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# Autologous Fat and its Derivatives in Clinical Practice: A Narrative Review of Global Regulatory Frameworks

**Devi Prasad Mohapatra, Srinath R, Tanya Gupta**

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## ABSTRACT

Autologous fat grafting has transitioned from traditional reconstructive soft-tissue filling to an expansive platform for reconstructive surgery, regenerative medicine, and point-of-care cellular therapy. This clinical evolution has driven the development of various adipose-derived derivatives, including micro-fat, nano-fat, micro-fragmented adipose tissue (MFAT), and enzymatically isolated stromal vascular fraction (SVF). However, clinical translation is complex due to a highly fragmented global regulatory landscape.

Central to international oversight are the thresholds of "minimal manipulation" and "homologous use". Crossing these thresholds, such as utilizing enzymatic digestion to isolate SVF or applying adipose tissue for non-homologous indications like joint regeneration, generally triggers classification as a drug, biologic, or Advanced Therapy Medicinal Product (ATMP). Such classifications demand stringent clinical trial validation, Good Manufacturing Practice (GMP) compliance, and pre-market approvals under frameworks like the US FDA and EU EMA. Conversely, jurisdictions like Australia and Japan offer alternative pathways, including hospital-based exclusions or tiered clinical practice oversight under the Act on the Safety of Regenerative Medicine (ASRM). Evolving guidelines under India's CDSCO similarly categorise enzymatic processing as substantial manipulation, defining the final output as a "New Drug".

This narrative review compares these regulatory pathways, highlighting how jurisdictional variation drives a geographic split in clinical innovation and underscores the necessity of regulatory literacy for clinicians and device developers alike.

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## INTRODUCTION

Autologous fat grafting has evolved from a reconstructive and aesthetic soft-tissue filling technique into a broader platform for tissue repair, regenerative surgery, and point-of-care cellular therapy. Conventional fat grafting is widely used in plastic surgery for restoration of contour, correction of volume deficiencies, scar modulation, breast reconstruction, facial rejuvenation, and treatment of post-traumatic or post-surgical deformities. The appeal of adipose tissue lies not only in its abundance and ease of harvest, but also in its biological composition. In addition to mature adipocytes, lipoaspirate contains stromal, vascular, immune, and progenitor cell populations that may contribute to angiogenesis, extracellular matrix remodeling, and tissue repair.

*Department of Plastic Surgery, JIPMER, Pondicherry, India*
***Correspondence:** *Devi Prasad Mohapatra (devimohapatra1@gmail.com)*

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The expansion of clinical indications has been accompanied by the development of several adipose-derived products and processing techniques. These include macro-fat and micro-fat grafting for structural volume restoration, nano-fat for skin quality and scar modulation, mechanically fragmented adipose tissue, and stromal vascular fraction obtained either by mechanical or enzymatic methods. While, these procedures are often performed using autologous tissue at the point of care, their regulatory classification varies substantially depending on the degree of processing, intended clinical use, and jurisdictional interpretation of cell- and tissue-based products.

Two regulatory concepts are central to the global oversight of autologous fat and its derivatives: minimal manipulation and homologous use. Minimal manipulation generally refers to processing that does not alter the relevant structural or biological characteristics of the harvested tissue. Homologous use refers to the use of a tissue for the same basic function in the recipient site as in the donor site. In the context of adipose tissue, these distinctions are critical. Fat grafting for soft-tissue contour restoration is more likely to be regarded as homologous, whereas the use of adipose-derived cellular products for joint disease, neurological disorders, or other non-adipose indications may be interpreted as non-homologous. Similarly, washing, filtering, centrifugation, or sizing may fall within minimal manipulation in several jurisdictions, whereas enzymatic digestion, cell isolation, culture expansion, or extensive cell selection commonly trigger classification as a drug, biologic, or advanced therapy medicinal product.

The regulatory landscape remains heterogeneous. In the United States, the Food and Drug Administration applies a risk-based framework for human cells, tissues, and cellular and tissue-based products, with strict interpretation of minimal manipulation and homologous use. In the European Union, adipose-derived products may fall under the Advanced Therapy Medicinal Products framework when substantially manipulated or used for non-homologous purposes. Australia, Japan, and India have adopted distinct pathways that differ in their treatment of hospital-based exemptions, point-of-care processing, clinical oversight, and investigational use. These variations influence not only clinical practice, but also device development, patient access, research translation, and the marketing of unproven regenerative interventions.

For plastic surgeons and clinicians using autologous fat-based therapies, regulatory literacy is now essential. Procedures that appear technically similar in the operating room may be treated differently by regulatory agencies depending on the method of processing and intended indication. A clearer understanding of these frameworks is necessary to promote ethical clinical translation, protect patients from inadequately validated interventions, and guide responsible innovation in adipose-derived regenerative therapies.

This narrative review aims to summarize and compare the regulatory frameworks governing the clinical use of autologous fat and its derivatives across selected major jurisdictions. The review focuses on point-of-care autologous fat grafting, mechanically processed adipose tissue, nano-fat, micro-fragmented adipose tissue, stromal vascular fraction, and culture-expanded adipose-derived cellular products, with particular emphasis on the regulatory thresholds of minimal manipulation, homologous use, same-surgical-procedure exceptions, hospital exemptions, and requirements for clinical trial or marketing authorization.

The primary outcome of interest was the regulatory status of autologous fat and its derivatives in clinical practice across selected jurisdictions. Secondary outcomes included identification of common regulatory thresholds, practical implications for clinicians, implications for device developers, and the influence of regulatory variation on clinical translation and patient access.

## MATERIALS AND METHODS

This article was designed as a narrative review of international regulatory frameworks applicable to the clinical use of autologous fat and adipose-derived products. The review focuses on autologous adipose-derived interventions used in clinical practice or translational regenerative medicine. These include conventional autologous fat grafting, micro-fat, nano-fat, mechanically fragmented, or micro-fragmented adipose tissue, stromal vascular fraction,

adipose-derived stem/stromal preparations, and culture-expanded adipose-derived cellular products. The review emphasizes point-of-care procedures in which adipose tissue is harvested, processed, and re-administered to the same patient, either during the same surgical episode or within a regulated clinical pathway.

The principal regulatory concepts examined were minimal manipulation, substantial manipulation, homologous use, non-homologous use, same-surgical-procedure exemptions, hospital exemptions, device-level oversight, clinical trial requirements, good manufacturing practice requirements, and marketing authorization pathways.

The jurisdictions selected for comparison were the United States, the European Union, Australia, Japan, and India. These regions were chosen because they represent distinct and influential regulatory models for autologous cell- and tissue-based interventions. The United States and European Union provide mature risk-based regulatory systems with well-defined pathways for biologics and advanced therapy medicinal products. Australia and Japan provide examples of frameworks that incorporate specific pathways for autologous or regenerative medicine procedures within hospital or clinical practice settings. India was included because of its evolving regulatory position on stem cell and regenerative medicine products, particularly in relation to clinical trials and investigational cell-based interventions.

Relevant literature and regulatory documents were identified through searches of biomedical databases, regulatory agency websites, government publications, legal guidance documents, and peer-reviewed articles addressing adipose tissue-derived therapies. Searches were conducted using combinations of the following terms: "autologous fat grafting," "adipose-derived stem cells," "stromal vascular fraction," "micro-fragmented adipose tissue," "nano-fat," "minimal manipulation," "homologous use," "same surgical procedure exception," "advanced therapy medicinal product," "biologicals framework," "regenerative medicine regulation," "cell therapy regulation," "FDA HCT/P," "EMA ATMP," "TGA autologous cell therapy," "Japan Act on the Safety of Regenerative Medicine," and "India stem cell regulation."

## RESULTS

Information was extracted under the following headings: regulatory authority, governing statute or framework, classification of autologous fat and derivatives, criteria for minimal manipulation, interpretation of homologous use, treatment of enzymatic digestion and cell isolation, treatment of mechanical processing, availability of same-surgical-procedure or hospital-based exemptions, requirements for clinical trial authorization, and requirements for manufacturing or marketing approval.

## DISCUSSION

### Biomechanical Classification and Regulatory Thresholds

Autologous fat grafting has expanded from conventional aesthetic lipofilling to advanced applications in regenerative medicine, reconstructive surgery, and orthopedics.[1,2] Human adipose tissue acts as a structural lipid reservoir and a biological niche containing a heterogeneous population of cells, including adipose-derived stem/stromal cells (ASCs), endothelial progenitor cells, pericytes, and macrophages,[3,4,5] Accessing these regenerative components at the point-of-care (POC) involves two primary processing pathways: mechanical fragmentation to yield micro-fragmented adipose tissue (MFAT), or enzymatic digestion, typically with collagenase, to isolate the stromal vascular fraction (SVF).[6,7]

Globally, regulatory authorities apply risk-based frameworks to classify these autologous POC procedures.[10] The core legal determination rests on whether the processing of harvested lipoaspirate constitutes "minimal manipulation" and whether the clinical re-implantation is for "homologous use".[12] When a procedure exceeds these thresholds, processed fat is no longer regulated as a standard tissue graft under clinical practice guidelines; instead, it is classified as a commercial drug, biologic, or Advanced Therapy Medicinal Product (ATMP), requiring stringent pre-market approvals, Good Manufacturing Practice (GMP) compliance, and clinical trial validation.[5,8,9]

## Jurisdictional Analysis of Point-of-Care Regulatory Frameworks

*United States: Food and Drug Administration (FDA)*

The United States FDA regulates human cells, tissues, and cellular and tissue-based products (HCT/Ps) under a tiered, risk-based system codified in 21 CFR Part 1271.[10] Under Section 361 of the Public Health Service (PHS) Act, HCT/Ps can be clinical tools without pre-market approval, if they meet all criteria in 21 CFR 1271.10(a): minimal manipulation, homologous use, no combination with non-exempt agents, and no systemic, or metabolic dependency unless designated for autologous use.[11,12]

The FDA classifies adipose tissue as structural tissue. Under 21 CFR 1271.3(f)(1), minimal manipulation for structural tissue means that processing does not alter the original relevant characteristics of the tissue relating to its utility for reconstruction, repair, or replacement, which are defined as cushioning, buffering, and support.[12] Consequently, enzymatic digestion using collagenase to isolate SVF is legally classified as "more-than-minimal manipulation" because it destroys the structural tissue matrix.[7] Furthermore, the FDA narrow-defines homologous use: adipose tissue transplanted for breast reconstruction or volume augmentation is considered homologous, whereas its injection into joints to treat orthopedic conditions (e.g., knee osteoarthritis) is non-homologous because joint lining is not adipose tissue.[12,15]

The "Same Surgical Procedure Exception" under 21 CFR 1271.15(b) exempts clinical establishments from Part 1271, if the HCT/P is harvested and re-implanted into the same patient in its original form within a single operation.[10] While basic processing steps like rinsing, cleansing, sizing, and centrifugation are permitted under this exception, enzymatic dissociation, or extensive cell selection violates the requirement that the tissue remain in its "original form," thereby subjecting the clinic to federal prosecution for distributing an unapproved drug under Section 351 of the PHS Act.[16,17]

## FDA and CBER Device-Level Regulations

To consolidate point-of-care cell-processing oversight, the FDA transferred regulatory authority over devices that process autologous HCT/Ps from the Center for Devices and Radiological Health (CDRH) to the Center for Biologics Evaluation and Research (CBER).[18,19,20] This administrative shift targets devices where the biological output mediates the intended therapeutic effect.[23] CBER created specific product codes under 21 CFR 878.5040 (Suction Lipoplasty System) to distinguish and regulate these point-of-care processing technologies.[21,22,23] (Table 1)

**Table 1:** List of the Center for Biologics Evaluation and Research (CBER) created product codes for point-of-care processing technologies.

| Product Code | Device Classification & Title | Legal Definition | Regulatory Agency Jurisdiction | Permissible Clinical Use |
|---|---|---|---|---|
| QKL [cite: 23] | Class II: Lipoaspirate washing system for aesthetic body contouring | A non-suctioning system designed to wash, filter, concentrate, and/or fragment autologous adipose tissue without further manipulation (e.g., no enzymes or cell selection)23 | CBER (Center for Biologics Evaluation and Research) 21,23 | Restricted to aesthetic and reconstructive body contouring of soft tissues |
| QUB [cite: 23] | Class II: Suction Lipoplasty System for Removal and Transfer23 | An integrated system containing a powered suction pump, canisters, and syringes designed for the removal and immediate transfer of autologous fat without further manipulation23 | CBER (Center for Biologics Evaluation and Research)20,23 | Restricted to aesthetic body contouring and reconstructive procedures23 |
| QPB [cite: 23] | Class II: Suction Lipoplasty System23 | Standard suction systems used exclusively to aspirate and remove fat tissue from the patient's body for disposal23 | CDRH (Center for Devices and Radiological Health)23 | Restricted to fat tissue removal with no return or re-implantation to the body23 |

### European Union: European Medicines Agency (EMA)

In the European Union, cell therapies are governed by Regulation (EC) No 1394/2007, which establishes the centralized framework for Advanced Therapy Medicinal Products (ATMPs).[24,25] An autologous cell- or tissue-based product is classified as an ATMP, specifically as a somatic cell therapy medicinal product (sCTMP), or a tissue-engineered product (TEP), if it contains engineered cells that have undergone "substantial manipulation" or are intended for a "non-homologous" clinical function.[13]

The EMA's Committee for Advanced Therapies (CAT) provides scientific recommendations on ATMP classifications.[26,27] CAT has determined that enzymatic digestion of lipoaspirate to isolate SVF is a substantial manipulation, as it destroys the extracellular matrix and alters the biological characteristics of the tissue. Therefore, autologous, enzymatically isolated SVF is classified as an ATMP and requires centralized marketing authorization.[5]

Conversely, mechanical processing of fat (e.g., Cell-Assisted Lipofilling or CAL, and MFAT) is considered non-substantial manipulation, as the essential function of the cellular matrix remains identical to the donor fat.[28,29] However, if mechanically processed adipose tissue is applied to a non-homologous site to perform a non-homologous function, such as injecting MFAT into a patient's temporomandibular joint (TMJ) or knee joint to treat osteoarthritis, the heterologous clinical application automatically classifies the graft as an ATMP. Under these conditions, the procedure must comply with GMP standards and undergo full clinical trial authorization.[5]

For small-scale clinical applications, Member States can apply for the "Hospital Exemption" under Article 3(7) of Directive 2001/83/EC.[30] This pathway allows the non-routine manufacture and clinical use of custom-made, non-standardized ATMPs within a single hospital environment under the exclusive responsibility of a medical practitioner, bypassing centralized EMA marketing authorization while adhering to national GMP licensing.[5]

### Australia: Therapeutic Goods Administration (TGA)

The TGA regulates human cell and tissue-based products under the Biologicals Regulatory Framework, which assigns risk-based classes from Class 1 (lowest risk) to Class 4 (highest risk).[31,32] The TGA updated its framework to address the unregulated marketing of unproven autologous cell therapies.[32]

Under the revised guidelines, autologous human cell and tissue products are excluded from TGA regulation via the Excluded Goods Order only if they satisfy strict clinical criteria: the product must be collected and manufactured in an accredited hospital, the processing and administration must be under the direct supervision of a registered medical or dental practitioner for a patient under their care, and the therapy must not be advertised directly to consumers.[32]

When these conditions are met, the exclusion from TGA oversight applies regardless of the level of manipulation (including enzymatic SVF isolation) or the clinical application.[35] If the procedure is performed outside an accredited hospital (e.g., in a private clinic), the product falls within the Biologicals Regulatory Framework.[32] If it undergoes minimal manipulation (such as freezing, trimming, or washing) and is intended for homologous use, it is regulated as a Class 2 Biological.[33] If the product undergoes enzymatic digestion or is used for non-homologous indications, it is classified as a Class 3 or Class 4 Biological, requiring pre-market registration, GMP-compliant manufacturing, and randomized clinical trials.[18,19]

### Japan: Pharmaceuticals and Medical Devices Agency (PMDA)

Japan has established a progressive regulatory pathway for regenerative therapies, separating clinical medical services from commercial manufactured products.[36] The Act on the Safety of Regenerative Medicine (ASRM, Law No. 85 of 2013) governs clinical procedures provided at medical institutions, while the Pharmaceuticals and Medical Devices Act (PMD Act) regulates commercialized products.[38] The ASRM stratifies regenerative medicine therapies into three risk tiers to determine administrative oversight.[37]

Under this system, point-of-care autologous fat transfers processed via mechanical fragmentation (without culture expansion) are categorized as Class III regenerative medicine.[40,42] This requires the

clinic to submit a detailed "Regenerative Medicine Provision Plan" to a Certified Committee for Regenerative Medicine (CRM) and file a notification with the Ministry of Health, Labour and Welfare (MHLW).[37]

If the procedure requires ex vivo cell expansion (such as culturing autologous ADSCs over several weeks to obtain 100–200 million cells), it escalates to a Class II classification.[37] This tier demands clinical protocol review by a government-accredited Certified Special Committee for Regenerative Medicine (CSCRM) and dictates that all cellular processing occurs within a government-licensed Cell Processing Center (CPC).[37,43]

### India: Central Drugs Standard Control Organization (CDSCO)

In India, cell-based therapies are regulated under the Central Drugs Standard Control Organization (CDSCO) and governed by the New Drugs and Clinical Trials Rules 2019.[44] The national regulatory stance, aligned with the National Guidelines for Stem Cell Research (NGSCR-2017), designates all cell-based interventions beyond standard hematopoietic reconstitution for approved hematological indications as investigational.[45]

Under CDSCO rules, minimal manipulation includes processes like isolation, centrifugation, washing, suspension, cutting, and cryopreservation,

**Table 2:** Comparison of the regulatory criteria, exceptions, and procedural pathways governing point-of-care autologous fat transfers across major jurisdictions.

| Country/ Region | Primary Regulatory Agency | Governing Statute | Same Surgical Procedure Exception | Definition of Minimal Manipulation | Non-Homologous Clinical Use Classification |
|---|---|---|---|---|---|
| United States | FDA (CBER)[23] | 21 CFR Part 1271; PHS Act Sections 361 & 351[10] | Exempt under 21 CFR 1271.15 (b) if tissue remains in its "original form" (rinsing, cleansing, sizing, centrifugation permitted)[14] | Processing must not alter the tissue's utility to provide structural cushioning and support (enzymatic digestion is non-minimal)[12] | Classified as a commercial biological drug (Section 351); requires IND and BLA[12] |
| European Union | EMA (CAT)[27] | Regulation (EC) No 1394/2007 (ATMP Regulation)[24] | Regulated at national level under the Hospital Exemption scheme (Directive 2001/83/EC Art. 3(7))[30] | Non-substantial if processing preserves the structural and essential biological characteristics (enzymatic digestion is substantial)[5] | Classifies the graft as an ATMP (TEP or sCTMP); requires centralized marketing authorization[5] |
| Australia | TGA[32] | Therapeutic Goods Act 1989; Biologicals Framework[32] | Fully excluded from TGA regulation via Excluded Goods Order if manufactured and used in an accredited hospital[32] | Trimming, washing, freezing, and filtration are minimal; enzymatic cell isolation is Class 3[19] | Regulated as a Class 3 or Class 4 Biological if performed outside an accredited hospital[32] |
| Japan | PMDA / MHLW[39] | Act on the Safety of Regenerative Medicine (ASRM); PMD Act[38] | Regulated as clinical practice under ASRM Class III local committee review[36] | Non-cultured tissue is Class III (low risk); cultured somatic cells are Class II (moderate risk)[37] | Governed under clinical practice ASRM Class II, or Class III based on cell culture status[41] |
| India | CDSCO[44] | New Drugs and Clinical Trials Rules 2019; Drugs & Cosmetics Act[44] | Same-surgery exemption applies only if processing is restricted to rinsing, cleaning, or sizing[44] | Washing, centrifugation, cutting, and shaping are minimal; enzymatic digestion (SVF) is substantial[44] | Classified as a "New Drug"; requires Central Licencing Authority approval and clinical trials[44] |

provided these steps do not alter the biological characteristics of the cells. Autologous cells harvested and re-implanted during the same surgical procedure are exempt from clinical trials only if the processing steps do not exceed rinsing, cleaning, or sizing.[46]

Any point-of-care procedure involving enzymatic digestion (SVF), or ex-vivo culturing is classified as substantial manipulation[44]. This classification defines the output as a "New Drug," requiring clinical trial protocols to be reviewed by the Institutional Committee for Stem Cell Research (IC-SCR) and Central Licensing Authority (CDSCO) approval before clinical administration.[44] To support clinical translation, the CDSCO permits an accelerated approval process; if a product demonstrates safety and significant efficacy trends during Phase II trials for serious or life-threatening unmet medical needs, conditional marketing approval may be granted, with mandatory Phase IV trials to validate clinical outcomes.[44]

### Global Regulatory Alignment and Key Parameters

The table (table 2) provides a direct comparison of the regulatory criteria, exceptions, and procedural pathways governing point-of-care autologous fat transfers across these major jurisdictions:

### Strategic Implications for Clinical Translation

The fragmentation of international regulatory standards for point-of-care autologous fat processing shapes clinical practice, product development, and cell therapy business models.[47,48] The strict drug-like classification of autologous SVF in the United States and Europe has constrained the adoption of enzymatic processing technologies in Western clinics.[5] Because isolating SVF requires clinical trials and centralized marketing authorization, clinical interest has shifted toward mechanical processing devices (MFAT).[9]

These closed-loop mechanical devices can be cleared under device-level pathways (such as the FDA 510k Class II or CBER QKL codes) for reconstructive surgery.[23] However, clinical use remains restricted by homologous use rules; while a surgeon can legally use a mechanical system to wash and inject fat to augment soft tissue, using the same output for joint regeneration is considered non-homologous and classified as an unapproved drug application.[12]

This regulatory barrier has led to a geographic split in clinical innovation. In jurisdictions with clinical-procedure pathways like Japan's ASRM and Australia's hospital exclusions, medical institutions can legally offer autologous adipose-derived cell therapies directly to patients. This localized oversight supports rapid translation and real-world evidence collection, but it also creates a market for unproven medical tourism. Patients seeking advanced autologous therapies often travel to clinics in these permissive environments, bypassing the clinical trials required in their home countries.[34]

For device developers and clinical researchers, navigating these systems requires a dual approach.[47] Point-of-care systems must be designed as closed-loop, automated, non-enzymatic units to maintain a minimal manipulation classification.[49,50] At the same time, clinical protocols must align with localized exemptions, such as same-surgical exceptions or hospital exemptions, to validate safety and efficacy before embarking on the commercial drug approval pathways required for global market expansion.[51]

### Limitations of the Review

As a narrative review, this article does not attempt formal risk-of-bias assessment or quantitative synthesis. Regulatory documents may also be revised over time, and interpretation may vary according to local legal context, institutional setting, specific processing method, intended use, and claims made by the clinician or manufacturer. Therefore, the review should be interpreted as a clinically oriented synthesis of available regulatory frameworks rather than legal advice or a substitute for jurisdiction-specific regulatory consultation.

## CONCLUSION

Autologous fat, and its derivatives occupy a unique position at the interface of surgery, regenerative medicine, and cell-based therapy. While conventional fat grafting remains broadly accepted as a clinical procedure, increasing manipulation of adipose tissue and expansion into non-homologous indications have brought these interventions under closer regulatory scrutiny. Across jurisdictions, the key determinants of regulatory classification are the degree of manipulation, intended clinical use, point-of-care processing, and claims of therapeutic efficacy. Although regulatory

frameworks differ internationally, a common direction is evident: procedures that preserve tissue structure and remain within homologous clinical use are treated more permissively, whereas enzymatically isolated, culture-expanded, or non-homologously applied adipose-derived products are increasingly regulated as biologics, drugs, or advanced therapy products. For clinicians, responsible use of autologous fat-based therapies requires not only technical competence but also regulatory awareness, transparent patient communication, and commitment to evidence-based clinical translation.

### Disclosure for use of AI

Artificial intelligence assisted tools were used during the preparation of this manuscript to support language refinement, synthesis of the literature review, identification and search of relevant references, extraction of key information from selected references using Notebook LM, and organization of references in the required citation format. These tools were used only as supportive aids in the writing and review process. The final manuscript was thoroughly reviewed, edited, and approved by the study authors. All factual content, interpretations, regulatory statements, and references were independently checked by the authors. The cited references were matched with the source documents, and the corresponding author takes full responsibility for the accuracy, integrity, and final content of the manuscript.

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