be authorised by the national competent authority, and traceability, pharmacovigilance and quality standards must be equivalent to those at Union level [67,73]. This is authorisation of provision without market authorisation. It is not a commercial back door: non-routine, hospital, same Member State, individual patient and custom-made are cumulative restraints.

Implementation remains fragmented. Member States differ in interpreting non-routine manufacture and

in their quality, safety and efficacy requirements, and the EU still lacks a unified system for monitoring outcomes after hospital-exemption treatment [89]. The Commission's pharmaceutical package reached provisional political agreement on 11 December 2025 and advanced through Coreper and the European Parliament's health committee in March 2026, but the final agreed hospital-exemption text was not available at the cut-off of this article [76]. The lesson is methodological: an exemption deserves defence only if it creates data. From 7 August 2027, Regulation (EU) 2024/1938 will create a parallel authorisation for substances-of-human-origin preparations, coupled to an approved clinical-outcome monitoring plan [77,78]. That outcome requirement is the direction in which all adaptive provision should move.

Conditional authorisation and evidence loops

EU conditional marketing authorisation is not the Japanese model under another name. It requires a positive benefit-risk balance, a likelihood that comprehensive post-authorisation data can be provided, an unmet medical need, and a finding that the benefit of immediate availability outweighs the risk of missing data. It is valid for one year and renewable annually, and may be converted, suspended or revoked [81]. PRIME supplies enhanced early regulatory support based on unmet need and preliminary clinical evidence [84]; accelerated assessment can reduce the standard timetable from 210 to 150 days for products of major public-health interest [83]; and authorisation under exceptional circumstances addresses cases in which comprehensive data cannot be obtained because the condition is rare, collection is impossible or it would be unethical [82].

Case	Adaptive entry	Confirmatory outcome	Regulatory lesson
Holoclar (EU)	Conditional marketing authorisation, 17 February 2015	Additional evidence supplied; converted to standard authorisation 22 February 2024; 75/104 successful implants at 1 year [86]	Successful completion of the adaptive bargain
Alofisel (EU)	Authorised 2018; initial benefit considered modest	ADMIRE-CD II failed to show superiority to placebo; benefit no longer demonstrated; withdrawn December 2024 [85]	Failure can and should terminate access
Roctavian (EU)	Conditional authorisation, 24 August 2022	Long-term effectiveness and safety obligations, corticosteroid study and patient registry; annual review [88]	Access tied to specified post-authorisation evidence
HeartSheet (Japan)	Conditional/time-limited approval on 7 uncontrolled patients, September 2015	Superiority not demonstrated; full approval refused 19 July 2024; sales ended [109,112,113]	Exit rule worked, but entry threshold and nine-year exposure were questionable
Stemirac (Japan)	Conditional/time-limited approval on 13 analysed uncontrolled patients, December 2018	Full-approval application filed 17 November 2025; outcome unverified at cut-off [110,111,113]	Long conditional term can postpone rather than resolve uncertainty

Table 2: Adaptive regulation as a testable evidence loop: selected European and Japanese cases.

Off-label medicine, devices, PRP and exosomes

The European Commission states the competence boundary expressly: off-label use is not directly regulated in EU pharmaceutical law; Union rules regulate placing products on the market **and not the way products are ultimately used in medical practice**. Departure from an authorised indication remains the prescribing physician's responsibility under national law [80]. The Medical Device Regulation supplies the parallel warning for devices: CE conformity is assessed against the manufacturer's declared **intended purpose**, expressed in labelling, instructions, promotional material and clinical evaluation [79]. A CE mark is therefore not a Union-wide authorisation of every clinical use, any more than an FDA 510(k) clearance

is.

For PRP and exosomes, the most scientifically honest European answer in 2026 is that classification remains unfinished. The SoHO Coordination Board's list adopted on 16 March 2026 formally records PRP, platelet-rich fibrin, lyophilised PRP, PRP combined with adipose cells, autologous conditioned serum, secretomes including exosomes, and stromal vascular fraction among items requiring regulatory-status opinions [90]. No exosome product appears in EMA's list of authorised ATMPs [71]. Uncertainty is not permission: in October 2025 France's ANSM suspended advertising by Linden Clinics for stem-cell and exosome therapies after finding the advertised intervention to be an unauthorised medicinal product and ATMP [91].

The PMDA/MHLW grammar: two statutes, two objects

Product approval under the PMD Act; provision under ASRM

Japan provides the clearest statutory demonstration that market authorisation and the medical act are distinct permissions. The Pharmaceuticals and Medical Devices Act (PMD Act) governs commercial regenerative medical products: processed live human or animal cells intended to reconstruct, repair or form structures or functions, or to treat or prevent disease, as well as gene-therapy products [104,107]. PMDA performs the technical review and MHLW makes the approval decision. The Act on the Safety of Regenerative Medicine (ASRM), in force since 25 November 2014, governs **provision**, in research and in private clinical practice, of interventions using specified processed cells; after an amendment effective 31 May 2025 it also covers specified nucleic acids and related technologies [96-98,114].

The regimes are deliberately mutually exclusive. PMD Act clinical trials are excluded from ASRM; a specified processed-cell product excludes a product already classified as a regenerative medical product; and use of an approved regenerative medical product within its approved conditions falls outside ASRM. Off-label or non-product provision falls back into the provision regime [96]. The division of labour is exact: PMDA/MHLW decide whether a product may be sold; ASRM decides whether a hospital or clinic may provide a regenerative intervention that may never become a commercial product.

The provision plan is a safety gate, not an efficacy approval

Before provision, the administrator of a hospital or clinic must submit a regenerative-medicine provision plan to MHLW after obtaining the opinion of a certified committee on compliance with statutory provision standards. Class I and II plans require a specific certified committee; Class III may use a committee certified for Class III. Class I plans are subject to a ministerial waiting period of 90 days, which may be extended or shortened [96]. Risk classification places pluripotent, allogeneic, transfected and animal cells principally in Class I; autologous mesenchymal or non-homologously used somatic cells in Class II; and autologous somatic cells for homologous use in Class III [114].

The critical limitation is that the plan is submitted, not individually approved for efficacy. In July 2026 an MHLW working group began considering a system to assess whether privately provided regenerative medicine is appropriate, acknowledging that the existing regime contains no system by which government individually verifies efficacy or safety [115]. Official fiscal-year 2024 data make the scale impossible to dismiss: 4,387 treatment-side periodic reports versus 91 research reports, and 95,168 persons treated

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versus 823 research participants. Class II and III accounted for 99.6% of reports [99]. Japan has therefore created not a narrow compassionate exception but a national market in provision without product authorisation.

PRP sits within that provision system as Class III regenerative medicine, and MHLW uses facial PRP as the worked example for counting administrations [99,114]. A committee recommended excluding PRP when used with a PMD Act-approved device strictly within its approved indication, but actual implementation of that carve-out was not confirmed at the article's cut-off [114]. Exosomes reveal the opposite gap: because they are not cells they remain outside ASRM. A 31 July 2024 MHLW communication stated that no exosome medicine with demonstrated efficacy and safety had obtained regulatory approval, yet imposed no notification, approval or penalty; regulation was under active review in July 2026 [100,114,115].

Conditional and time-limited product approval

Article 23-26 of the PMD Act permits conditional and time-limited approval where the product is heterogeneous, efficacy for the proposed indication is predicted, and marked adverse effects do not make it valueless. The term may not exceed seven years and may be extended by up to three; all patients are in principle enrolled in post-marketing surveillance, and the sponsor must obtain a new ordinary approval within the granted term or face revocation [107,108]. Unlike EU conditional authorisation, which is renewed annually and requires that comprehensive data are likely to be provided, Japan's entry threshold does not require confirmatory trial results [81,108].

The PMDA list through May 2026 contains 29 distinct approved regenerative medical products. Seven are marked as conditionally and time-limited approved, including HeartSheet, Stemirac, Collategene, Akuugo, Elevidys and, on 6 March 2026, RiHEART — an allogeneic induced-pluripotent-stem-cell-derived cardiomyocyte sheet — and AMCHEPRY, raguneprocel for Parkinson's disease [105,106]. Japan's scheme has therefore delivered genuinely first-in-class access. The question is not whether acceleration occurred; it is whether the evidentiary loop closes quickly and reliably enough to justify patient exposure and public reimbursement.

Heart Sheet: both the defence and the indictment

Heart Sheet entered conditional approval in September 2015 on a non-randomised seven-patient study without a primary efficacy endpoint; left-ventricular ejection fraction was unchanged in five patients and worsened in two [112,113]. It was nevertheless covered by national insurance at ¥14,760,000 per treatment [112,113]. Post-marketing evaluation eventually included 49 analysed treated patients and 102 external controls. Superiority was not demonstrated for time to cardiac death or secondary efficacy endpoints, and on 19 July 2024 the competent committee refused regular approval; Terumo ended sales while continuing follow-up [109].

This case must not be used simplistically. It defends adaptive regulation because the exit rule worked: a product that failed confirmation left the market, and even critics described the final scientific decision as fair [112,113]. It indicts the entry standard because nine years of reimbursed exposure followed evidence that did not show improvement. Stemirac repeats the concern: conditional approval followed an

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uncontrolled single-centre study of 13 analysed patients; a full-approval application was filed only on 17 November 2025, and its outcome was not verified by the cut-off [110,111,113]. The reform prescription is not to abolish adaptive approval but to initiate confirmatory trials before access, pre-specify endpoints and automatic withdrawal, minimise external-control dependence and separate reimbursement decisions from scientific optimism.

The 2026 safety correction

Japan's own recent enforcement record shows the system learning. MHLW's March 2026 alert required providers to recognise fatal pulmonary-embolism and arrhythmia risks from intravenous cell administration, document concomitant medicines and maintain emergency capability, including trained treating physicians [101]. A self-inspection request of 31 July 2026 followed deaths reported in August 2025 and March 2026 and improvement orders in January and July 2026. It required treatment providers to re-examine whether contemporary scientific evidence shows expected benefit sufficient to outweigh risk, whether standard treatment is inadequate, and whether the scientific basis satisfies the official literature checklist [102]. Adaptive regulation worthy of defence looks exactly like this: data acquisition, transparent failure, enforceable correction and continued revision — not permission without surveillance.

The ANVISA Grammar: Market Entry Is Not Clinical Endorsement

Advanced therapy products and good practices

Brazil built a dedicated advanced-therapy architecture over roughly five years. Good practices in human cells for therapeutic use and clinical research are now governed by RDC 836/2023, which succeeded RDC 508/2021 and RDC 214/2018, and which defines manipulação mínima in its Article 6 and the associated paragraph [26]. RDC 505/2021 governs the registration of advanced therapy products, setting out which products trigger the PTA regime, which are non-registrable, the thirty-day tacit-approval mechanism for certain gene-therapy submissions, and the follow-up obligations after approval [27]. Clinical trials with advanced therapy products follow their own instrument and are subject to prior ANVISA authorisation [28], and specific good-manufacturing requirements for PTAs were established by Normative Instruction 270/2023 [29]. Registered advanced therapy products do exist in Brazil — ANVISA's own communications and approval-letter pages name Kymriah, Yescarta, Carvykti, Luxturna, Zolgensma, Upstaza and Elevidys [35,36] — and the agency publishes monitoring reports on them [35]. The Brazilian system is not a vacuum; it is a young but functioning advanced-therapy regime.

Research with human beings acquired a statutory framework in Lei 14.874 of 28 May 2024, which creates a National System of Ethics in Research with Human Beings, fixes deadlines for ethics committee review with a tiered appeal structure, and establishes obligations of post-study access [33]; it was subsequently regulated by decree [34]. For a clinician who intends to generate data rather than merely to consume it, this statute is the single most consequential Brazilian development of the decade, because it makes the pathway from clinical observation to authorised protocol both faster and more predictable.

Nota Técnica 29/2024: the pivotal instrument for PRP

The most important Brazilian sanitary document for orthobiologics is not a resolution but a technical note. In Nota Técnica nº 29/2024/SEI/GSTCO/GGBIO/DIRE2/ANVISA the agency held that PRP is a product of conventional therapy rather than an advanced therapy product, and that it is not subject to registration

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[30]. Had the note stopped there it would have been read, predictably and wrongly, as sanitary permission to treat. It did not stop there. The same document states that “a Anvisa não possui competência legal para reconhecer o uso clínico e as indicações de terapias” and that “a responsabilidade pelo reconhecimento das indicações de procedimentos terapêuticos recai sobre o Ministério da Saúde e os Conselhos Profissionais” [30].

This is the cleanest available articulation, by a regulator about its own limits, of the thesis of this article. Sanitary silence is not clinical endorsement, and sanitary permission is not professional authorisation. The note is also the reason the CFM was later able to regulate PRP without trespassing on sanitary competence: it simply incorporated the note by reference [41].

Devices: registration certifies the right to sell, not efficacy

Brazilian device regulation is frequently misread in marketing materials. RDC 751/2022 establishes risk classification and the notification and registration regimes, with lower-risk classes I and II subject to notification and higher-risk classes III and IV to registration; the definitions in the resolution frame these as the authorisation to manufacture, import and commercialise [31]. No article of RDC 751/2022 certifies clinical efficacy for any indication. RDC 848/2024, on essential requirements of safety and performance, places the burden of demonstrating indication, performance and safety on clinical evaluation conducted by or for the manufacturer [32]. A laser or radiofrequency platform holding ANVISA registration therefore carries no implication whatsoever that a particular clinical application of it is authorised, and advertising “ANVISA-approved treatment” on the basis of a device registration misstates the law.

The CFM Grammar: Who May Perform

The general rule

The operative general instrument is Resolução CFM nº 2.327/2022, which revoked the long-standing Res. 1.499/1998. Its Article 2 forbids physicians from performing procedures that have been evaluated and not authorised by the CFM. Its Article 3 provides that off-label prescriptions must follow the norms in force at the CFM — a formulation that neither prohibits off-label prescribing nor leaves it unregulated. Its Article 4 forbids linking a physician's name or image to advertising of methods not authorised by the Council [38]. Read together with the Code of Medical Ethics (Res. 2.217/2018), the structure becomes clear: Article 32 of the Code requires the physician to use all available and scientifically recognised means of diagnosis and treatment; Article 102 forbids indicating a therapy that is not scientifically recognised, with a single paragraph permitting therapy still in experimental phase when accepted by competent bodies and with the patient's or legal representative's informed consent; Article 100 requires protocol approval by the competent ethics body; Article 113 forbids publicising treatments not recognised outside the scientific milieu; and Article 114 forbids advertising a specialty not registered with the Council [37].

Recognition of new procedures now has its own procedural instrument. Resolução CFM nº 2.428/2025 establishes the criteria and protocol for recognising new medical procedures and therapies, defines what constitutes an experimental medical procedure, revokes Res. 1.982/2012, and imposes a two-year bar before a rejected request may be resubmitted [39]. This matters strategically: there is a defined, published route by which a field can convert accumulated evidence into professional authorisation. Regenerative medicine's complaint that “the Council does not recognise us” is, in part, a complaint about a door that

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has an address.

Resolução CFM nº 2.464/2026: PRP becomes a recognised adjuvant

On 2 July 2026 the CFM adopted Resolução nº 2.464/2026, in force from 15 July 2026, regulating PRP as an adjuvant medical procedure for specific musculoskeletal conditions [41,42]. The essential architecture, as published, is: authorisation as an adjuvant rather than a primary therapy, for four conditions — knee osteoarthritis, lumbar discopathy, lateral epicondylitis and meniscal repair; autologous use only; processing “exclusivamente nos termos da Nota Técnica nº 29/2024 da Anvisa”; an express prohibition on the addition of stem cells, bone marrow aspirate concentrate, stromal vascular fraction or microfragmented adipose tissue; and the declaration that indication, application and follow-up are atos médicos [41,43]. The resolution is reported by the Council to revoke Res. 2.128/2015, which had classified PRP use as experimental and confined it to CEP/CONEP protocols [40,43].

Four features deserve emphasis for practice. First, the authorisation is narrow: four conditions, not “musculoskeletal disease”. Second, it is conditional: adjuvant, autologous, processed to a specified sanitary standard. Third, it explicitly fences off the cell-based combinations that many clinics had begun to bundle with PRP, which remain outside the authorisation. Fourth, the professional-competence declaration in Article 8 is already contested: the Conselho Federal de Enfermagem has filed a public civil action seeking suspension and annulment of Articles 8 to 12 [44]. The outcome of that litigation is not established here. Practitioners should note that a resolution under judicial challenge is still in force unless and until suspended, and should follow the docket rather than the commentary.

Cell therapy in Brazil remains experimental for clinical purposes

Two CFM opinions remain the reference points. Parecer CFM nº 43/2016 addressed the use of bone marrow aspirate for orthopaedic lesions, and Parecer CFM nº 2/2020 addressed regenerative therapies using tissues with high stem-cell content, including adipose-derived stromal vascular fraction obtained by mechanical processing; the latter concluded that such treatments may not be advertised or commercialised (“não podendo os tratamentos serem anunciados, nem comercializados”) [47,48]. Combined with the explicit exclusion of cell-based additions from Res. 2.464/2026, the Brazilian position on cellular orthobiologics is coherent even if unwelcome to some: research yes, commerce no.

A further structural fact is easy to miss and materially affects how physicians may present themselves. Under Resolução CFM nº 2.380/2024, which homologates the list of medical specialties and areas of practice, neither “medicina regenerativa” nor “longevidade” nor “medicina estética” appears as a specialty or as an area of practice [49]. Combined with Article 114 of the Code of Medical Ethics [37], the practical consequence is direct: a physician may lawfully practise regenerative interventions within their registered specialty, but may not advertise “regenerative medicine” or “longevity medicine” as a specialty. This is a communications constraint, not a clinical one, and it is one of the most commonly breached rules in the field.

Five intervention classes: from biological promise to clinical permission

Regulatory analysis becomes clinically useful only when it is tied to the evidence for the exact intervention, route and indication. The words peptide, PRP, bone marrow, nanofat and exosome are marketing nouns,

not transferable therapeutic claims. Each name can conceal different active substances, processing steps, dose units and legal identities. (**Table 3**) therefore places the five classes on an evidence ladder extending from mechanism to controlled human effect.

One conclusion applies across the group: no class reviewed here has demonstrated structural disease modification in a controlled human trial. RESTORE found no benefit on medial tibial cartilage volume with PRP [129]; the largest cell-product comparison found no MRI improvement with BMAC or SVF [144]; and microfragmented adipose tissue produced no radiographic or MRI change despite symptomatic improvement [149]. Symptom relief may still matter. It must not be renamed regeneration.

Class	What it is	Strongest human signal	Most important negative or limiting evidence	Maturity	Principal regulatory hinge	Appropriate clinical posture
Experimental peptides	Synthetic molecules such as BPC-157, TB-500 fragment, CJC-1295, ipamorelin, GHK-Cu, MOTS-c and epitalon; distinct from approved peptide medicines	CJC-1295 has human pharmacodynamic activity; controlled BPC-157, TB-500 and topical GHK-Cu trials are recruiting [123,125-127]	The only randomised BPC-157 dataset is an inadequately reported 53-person abstract; FDA found no human use data for MOTS-c and inadequate evidence for TB-500/KPV [119,120]	Unsupported for routine regenerative use	Compounding eligibility is not product approval; molecule, salt, route and indication must match	Approved peptide medicines for approved indications, or registered trials only
PRP	Autologous peripheral-blood platelet concentrate; leukocyte content, platelet dose and activation differ	Long-term signal versus corticosteroid in lateral epicondylitis across 26 RCTs and 1,877 patients [134]	RESTORE showed no pain or cartilage-volume advantage over saline; Achilles and intradiscal trials were negative [129,135,137,138]	Promising but indication- and preparation-dependent	Device status does not prove efficacy; Brazil authorises only four adjunctive indications [30,41]	Narrow indication-specific use, product characterisation and non-regenerative consent
BMA/BMAC	Unprocessed marrow aspirate versus its centrifuged concentrate; not synonymous with stem-cell therapy	Some improvement from baseline and small statistical advantages over hyaluronic acid [141]	No difference from saline in the only placebo-controlled RCT; equivalent to PRP at 24 months; no superiority to corticosteroid [142-144]	Investigational	Manipulation and homologous use define product status; invasiveness does not create permission	Trials or prospective registries; disclose lack of superiority to simpler comparators
Nanofat / MFAT / SVF	Mechanically emulsified fat, architecture-preserving microfragmented tissue and isolated stromal vascular fraction are different products	MFAT and PRP both improved symptoms; a subgroup had more MCID responders with MFAT [149]	No overall superiority or structural change; SVF not superior to corticosteroid; aesthetic nanofat evidence is small and uncontrolled [144,149,153]	Promising but heterogeneous for knee symptoms; otherwise investigational	Degree of manipulation and destination tissue can move the same harvest from a procedure to a regulated biologic	Process-specific classification, trials or registries, and harvest-risk disclosure
Exosomes / EV preparations	Cell-derived vesicles or culture supernatants; conditioned medium is not a characterised EV product	A 28-person split-face cosmetic study reported better aesthetic scores [165]	Only 8 of 40 human studies were randomised; 87.5% were uncontrolled and 40% reported no EV characterisation [164]	Investigational; unsupported for routine injection	Drug/biologic identity in the US; outside ASRM in Japan; cosmetic identity cannot authorise injection	Do not inject outside an authorised clinical trial; define source, purification, dose and potency

Table 3: Evidence maturity and appropriate clinical posture for five intervention classes.

Therapeutic peptides: compoundable is not approved

The first obligation is to separate approved peptide medicines from experimental compounds sold under a regenerative or longevity narrative. Tesamorelin, for example, is an approved medicine for a defined metabolic indication; that approval says nothing about BPC-157, TB-500, CJC-1295, ipamorelin, GHK-Cu, MOTS-c or epitalon [124]. Nor are near-names equivalent: TB-500 is a short thymosin-beta-4 fragment, and BPC-157 free base and acetate are separately evaluated bulk substances [118,120,126]. The word *peptide* creates no class-wide permission.

Human evidence remains strikingly thin. FDA's review identified one randomised BPC-157 dataset: a 2005 meeting abstract in 53 people with ulcerative colitis, of whom 46 completed treatment. Disease Activity Index changed by -3.2 with BPC-157 and -1.6 with placebo, but the between-group confidence interval crossed zero and essential methods were missing [119]. Small uncontrolled reports included 17 intra-articular knee injections, 12 intravesical administrations and two intravenous volunteers; they cannot establish efficacy or characterise long-term risk [119]. CJC-1295 increased growth hormone two- to ten-fold and IGF-I 1.5- to three-fold in healthy adults, but the study measured pharmacodynamics, not healing, function or clinical recovery [123]. FDA found no human-use data for MOTS-c and insufficient human evidence for TB-500 and KPV [120].

The first modern controlled programmes are only beginning. A 120-person phase 2 trial of BPC-157 for MRI-confirmed hamstring injury, an 80-person phase 1/2 TB-500 cardiovascular study and a 60-person split-wound trial of topical GHK-Cu were recruiting without posted results at the review cut-off [125-127]. Trial registration is evidence that a question exists, not that an effect exists. Safety uncertainty is equally material: FDA identifies aggregation, peptide-related impurities, immunogenicity and incomplete API characterisation as class problems, and records serious events with intravenous ipamorelin and other growth-axis secretagogues [117].

The regulatory lesson is precise. A favourable advisory vote about whether a bulk substance may be eligible for pharmacy compounding would concern a supply channel, not marketing authorisation, efficacy or reimbursement [118-122]. Brazil removes even that ambiguity: ANVISA stated on 2 July 2026 that BPC-157, TB-500, GHK-Cu, CJC-1295 and ipamorelin were not registered in any category and were illegal for health use, including aesthetic use [128]. The curious physician's space is the registered trial or the approved peptide medicine, not mechanism-based prescribing of an unregistered research compound.

PRP: the indication matters more than the label

PRP is not one reproducible intervention. Leukocyte-rich and leukocyte-poor preparations, platelet concentration, activation, injection number and route vary, and combining PRP with marrow concentrate, SVF, microfragmented fat or recombinant growth factors creates a different intervention [30,41,129]. This heterogeneity explains why a positive meta-analysis and a negative high-quality trial can both be true without either settling the whole field.

For knee osteoarthritis, RESTORE randomised 288 participants to three weekly leukocyte-poor PRP or saline injections. At 12 months, the between-group pain difference was -0.4 points on an 11-point scale (95% CI -0.9 to 0.2), and the cartilage-volume difference was -0.2% (95% CI -1.9% to 1.5%): neither was

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significant [129]. A 2026 meta-analysis reported clinically relevant symptomatic benefit across follow-up periods, illustrating the remaining synthesis dispute [140]. AAOS states that PRP may reduce pain and improve function but grades the recommendation as limited, whereas ACR strongly recommends against PRP for knee or hip OA and AAHKS does not endorse routine use in advanced disease [64,131,132]. Honest consent must disclose that disagreement.

The signal is more coherent in lateral epicondylitis. In a 2025 meta-analysis of 26 randomised trials and 1,877 patients, corticosteroid performed better before two months, while PRP favoured pain at more than six months by a mean 1.60 points [134]; another synthesis found a similar long-term pattern but substantial heterogeneity [133]. The conclusion cannot be exported indiscriminately. A 240-person sham-controlled trial in chronic midportion Achilles tendinopathy found no functional benefit at six months [137,138]. A 98-person intradiscal trial found no significant clinical benefit and recorded one case of spondylodiscitis [135]. Meniscal-repair augmentation remains promising but rests on low-level studies [136], while the broader Cochrane assessment found very-low-quality evidence for soft-tissue injuries [139].

PRP therefore offers the best example of narrow authorisation done properly. Brazil permits it as an adjunct for four named musculoskeletal conditions, prohibits untested additives and refuses generic authorisation [30,41,43]. A physician may reasonably defend indication-specific PRP while rejecting claims of cartilage regeneration, universal efficacy or a class effect.

BMA and BMAC: more invasive is not more effective

BMA is unprocessed marrow aspirate; BMAC is its centrifuged concentrate. Neither term is synonymous with cultured mesenchymal stromal-cell therapy. BMAC typically contains less than 0.01% MSCs, making direct-to-consumer use of the phrase stem-cell therapy biologically and clinically misleading [132]. Product characterisation should report at least harvest site and technique, volume, total nucleated cells, viability and, where available, CFU-F or relevant cellular markers.

The controlled evidence does not establish superiority. In a bilateral-knee trial, 25 patients received BMAC in one knee and saline in the other; both knees improved, with no between-knee pain difference through six months [142]. In a 90-patient randomised trial, BMAC and leukocyte-rich PRP produced equivalent IKDC and WOMAC outcomes at two years [143]. In a 480-person four-arm phase 2/3 trial, BMAC, SVF and umbilical-cord tissue were not superior to corticosteroid at 12 months, and no group demonstrated MRI improvement [144]. A systematic review of eight level-1 trials and 937 patients found statistically significant BMAC advantages over hyaluronic acid at six and twelve months, but the differences remained below the minimum clinically important difference [141].

For hip osteoarthritis, a 2024 review found only five studies and 182 patients, without a numerical pooled estimate adequate to establish routine efficacy [145]. AAOS consequently makes no recommendation for or against BMAC in knee OA [146], and AAHKS states that PRP, BMAC and MSC injections cannot be recommended routinely for advanced hip or knee OA and have not been shown to restore cartilage [132]. The appropriate posture is prospective study or registry use with explicit disclosure that the added invasiveness and cost have not produced demonstrated superiority.

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Nanofat, MFAT and SVF: describe the process, not the marketing noun

Nanofat, micro fragmented adipose tissue and stromal vascular fraction are not interchangeable. Nanofat is mechanically emulsified to particles below 0.1 mm and is described as devoid of viable adipocytes; MFAT attempts to preserve microarchitecture; SVF is an isolated heterogeneous cellular fraction [154]. Mechanical sizing, filtration, enzymatic digestion, culture, cryopreservation and destination tissue each change both product identity and regulatory consequence.

For knee OA, a level-1 trial randomised 118 patients to MFAT or PRP. Both improved clinically, with no overall between-group difference. In moderate-to-severe OA, 75.0% of MFAT recipients versus 34.6% of PRP recipients reached the IKDC minimum clinically important difference, but adverse events were more frequent with MFAT and neither radiographs nor MRI showed structural change [149]. A second trial concluded equivalence at 12 months but stopped at 71 participants after a regulatory change and had only 56% power for its principal MCID [150]. Reviews describe heterogeneous symptomatic results and no consistent cartilage regeneration [151,152]. In the four-arm trial, SVF was not superior to corticosteroid and four SVF products failed endotoxin release criteria [144].

Aesthetic Nanofat evidence is less mature. A 15-person facial-wrinkle study reported improvement at seven months but lacked a meaningful control and did not provide numerical effect estimates in the indexed record [153]. The procedure also adds liposuction-related morbidity. It cannot be justified by importing knee MFAT evidence or by citing a narrative review as if it were a trial.

The regulatory hinge is manipulation and intended function. FDA treats adipose tissue as structural tissue and generally regards disruption to isolate SVF as more than minimal manipulation [6,148]. An EMA/CAT opinion found one specific autologous SVF preparation for cosmetic lipofilling outside the ATMP definition, but expressly non-generic classification principles prevent that result from becoming a class-wide exemption [155,158]. Japan likewise assigns risk class according to culture and homologous destination: fat used for breast reconstruction and adipose cells infused for diabetes are not the same regulatory act [172].

Exosomes and extracellular vesicles: compelling biology, immature translation

An extracellular-vesicle preparation is not defined by the word exosome on a vial. Source cell, culture conditions, isolation, purification, particle and protein dose, identity markers, potency, sterility and storage determine what the intervention actually is. In a 2024 scoping review of 40 published human studies, only eight were randomised, 35 had no control group and 16 reported no EV characterisation; 605 people had received an EV intervention across three decades [164]. This is a translation programme, not a mature therapeutic class.

The most persuasive positive study was a 28-person, 12-week split-face trial combining an adipose-derived exosome-containing solution with microneedling. The treated side had a better Global Aesthetic Improvement Scale result at the final visit ($P=.005$), but the study was small, used surrogate cosmetic endpoints and did not establish a general injectable therapeutic effect [165]. The safety record includes seven cases of necrotising granulomas after aesthetic treatment and a case of leukocytoclastic vasculitis, eccrine necrosis and skin necrosis after intradermal lyophilised material [166,167]. FDA and CDC have also reported serious adverse events and bacterial infections associated with unapproved products [12,162].

Regulatory gaps make the risk harder to observe. FDA treats exosomes used to treat disease as drugs and biological products requiring premarket review and has continued enforcement against marketed products [12,161,163]. Japan expressly leaves EVs outside ASRM, yet a survey identified 669 medical institutions advertising exosome or culture-supernatant interventions; the same gap excludes these interventions from the ASRM adverse-event system [168-170]. In the European Union, human-origin materials cannot be converted into an injectable cosmetic: cosmetics law prohibits human-origin cells, tissues or products and excludes injected products from the cosmetic definition [159]. In Brazil, the Brazilian Society of Dermatology reports that ANVISA's cosmetic classification confines such products to topical use and does not permit injection [173].

Exosomes therefore supply the clearest test of the article's silence rule. A gap in a provision law does not create authorisation; a cosmetic registration does not become an injectable indication; and the absence of mandatory adverse-event capture cannot be offered as evidence of safety. Until a specific, characterised product demonstrates clinical benefit and obtains the permissions required for its route and indication, the legitimate path is an authorised trial, not a cash-pay injection.

#	Divergence	Sanitary layer	Professional layer	Practical lesson
1	PRP in Brazil, Sept 2024 - Jul 2026	ANVISA: conventional therapy product, no registration required [30]	CFM Res. 2.128/2015: clinical use experimental, CEP/CONEP only [40]	Sanitary permission coexisted with professional prohibition for almost two years
2	PRP in the United States	Separator device cleared, Class II, code ORG [14]	No cleared therapeutic claim; 510(k) states PRP “has not been evaluated for any clinical indications” [13]	A cleared instrument is not a cleared treatment
3	Medical devices in Brazil generally	RDC 751/2022 notification or registration = right to manufacture, import, sell [31]	RDC 848/2024 places proof of indication and performance on clinical evaluation [32]	“ANVISA-registered” never means “indication proven”
4	Specialty recognition vs product availability	Registered PTAs exist in Brazil (Kymriah, Yescarta, Carvykti, Luxturna, Zolgensma, Upstaza, Elevidys) [35,36]	“Medicina regenerativa” and “longevidade” are neither specialties nor areas of practice [49]	Approved products, unrecognised field: practise within your specialty, do not advertise a new one
5	Hormone implants (“chip da beleza”)	ANVISA prohibited use and sale in Oct 2024, then modulated the measure in Nov 2024 to permit therapeutic use [50,51]	CFM had already restricted androgenic/anabolic prescription for aesthetic and performance purposes	The professional norm came first; the CFM itself called the initial blanket sanitary ban excessive [51]
6	Profession versus profession	Not a sanitary question	Res. 2.464/2026 Art. 8 declares PRP indication, application and follow-up to be atos médicos [41]; Cofen filed a public civil action against Arts. 8-12 [44]	Professional authorisation is contested between councils, not only against regulators
7	Practice-of-medicine carve-outs are unstable	LDT rule vacated Mar 2025 and text reverted Sept 2025 [21]	Two appellate courts rejected practice-of-medicine defences for SVF, 2021 and 2024 [23,24]	The same shield narrowed for cell therapy and widened for diagnostics in the same period
8	EU hospital exemption vs Japan ASRM	EU: non-routine, custom-made, hospital-only, same Member State,	Japan: clinic or hospital provision after ASRM plan and committee opinion; 95,168	Both authorise provision without product MA, but Japan's space is vastly broader

		individual prescription [67,73]	treatment patients in FY2024 [96,99]	
9	Conditional authorisation	EU: four cumulative criteria, 1-year renewable authorisation [81]	Japan: efficacy need only be predicted; up to 7 years plus 3-year extension [107,108]	The label 'conditional' conceals radically different evidence and exposure periods
10	PRP classification	EU: formally listed as requiring a SoHO regulatory-status opinion [90]	Japan: Class III ASRM provision; Brazil: conventional product without registration, then CFM-limited act [30,41,99,114]	The same autologous preparation is unclassified, safety-regulated or professionally indication-limited
11	Exosomes	EU and Japan: no authorised product; EU status boundary unresolved; Japan outside ASRM [71,90,100,114]	US: unapproved drug/biologic [12]; no primary Brazilian exosome norm confirmed	A regulatory gap is never evidence of permission
12	Marketing status vs reimbursement	EU conditional MA does not itself settle national reimbursement	Japan reimbursed HeartSheet during a 9-year conditional period before efficacy failed [109,112,113]	Funding is a fifth permission and can amplify the consequences of weak entry evidence

Table 4: Twelve documented divergences across product, provision and professional regulation.

The norm moves, and clinicians move it

The strongest empirical answer to the claim that regulation is a wall rather than a frontier comes from decisions in which authorities changed status because evidence matured, or withdrew privilege because it did not. Brazil supplies two constructive trajectories; Europe and Japan supply the necessary controls. Ozone therapy. Classified as an experimental procedure in 2018, it was authorised by Resolução CFM nº 2.445 of 21 August 2025 for a defined set of indications — four wound-related and two musculoskeletal — with the 2018 instrument revoked [45,46]. Seven years from “experimental” to “authorised for named indications”.

Platelet-rich plasma. Classified as experimental by Res. 2.128/2015 [40], it was authorised as an adjuvant for four musculoskeletal conditions by Res. 2.464/2026 [41,43]. Eleven years, and the authorisation arrived with the participation of the relevant specialty society in the Council's thematic plenary [65]. Neither transition happened because clinicians ignored the norm. Both happened because evidence accumulated in forms the Council could evaluate, and because the specialty societies engaged with the recognition process that Res. 2.428/2025 now formalises [39]. That is the central practical claim of this article: the frontier is moved by data, not by defiance. Every patient treated outside a protocol and never followed up is a patient whose experience cannot contribute to moving it; every well-documented cohort, registry entry and published trial — including the negative ones — is a brick in the road.

The European adaptive bargain. Holoclar shows that conditional authorisation can mature into standard authorisation when obligations are fulfilled [86]. Alofisel shows the converse: after a confirmatory trial failed to verify benefit, the product was withdrawn and the Commission revoked its authorisation [85,95]. Roctavian shows a third pattern, in which a product may retain standard authorisation while long-term follow-up and registry obligations continue [88]. Adaptation is thus not leniency. It is a reversible evidence contract.

The Japanese stress test. Heart Sheet received conditional and time-limited approval after an uncontrolled

seven-patient study, entered reimbursed practice, and remained available for roughly nine years before full approval was refused when efficacy was not confirmed [109,112,113]. Stemirac was conditionally approved after 13 analysed patients in an uncontrolled single-centre study; its full-approval application was filed in November 2025, but the outcome was not established at the time of this review [110,111]. These cases show why early access must be coupled to credible comparators, enforceable milestones and an exit that functions before uncertain care becomes an entitlement.

Honesty about the evidence is part of the argument, not a concession against it. For knee osteoarthritis, the European ESSKA-ORBIT consensus on injectable orthobiologics supports the use of PRP within defined parameters [61], and a 2025 meta-analysis of randomised trials found clinically significant improvement influenced by platelet concentration [62]; the American Academy of Orthopaedic Surgeons guideline on non-arthroplasty management of knee osteoarthritis rates the supporting evidence for PRP as limited [64]. For lateral epicondylitis, by contrast, a 2026 meta-analysis of randomised trials found that PRP did not improve pain or function compared with placebo [63] — and that condition is nonetheless among the four authorised by Res. 2.464/2026. A physician who cites [61] and [62] to a patient while suppressing [63] is not defending regenerative medicine; they are damaging it. The credibility of the field rests on our willingness to publish and quote our own null results.

The cost of the alternative is measurable. In 2021 there were 1,480 businesses operating 2,754 clinics marketing purported stem-cell interventions direct to consumers in the United States, more than four times the 2016 figures of 351 businesses and 570 clinics [54]; of those 1,480, 1,023 were still online and selling in February 2023, with 300 of them marketing allogeneic perinatal interventions across 562 clinics [55]. The global market in unproven stem-cell interventions has been estimated at roughly US\$2.4 billion and 60,000 patients annually [56]. The clinical harm is not hypothetical: three patients suffered vision loss after intravitreal injection of autologous “stem cells” for age-related macular degeneration, reported in the New England Journal of Medicine in 2017 [53]. The International Society for Cell and Gene Therapy opposes premature commercialisation of unproven cell- and gene-based interventions while supporting access through pathways that require evidence, and notes the specific pathology of “pay-to-participate” studies that are unblinded, uncontrolled and unauthorised [58]. Analyses of the field have documented that unproven interventions complicate the development of a rigorous evidence base [57] and erode the regulatory authority and public trust on which legitimate translation depends [56]. FDA has for its part published consumer-facing guidance urging patients to verify whether a regenerative product is FDA-approved or being studied under an IND before accepting treatment [66]. Every one of those clinics makes the next resolution harder to win.

An operational framework: what a physician may legitimately do

(Table 5) converts the preceding analysis into the decision a clinician actually faces. It retains the Brazilian practitioner as its clinical reference point while showing how the same status maps onto the United States, European Union and Japan.

Status of the intervention	Brazilian requirements	Comparative route: US / EU / Japan	May it be charged for?	May it be advertised?
Recognised procedure with	Product processed per NT 29/2024;	US: lawful product plus	Yes, as ordinary	Yes, factually

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Status of the intervention	Brazilian requirements	Comparative route: US / EU / Japan	May it be charged for?	May it be advertised?
authorised indication (e.g. PRP as adjuvant in the four conditions of Res. 2.464/2026)	autologous; adjuvant framing; indication, application and follow-up performed by a physician; standard record-keeping and consent [30,41]	practice-of-medicine rules [4,13]. EU: central MA or lawful national route [72-75]. Japan: approved product within conditions, or ASRM plan if outside them [96]	clinical care	and within advertising rules; no specialty claim for an unrecognised field [37,49]
Registered medicine used off-label	Permitted, following CFM norms in force (Res. 2.327/2022 Art. 3), with documented rationale and consent [38]	US: permitted medical practice, promotion restricted [4]. EU: physician responsibility under national law [80]. Japan: use outside approved conditions falls into ASRM [96]	Yes	No promotion of the unapproved indication
Experimental procedure (e.g. cell-based orthobiologics in Brazil)	Only within an approved protocol: ethics committee approval, Lei 14.874/2024 framework, ANVISA authorisation where a PTA is involved; Code of Ethics Arts. 100 and 102 [26,27,33,37,47,48]	US: IND, expanded access or Right to Try [7,17,18]. EU: authorised trial, hospital exemption or national compassionate/named-patient route [72-75]. Japan: ASRM research plan or PMD Act trial [96]	No. Parecer CFM 2/2020 states such treatments may not be advertised or commercialised [48]	No. Code of Ethics Art. 113 restricts communication to the scientific milieu [37]
Unproven intervention for an individual patient outside a trial	Only under the conjunctive conditions of Declaration of Helsinki para. 37: approved options inadequate AND trial enrolment impossible; expert advice sought first; consent obtained; data recorded and shared; must subsequently become the object of research [52]	US: single-patient expanded access [17]. EU: named-patient or compassionate route under national rules [74]. Japan: ASRM plan and committee route [96]	Cost recovery only where the applicable framework permits it; never as a commercial offering	Never
Product without lawful market status (e.g. exosome preparations marketed as therapy)	No sanitary basis identified; see Section 13 on the absence of a confirmed Brazilian norm	US: unapproved drug/biologic [12]. EU: no authorised exosome ATMP and unresolved SoHO boundary [71,90]. Japan: no approved product and outside ASRM pending review [100,114,115]	No	No

Table 5: Global decision framework by intervention status.

Four rules of thumb summarise the table. First, classify before you treat. Ask what the material has become after processing and intended use, not what anatomical name it had at harvest. Second, separate the product from the act and from the route of provision. A cleared device does not approve its output; an approved product does not automatically authorise every indication; a hospital exemption or ASRM plan does not create a general marketing authorisation; and sanitary silence does not erase professional law. Third, when the answer is experimental, prefer the protocol. It converts uncertain care into knowledge. Fourth, do not confuse payment with proof. HeartSheet demonstrates that reimbursement can precede and outlive reliable confirmation of efficacy [109,112,113].

The line between the curious physician and the entrepreneur of hope

The 2024 revision of the Declaration of Helsinki, adopted by the 75th WMA General Assembly, states at paragraph 37 that when an unproven intervention is used to attempt to restore health or alleviate suffering for an individual patient because approved options are inadequate or ineffective and enrolment in a clinical trial is not possible, it should subsequently be made the object of research designed to evaluate safety and efficacy; that physicians must first seek expert advice, weigh possible risks, burdens and benefits, and obtain informed consent; that they must record and share data when appropriate and

avoid compromising clinical trials; and that such interventions must never be undertaken to circumvent the protections for research participants set out in the Declaration [52].

That single paragraph is, in effect, the professional charter of the curious physician, and three of its features are load-bearing. It is conjunctive: inadequate approved options and impossible trial enrolment, not either alone. It is prospectively obligating: the intervention “should subsequently be made the object of research”, which converts a one-off act into a research duty. And its final sentence supplies the anti-circumvention principle that maps precisely onto the CFM's position that cell therapies may not be advertised or commercialised [48] and onto FDA's position that an IND is not marketing authorisation [7].

From this, six operational commitments follow. They are not a regulatory checklist; they are what distinguishes a physician who deserves the latitude the norms allow from one who is merely using it.

1. Classify honestly. Determine the product's status under the applicable product law before, not after, treating, and use the formal consultation mechanisms that exist for uncertain cases [8,70,104].
2. Separate product, provision and professional act. Confirm each permission independently: marketing authorisation, trial or special provision route, and medical-professional legitimacy [30,38,72-75,96].
3. Prefer the protocol. Where an act is experimental, the approved protocol is not an obstacle but the route that lets the patient's experience count for anyone else [33,37,39,75,96].
4. Consent in writing, in the patient's language, with the uncertainty named. State that the intervention is not recognised for the indication, what the alternatives are, what is unknown, and what the costs are [37,52].
5. Register outcomes prospectively and publish, including negatives. The 2026 null result for PRP in lateral epicondylitis [63] is as much a contribution of the field as the positive knee data [61,62]; Alofisel and HeartSheet show why confirmatory failure must change status [85,95,109,112].
6. Never advertise, and never sell, the unrecognised. This is a recurrent enforcement boundary in the United States, Europe, Japan and Brazil, and the practice that has cost regenerative medicine most of the credibility it has lost [12,37,48,58,72,91,101,102].

There is a legitimate scholarly defence of the adaptive approach that all of this presupposes. Regulators have adapted existing frameworks to regenerative medicine and, where adaptation proved insufficient, built new ones intended to be flexible and forward-facing, with the central challenge being the balance between safety, efficacy, quality, manufacturing consistency, rapid translation, innovation and access [59]. The jurisdictional dispute over autologous cell therapy was recognised in the legal literature more than a decade ago as raising precisely the questions of access, alternative oversight mechanisms and the peculiar difficulty of autologous products that remain unresolved today [60]. Regenerative medicine's interest lies in participating in that regulatory science, not in claiming exemption from it.

Limitations

This is a perspective article and its argument is doctrinal rather than empirical. Several specific limitations

should be stated plainly, because a paper arguing for regulatory honesty cannot be selectively opaque about its own gaps.

- **Exosomes in Brazil:** No ANVISA resolution, technical note or opinion, and no CFM resolution or opinion, specifically addressing exosomes or extracellular vesicles was confirmed from a primary official source in preparing this article. The Brazilian position is therefore stated as unconfirmed, not as permissive. The American position is documented [12].
- **Resolução CFM nº 2.464/2026:** The opening articles were obtained from the Council's published text; the advertising, research and revocation provisions are described from the Council's own news release and the Cofen filing rather than quoted from the full primary text [41,43,44]. The published DOU record and the CFM communication also differ as to whether Res. 2.128/2015 is formally revoked, and as to the page of publication. Readers should consult the consolidated text.
- **Pending litigation:** The disposition of the Cofen public civil action against Articles 8 to 12 of Res. 2.464/2026 [44], and of the certiorari petition in California Stem Cell Treatment Center [25], are not established here.
- **Act numbers for the hormone-implant measures:** The October and November 2024 ANVISA measures are described through the CFM's contemporaneous communications [50,51]; the resolution numbers were not confirmed from a primary sanitary source.
- **Market data:** No Brazil-specific quantification of the direct-to-consumer orthobiologic or stem-cell market was located; the figures cited are United States and global [54,55,56].
- **Society positions:** Consensus or position documents from several relevant regenerative-medicine societies were not located as primary sources and are therefore not cited; the specialty-society engagement referenced in Section 7 rests on the Brazilian orthopaedic society's account of the CFM thematic plenary [65].
- **European Union:** Hospital exemption remains implemented nationally, and this review does not quantify authorisations by Member State or resolve the final form of pending pharmaceutical-legislation reform. PRP, secretomes and exosomes were still listed for regulatory-status clarification by the SoHO Coordination Board in March 2026 [76,90].
- **Japan:** The outcome of Nipro's November 2025 full-approval application for Stemirac was not established [110]; national totals for certified committees, providing institutions and adverse events were not confirmed. Exosomes remained outside the ASRM framework, while a July 2026 working group was still considering regulation and the appropriateness of private-practice provision [100,115].
- **Clinical evidence audit:** Section 8 is a decision-focused narrative synthesis, not a systematic review or meta-analysis. It prioritises controlled trials, systematic reviews and authoritative guidelines but does not claim exhaustive coverage of every indication, formulation or proprietary preparation.
- **Product heterogeneity:** PRP, BMAC, MFAT, nanofat and EV preparations lack universally applied potency or dose specifications. Evidence for one preparation, source, route or indication should not be transferred to another without direct comparability.
- **Emerging peptide trials:** The registered BPC-157, TB-500 and GHK-Cu trials had no posted results

at the September 2026 cut-off [125-127]. Their inclusion documents prospective investigation, not clinical efficacy.

- **Brazilian exosome source:** The injectable-use restriction is described through the Brazilian Society of Dermatology's technical note reporting ANVISA's cosmetic classification [173]; the underlying primary ANVISA classification instrument was not independently confirmed.
- **Translation and legal interpretation:** Japanese statutory analysis relied on the official English translation of the ASRM and English-language PMDA/MHLW materials where available. National implementation, reimbursement and professional-law questions require local counsel or competent-authority confirmation before clinical reliance.
- **Currency:** Regulatory facts are stated as of retrieval in September 2026. Every instrument cited should be re-verified before it is relied on clinically, and the FDA count of approved cellular and gene therapy products [11] is time-stamped to retrieval rather than to a stated page revision date.

Conclusion

Science moves; norms follow, unevenly and at different speeds. Brazil shows professional recognition advancing from experimental to defined clinical use; the United States shows product classification being tested through enforcement and appellate litigation; Europe shows conditional authorisation maturing, persisting under obligations or being withdrawn; and Japan shows both the access created and the uncertainty amplified when medical provision and product approval follow separate statutes.

A physician standing in that landscape does not have to choose between being an obedient technician and being an outlaw. The global comparison defines a real and usable space only after four permissions are answered separately: what the intervention is, whether the product may be marketed, whether it may be provided through a trial or special statutory route, and whether the professional act is legitimate. A fifth question — who will pay — must never be allowed to answer the first four. Within that architecture, the responsible physician uses protocols and lawful access routes, names uncertainty in written consent, follows every patient, publishes negative as well as positive outcomes, and refuses to advertise evidentiary uncertainty as therapeutic fact.

Regenerative medicine deserves defending, and the strongest defence available to it is not the assertion of clinical freedom against regulation. It is a jurisdiction-independent discipline of reversible permission, prospective learning and enforced exit when benefit is not confirmed. The curious physician's legitimate space is therefore neither a loophole nor a waiting room. It is an evidence-generating practice bounded by classification, authorisation, provision, professional duty and transparent accountability. That is slower than a marketing campaign, but it is the only path by which promising biology becomes trustworthy medicine.

The five intervention classes make that final distinction concrete. PRP can be clinically defensible for a narrow indication without being structurally regenerative; BMAC and adipose products can be biologically rich without being superior to simpler comparators; experimental peptides can be pharmacologically active without being clinically validated; and exosome biology can be transformative while today's injectable preparations remain uncharacterised and unauthorised. The physician's task is not to extinguish

promise, but to state exactly where promise ends and permission begins.

Declarations

Ethics approval

Not applicable. This perspective article involved no human participants, human material or identifiable human data.

Consent for publication

Not applicable.

Availability of data and materials

All normative instruments, guidance documents, court decisions and published studies discussed are publicly available at the URLs given in the reference list.

Competing interests

The authors denied any relationship with manufacturers of orthobiologic devices, energy-based platforms, cell-processing systems or advanced therapy products, and any role in professional-society regulatory advocacy.

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