SAMe

AFTER EUROPE'S 2026 REVERSAL

A methyl donor at the intersection of nutrition, neuropsychiatry, hepatology and industrial quality: what the science actually supports

RESEARCH MONOGRAPH | 26 OCTOBER 2026

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INTABIOTECH

Critical synthesis • Chemistry and formulation • Human evidence • European regulatory analysis

Abstract

On 14 October 2026, the European Commission's public record of Article 4 novel-food consultations identified **S-adenosyl-L-methionine disulfate tosylate** as **"Not Novel in food supplements."** The designation followed a contrary novel-food assessment earlier in 2026 and represents an important development for the European supplement sector. It is not, however, a positive opinion on therapeutic efficacy, an unrestricted market authorisation for all food categories or permission to make disease-related claims. That distinction is the starting point -not the footnote- of a scientifically responsible assessment of SAMe.

S-adenosyl-L-methionine (SAMe; ademetionine; AdoMet) is a central endogenous metabolite that transfers methyl groups to DNA, RNA, proteins, phospholipids and other acceptors; it also connects methionine metabolism with polyamine synthesis and glutathione-dependent redox homeostasis. These mechanisms provide unusually compelling biological plausibility. Clinical evidence is more heterogeneous. Meta-analyses suggest a possible antidepressant effect as monotherapy, yet differ in strength and statistical conclusions. For osteoarthritis, placebo-controlled trials are inconclusive. In chronic liver disease, biochemical plausibility has not translated reliably into improvements in patient-important outcomes. Formulation, stereochemical integrity, dose expression, absorption, concomitant medication and national regulatory restrictions materially affect any practical interpretation.

The expanded analysis reconstructs the full Lithuanian regulatory explanation, integrates individual positive and negative depression trials, interrogates methionine-cycle flux and stereochemical quality, and proposes a complete research and industrial dossier. Its central conclusion is that SAMe deserves serious scientific interest and disciplined clinical research, not either uncritical enthusiasm or wholesale dismissal. Europe's classification change removes one regulatory uncertainty for a defined ingredient and use; it does not remove the obligation to demonstrate product quality, safety, lawful claims or meaningful benefits to consumers.

Keywords: *S-adenosyl-L-methionine; SAMe; ademetionine; disulfate tosylate; methylation; one-carbon metabolism; depression; osteoarthritis; liver disease; bioavailability; novel food; Regulation (EU) 2015/2283; health claims; pharmaceutical quality*.

PART I - FOUNDATION, EVIDENCE AND REGULATORY PRINCIPLES

1. The regulatory event: a reversal, not a therapeutic endorsement

The Commission's **Consultation process on novel food status** currently records "S-adenosyl-L-methionine disulfate tosylate," dated **14 October 2026**, as **"Not Novel in food supplements."** The formulation of the entry matters. It is not a blanket declaration that every chemical form called SAMe, every manufacturing process, or every intended food use is non-novel. Nor is it the same as an authorisation obtained through a safety assessment and inclusion in the Union list of authorised novel foods. It is the published outcome of a status determination under the framework of Regulation (EU) 2015/2283. [1,2]

The policy context is unusually instructive. In May 2026, an Article 4 consultation had initially treated the specified salt as novel because the documentary record had not demonstrated significant pre-15 May 1997 consumption of that precise substance as a food or food supplement. The October primary administrative record now documents the confirmation by Italy in February 2016, later technical documentation and the 17 September 2026 Working Group discussion that led to reconsideration. This chronology is examined in detail in Section 15. [23] It would be inaccurate to present the reversal as new toxicological evidence or an EFSA finding that SAMe improves health. The controversy was principally about **historical consumption and ingredient identity**, not about a new demonstration of clinical efficacy. [1,3]

The distinction also corrects a seemingly minor detail in the social-media graphic circulating among supplement operators: the Commission's public consultation list states **14 October**, whereas some promotional graphics state **15 October**. An editorial publication should use the primary public-record date and, if necessary, identify the discrepancy. [1]

Under Article 4 of Regulation (EU) 2015/2283, an operator must verify the novel-food status of its intended product and consult a competent Member State when the status is uncertain. A non-novel conclusion for **food supplements** does not automatically establish a pre-1997 history in ordinary beverages, fortified foods, meal replacements or other food matrices. Extension to other categories may require a fresh legal and technical analysis of identity, process, exposure and intended use. [2]

The three gates that must not be conflated

Gate 1 - Novel-food status: Is this specified ingredient novel for this specified use? The October consultation entry assists with the disulfate-tosylate form in food supplements.

Gate 2 - Product legality and consumer safety: Is the actual supplement compliant with applicable EU and Member State rules on composition, identity, contaminants, manufacturing, presentation, notification and safe intended intake? A non-novel conclusion does not answer all these questions. Under EU general food law, the food business operator retains responsibility for safety. [4,5]

Gate 3 - Lawful communication: Is the claimed benefit specifically authorised under Regulation (EC) No 1924/2006, and does the presentation avoid medicinal claims? Scientific papers describing treatment of depression or osteoarthritis do not automatically legitimise such claims for a marketed food supplement. [6,7]

This separation is commercially significant. Europe has clarified an entry route for a substance; it has not certified the promises made about it.

2. What SAMe is and why it matters inside living cells

SAMe is generated from **L-methionine and adenosine triphosphate (ATP)** through methionine adenosyltransferases (MAT). It is not simply another dietary amino acid. It is a chemically activated sulfonium-containing metabolite that occupies a central position in **one-carbon metabolism**. In biological terminology, SAMe is the predominant methyl-group donor for numerous enzyme-catalysed methylation reactions. [8,9]

Its importance rests on three connected biochemical functions.

Transmethylation. Methyltransferases use SAMe to transfer methyl groups to DNA, RNA, histones, other proteins, phospholipids, neurotransmitter-related compounds and small molecules. After donating the methyl group, SAMe becomes **S-adenosylhomocysteine (SAH)**, an inhibitor of many methyltransferases. Cellular methylation capacity is consequently influenced not by SAMe concentration alone but by the relationship between SAMe, SAH, enzyme activity, substrate availability and compartment-specific metabolic flux. The frequently cited SAMe/SAH ratio is a useful biochemical indicator; it is not a stand-alone clinical diagnostic test or proof that additional SAMe will benefit a particular person. [8,9]

Transsulfuration and redox regulation. Homocysteine formed downstream of SAH can enter the vitamin-B6-dependent transsulfuration pathway, providing cysteine for glutathione synthesis. SAMe can modulate enzymes in this network. The mechanistic chain helps explain research interest in hepatic oxidative stress. Nevertheless, supplying a precursor does not guarantee a sustained increase in clinically useful glutathione, nor does a laboratory change establish disease modification. [8,10]

Polyamine synthesis. Decarboxylated SAMe contributes aminopropyl groups required for polyamine metabolism, relevant to cell growth and differentiation. This is another reason to avoid simplistic statements that SAMe "turns on methylation" or universally produces a beneficial epigenetic effect. Biological methylation and growth pathways are regulated, context dependent and capable of producing very different outcomes in different tissues. [8,9]

Why the brain-liver-joint triangle is attractive, but not self-validating

The brain depends on highly controlled neurotransmitter metabolism, phospholipid turnover and epigenetic processes. The liver plays a major role in methionine and methyl-group homeostasis and is particularly exposed to metabolic and oxidative disturbances. Cartilage and synovial tissue contain methylation-sensitive

and inflammatory signalling networks. The commonality explains why these three areas became the historical focus of SAMe investigations. It **does not** establish that a single orally administered dose will have comparable effects in each tissue, or that altering a shared pathway necessarily improves symptoms. Mechanistic plausibility is the beginning of a clinical hypothesis, not its validation.

3. The supplement is not the endogenous molecule in a vacuum

For industrial, analytical and clinical purposes, "SAMe" is an insufficient product description. A food business must distinguish the **active SAMe moiety**, the **counterions used to stabilise it**, the **relative proportions of stereoisomers**, the **amount declared per daily dose** and the **finished-product delivery system**.

The October entry refers specifically to **S-adenosyl-L-methionine disulfate tosylate**. The United States Pharmacopeia describes this as a mixed disulfate–tosylate salt containing a mixture of diastereoisomers of the S-adenosyl-L-methionine ion. Its nominal molecular formula is **C22H34N6O16S4** and its relative molecular mass is approximately **766.80 g/mol**. The SAMe cation has the formula **C15H23N6O5S+** and a relative molecular mass of approximately **399.45 g/mol**. [11]

This seemingly technical distinction has immediate labelling consequences. On a purely stoichiometric basis, **400 mg of anhydrous, chemically pure disulfate-tosylate salt corresponds to approximately 208 mg of the SAMe cation**, not 400 mg of the active moiety (399.45/766.80 ≈ 52.1%). Conversely, providing 400 mg of SAMe cation would require approximately 768 mg of this pure salt before correcting for actual assay, moisture and other product-specific factors. This is a chemical calculation, not a proposed dose or a statement about every commercial label. Some manufacturers expressly declare the SAMe moiety rather than the gross salt mass. Their certificates of analysis and method of expression must be examined before comparison. [11]

The stability problem is equally real. SAMe can degrade and epimerise, with the kinetics influenced by formulation environment, moisture, temperature and pH. The physiological (S,S)-configured cofactor predominates in biological methyltransferase reactions, while other diastereomeric configurations can arise during handling. More recent biochemical work cautions against assuming that every alternative stereochemical form is universally inactive; nevertheless, **stereochemical composition is a legitimate quality attribute** and cannot be inferred from a total assay alone. [12,13]

A serious raw-material specification should therefore address identity; assay with the expression basis made explicit; stereoisomer profile; relevant degradants including SAH where justified; water content; residual solvents and processing impurities; elemental impurities; microbiology; packaging; storage; and stability under the actual conditions of transport and use. Compendial methods or suitably validated HPLC/UPLC methods can provide the analytical backbone. An impressive headline purity percentage is insufficient unless the method and specification are intelligible. [11–13]

4. Oral bioavailability: the neglected determinant of practical efficacy

For a molecule with recognised chemical instability, oral dosage form is not merely a marketing detail. Gastric resistance, dissolution at the appropriate intestinal pH, tablet integrity, storage and food effects can all influence systemic exposure.

A phase-I comparative pharmacokinetic investigation of a novel enteric-coated formulation (MSI-195) and a commercially available comparator found approximately **2.8-fold greater relative exposure**, based on area under the plasma concentration curve, for the investigational formulation in its specified comparison. In the same research programme, food delayed the time to maximum concentration and reduced exposure for the investigational product to approximately **55% of its fasted-state value**. These are **formulation-specific pharmacokinetic observations**, not evidence that all enteric-coated products are 2.8 times better, nor proof of superior symptom relief. [14]

The implications are methodological. Clinical trials carried out with injected SAMe cannot be assumed interchangeable with studies using ordinary oral tablets; neither can one oral formulation automatically be substituted for another on a nominal milligram-for-milligram basis. When published studies disagree,

differences in preparation, administered moiety, absorption, baseline nutritional status, clinical population and co-treatment may be genuine effect modifiers rather than mere statistical noise.

A company proposing a premium SAMe ingredient should be able to answer four questions: **What is being measured? How much active moiety reaches the product? How stable is it until the end of shelf life? What human exposure data support this particular formulation?** Without those answers, a dose comparison may be commercially attractive yet scientifically invalid.

5. Mood disorders: the most intriguing clinical signal, with important limits

Of the principal human indications investigated, depressive symptoms present arguably the most persuasive signal for further study. This is not equivalent to saying that a food supplement is an established treatment for major depressive disorder.

A 2024 systematic review and meta-analysis in *Progress in Neuro-Psychopharmacology & Biological Psychiatry* included **23 randomised trials and 2,183 participants**. In comparisons against placebo, SAMe monotherapy was associated with an improvement in depression ratings (**standardised mean difference [SMD] −0.58; 95% confidence interval −0.93 to −0.23; I^2 68%**). The relatively high heterogeneity warns that the magnitude is not uniform across studies. For adjunctive use alongside antidepressants, the same review found **no statistically significant advantage** over adjunctive placebo (**SMD −0.22; 95% CI −0.63 to 0.19**). The comparison with conventional antidepressants also did not demonstrate a significant difference, but a non-significant difference is not proof of formal therapeutic equivalence. [15]

Another 2024 review, based on **14 trials and 1,522 participants**, reported no statistically significant differences across several examined comparisons and emphasised small samples, disparate doses (200–3,200 mg/day) and short study duration (typically 2–12 weeks). The different conclusions illustrate a fundamental principle: the pooled result depends on which populations, preparations, trial designs and statistical comparisons are eligible. It is unsound either to advertise the favourable effect size without its heterogeneity or to dismiss all signals because another synthesis was inconclusive. [16]

There are at least five unresolved clinical questions. First, can positive findings be replicated in adequately powered, contemporary, preregistered trials? Second, are there definable responder phenotypes -such as patients with particular methylation-related biomarker patterns- or is the response non-specific? Third, how do formulation and delivered exposure influence clinical outcomes? Fourth, are any effects maintained beyond a few weeks? Fifth, can safety be adequately characterised in people taking serotonergic medication or living with bipolar-spectrum vulnerability?

SAMe is involved in pathways associated with neurotransmitter synthesis and turnover, but **"SAMe increases serotonin and therefore improves mood"** is not a satisfactory account of the human clinical mechanism. Neurotransmission is regulated by enzymes, receptors, transporters, brain circuits and feedback systems; peripheral SAMe changes should not be equated with central neurotransmitter concentrations. Any claim that it normalises mood in the general population requires a separate evidentiary and legal basis.

Clinical judgement: SAMe is a plausible investigational candidate for depressive symptoms and deserves better targeted trials. It should not displace established diagnosis, risk assessment, psychotherapy or guideline-supported pharmacotherapy. The promotional language of "neurotransmitter balance" is much more definite than the current evidence allows. [15–17]

6. Osteoarthritis: modest signals that do not establish joint restoration

SAMe has been studied for joint pain and function, including comparisons with non-steroidal anti-inflammatory drugs in older clinical programmes. However, when attention is focused on placebo-controlled evidence, conclusions become more restrained.

A Cochrane systematic review of **four trials involving 656 participants** found that the estimated reduction in osteoarthritis pain versus placebo was small and statistically uncertain (**SMD −0.17; 95% CI −0.34 to 0.01**), roughly equivalent to **0.4 cm on a 10-cm visual analogue pain scale**. Functional improvement was

not established. The review judged the trials and reporting to be of questionable quality and did not recommend routine SAMe use pending better evidence. [18]

These observations support a narrow research proposition: symptomatic benefit may merit further evaluation in well-selected knee or hip osteoarthritis populations. They do not establish cartilage regeneration, disease-modifying activity, prevention of joint degeneration or replacement of evidence-based interventions. A supplement labelled "joint health" may easily imply more than pain trials can prove; the precise wording must be assessed separately against EU health-claim law.

Clinical judgement: interesting but unconfirmed symptomatic potential; no robust basis for claims of structural joint repair.

7. Hepatology: a beautiful biochemical rationale and a harder clinical reality

The liver is an especially compelling setting for SAMe research. Hepatic methionine metabolism influences phosphatidylcholine synthesis, methylation reactions, redox handling and glutathione-related pathways. Observational and experimental work links disturbed one-carbon metabolism to several chronic liver disorders. None of this should be mistaken for proof that oral SAMe supplementation prevents progression of cirrhosis or steatotic liver disease. [8,10]

A double-blind randomised trial in alcohol-related liver disease allocated **37 patients** to approximately **1.2 g/day oral SAMe or placebo for 24 weeks**; both groups were also required to abstain from alcohol. Although overall biochemical variables improved during the study, **there were no significant between-group differences** in clinical, biochemical or histological outcomes. The improvement attributable to abstinence was not enhanced demonstrably by SAMe. [19]

A Cochrane review of **nine trials involving 434 participants** found no reliable demonstration of effects on mortality, liver-related mortality, transplantation or complications. That review subsequently had its own publication-history changes; its older trial set should therefore be interpreted with the subsequent randomised evidence rather than treated as a current complete evidence synthesis. The essential finding remains that patient-important hepatic benefits have not been convincingly established. [20]

Studies in cholestatic conditions have also produced conflicting findings. Intrahepatic cholestasis of pregnancy is a particularly inappropriate target for extrapolating self-medication claims: any proposed intervention must be evaluated against maternal–fetal outcomes, established treatment pathways and the absence of adequate SAMe pregnancy-safety evidence. The US National Institutes of Health accordingly describes evidence for liver disorders as inconclusive. [17]

Clinical judgement: hepatic mechanism is well grounded; the claim "supports liver function" cannot be treated as a clinical fact for a specific commercial SAMe product without relevant human evidence and lawful claim authorisation. Statements about preventing fibrosis, reversing fatty liver or improving survival are not justified by the trials reviewed here.

8. Epigenetics, healthy ageing and cancer: where scientific fascination demands restraint

SAMe's involvement in DNA and histone methylation makes it particularly attractive to the current longevity and epigenetic-wellness market. Yet methylation is not a scalar "health score." Epigenetic regulation depends on tissue, cell type, developmental state, DNA sequence, enzyme distribution, SAH inhibition, cofactor availability and disease biology. A global increase in methyl-donor availability does not imply correction of abnormal epigenetic patterns. [8,9]

Similarly, participation in polyamine metabolism and cell-growth signalling warrants intellectual caution in oncology. Laboratory and animal models can generate hypotheses about SAMe and tumour biology, but no general conclusion that SAMe prevents cancer, "repairs DNA methylation," slows biological ageing or is safe as an adjunct to cancer treatment follows from these biochemical observations. A legitimate research programme would need tissue-specific outcomes, disease-specific endpoints, clinically relevant exposures and a pre-specified safety framework.

The central lesson is that a mechanism can explain **why an experiment is worth doing** while remaining unable to predict **whether a consumer benefits**. Translating methylation biology into premium longevity claims without intervention trials would be scientifically and regulatorily premature.

9. Safety is not guaranteed by endogenous origin

The body synthesises SAMe. That fact does not make gram-scale external exposure risk free. Physiological endogenous production is regulated in time and space; an oral preparation changes systemic inputs under different kinetic constraints.

Reported undesirable effects are often gastrointestinal or nonspecific, but long-term safety data are limited. Particular attention is required for people with **bipolar disorder or a history of mania/hypomania**, because mood activation is a concern. Potential interactions with **serotonergic antidepressants, St John's wort, L-tryptophan and other serotonin-related agents** warrant clinical supervision; interaction warnings should be risk-based rather than converted into claims of predictable benefit. SAMe may also interfere with **levodopa** treatment. Pregnancy and breastfeeding require caution because reassuring safety data are inadequate. The NIH additionally discusses a theoretical concern relating to *Pneumocystis* in immunocompromised individuals; this remains a theoretical signal, not an established frequent clinical complication. [17]

Homocysteine requires a more nuanced discussion. SAMe enters a cycle that can produce homocysteine downstream of SAH, but cellular handling also depends on remethylation and transsulfuration pathways influenced by folate, vitamins B12 and B6, betaine, tissue conditions and genetic or disease factors. It is therefore incorrect to assert either that every SAMe supplement necessarily raises plasma homocysteine or that it cannot do so under any circumstances. Where sustained high intake is investigated clinically, a protocol may reasonably include homocysteine and relevant nutritional biomarkers as exploratory safety or mechanistic measures rather than as universally mandated consumer testing. [8,10]

The 2013 Norwegian VKM assessment underscores that the safety database was insufficient to derive a general tolerable upper intake level for SAMe and related compounds. This is **not** equivalent to concluding that all customary intakes are unsafe; it means a regulator should not pretend that an evidence-based universal upper level exists where the data cannot sustain one. [21]

10. Why trial doses cannot be copied directly onto supplement labels

Published trials have explored doses far higher than those used in some national supplement markets, often in the range of hundreds of milligrams to multiple grams per day, with routes including oral and parenteral administration. Those quantities are research exposures, **not recommendations for unsupervised consumer use**. [15–17]

An ethically sound European development project must simultaneously consider: the specific SAMe salt; the declared active moiety rather than gross salt weight; achievable exposure; target population; medication interactions; relevant national maximum-use rules or restrictions; and the legal distinction between a food supplement and a medicinal product. A trial showing an effect with a high-dose medical-grade preparation cannot be used automatically to defend the benefit of a low-dose supplement of unknown bioavailability.

Country-by-country conditions remain pertinent because substances other than vitamins and minerals are not fully harmonised at EU level. The appropriate path is a documented market-entry review in each destination Member State. Industry reporting cites national intake conditions for some countries, but reported numbers should not replace a current examination of national source law and competent-authority practice before a product specification or label is finalised. [3–5]

11. Health claims: the point where science meets enforceable law

Regulation (EC) No 1924/2006, in particular Articles 3, 5, 6 and 10, requires nutritional and health claims made in commercial communication to satisfy the relevant substantive rules and authorisation conditions. Claims that a food prevents, treats or cures a human disease are additionally incompatible with the standard

presentation of food supplements; such communications raise food-law and potentially medicinal-product classification issues. [6,7]

The EU health-claims register must be checked for the exact constituent and wording. A general biochemistry statement made in a scientific article is not necessarily an authorised consumer-facing claim. The historical regulatory record is particularly instructive: EFSA issued an Article 13 scientific opinion in 2010 addressing several proposed claims about maintenance of joints, including claim ID 1973, which is associated with SAMe in historical claims listings. The underlying novel-food determination in 2026 did not reopen or replace that health-claims assessment; product developers must ascertain the current legal status of any exact proposed wording. [22] The Commission's novel-food consultation listing is not an authorisation to write "improves depression," "regenerates cartilage," "detoxifies the liver," "increases neurotransmitters" or "reverses biological ageing" on a product package or commercial website. Even apparently softer formulations such as "mood support," "liver function" or "joint comfort" may qualify as health claims because they imply a relationship between the constituent and health. [6,7]

This produces a critical editorial distinction. **An independent scientific review may examine therapeutic trial data critically and cite published findings; a manufacturer's marketing communication about a commercial food supplement cannot simply import those therapeutic descriptions as promotional promises.** Disclosure of commercial interests, the surrounding context, branding and the intended audience all affect risk assessment. Scientific rigor and regulatory compliance are complementary, not interchangeable.

12. A hierarchy of current evidence

Domain	Biological plausibility	Human evidence reviewed	Defensible scientific position
Endogenous methyl donation / one-carbon metabolism	Strong	Established biochemical pathways	Core physiological role is well established; supplementation benefit is a separate question
Depressive symptoms	Strong mechanistic rationale	Heterogeneous RCTs; divergent 2024 meta-analyses	Possible monotherapy efficacy signal; insufficient basis for broad treatment claims or equivalence
Add-on to antidepressants	Plausible	2024 pooled comparisons not statistically significant	Benefit unconfirmed; interaction assessment essential
Knee/hip osteoarthritis	Plausible but indirect	Four placebo-controlled trials, 656 patients in Cochrane analysis	Small, uncertain symptomatic effect; no proof of cartilage repair
Alcohol-related liver disease	Strong hepatic rationale	RCTs including a negative 24-week placebo-controlled study	No reliable established benefit for survival, progression or histology
Cholestatic conditions, including pregnancy-associated cholestasis	Mechanistically plausible	Inconsistent and/or limited evidence	Insufficient for self-treatment claims; special safety concerns in pregnancy
Epigenetic rejuvenation / cancer prevention	Mechanistic hypotheses	No adequate clinical demonstration for broad claims	Research topic, not validated supplement benefit

This hierarchy is more useful than a single promotional verdict because the same molecule can have a proven endogenous function, a plausible intervention mechanism and an unproven consumer outcome at the same time.

13. The evidence that would genuinely change practice

The opportunity created by the 2026 regulatory clarification is not merely to launch additional labels. It is to design a **credible research-to-product programme** capable of converting reproducible findings into defensible quality attributes, clinically relevant information and, where justified, submissions for authorised claims.

Research workstream A - Chemical identity and analytical validity. Establish reference-standard traceability; assay of the SAMe moiety and total salt; stereoisomer profiles; SAH and other relevant degradants; validated dissolution; packaging protection; accelerated and real-time stability; and end-of-shelf-life label compliance. Comparative material should not be pooled under the generic term "SAMe" without these descriptors.

Research workstream B - Exposure and formulation. Conduct appropriate pharmacokinetic comparisons with pre-specified fasting/feeding status, the same active-moiety dose, a suitable comparator and exposure metrics. Resolve whether the formulation produces reproducible human exposure before undertaking expensive efficacy trials. An improvement in AUC is informative, but clinical benefit still requires direct measurement.

Research workstream C - Clinically coherent depression trials. Pre-register adequately powered, multicentre, randomised double-blind studies in carefully defined populations, with validated primary outcomes, independent safety oversight, longer follow-up, systematic assessment of manic switching and transparent medication protocols. Consider biomarker-defined subgroups only as hypotheses unless externally validated. Record actual composition and exposure rather than treating all commercial preparations as equivalent.

Research workstream D - Joint outcomes. Use sufficiently powered parallel-group trials with established pain and function instruments, clinically meaningful responder thresholds and pre-specified multiplicity control. Claims of structural benefit require direct imaging or validated structural outcomes, not only improvements in subjective discomfort.

Research workstream E - Hepatic outcomes. Distinguish disease mechanisms and patient groups rather than combining heterogeneous "liver health" populations. Where appropriate, prioritise hard outcomes or well-validated clinical surrogates over isolated transaminase changes. Ensure interventions do not distract from alcohol abstinence, weight management, antiviral therapy or standard management when indicated.

Research workstream F - Regulatory and health-economic translation. Maintain a country-specific legal matrix, perform systematic claim mapping against the EU register and test whether credible clinical effect sizes can be achieved within lawful supplement conditions. A formulation is commercially viable only if delivered exposure, price, safety and permissible communication work together.

14. Implications for ingredient developers and responsible manufacturers

The 14 October classification improves regulatory clarity for operators considering the defined stabilised salt in food supplements, but it also exposes a potential market failure: ingredients may be sold principally on the basis of their most favourable mechanism while the purchaser receives inadequate documentation about identity, actual SAMe content, stability and clinically relevant exposure.

For an ingredient manufacturer or technical distributor, the highest-value commercial asset is not a dramatic statement about "methylation" or the number of purported applications. It is an **auditable dossier** connecting the raw material to the finished product: exact form, validated purity and stereochemical characterisation, manufacturing controls, stability, justified dose, relevant exposure evidence, safety, destination-market compliance and an appropriately conservative claims assessment.

This positioning also avoids confusion between food supplements and medicines. A clinical publication may rationally propose evaluating SAMe in depressive illness, osteoarthritis or hepatology without asserting that a retail food supplement may be advertised as a treatment for those conditions. The two discussions belong

to distinct regulatory and evidentiary frameworks. A company that observes the distinction can protect both scientific credibility and long-term commercial value.

PART II - ADVANCED SCIENTIFIC, CLINICAL AND REGULATORY APPRAISAL

15. What the primary October 2026 administrative record actually says

A legally rigorous reading must begin with the document behind the Commission's public table, not with an infographic or a distributor's interpretation. The **14 October 2026 Article 4 consultation outcome**, issued with Lithuania's Institute of Hygiene as recipient competent authority, identifies the assessed material as **S-adenosyl-L-methionine disulfate tosylate**, also called disulfate *p*-toluenesulfonate. The document expressly recognises that the material may be commercially made by fermentation or chemical synthesis, identifies its intended use as a nutritional substance in food supplements, and reaches the conclusion **"Not novel in food supplements."** It does not prescribe a manufacturing specification, recommended dose, list of therapeutic indications or harmonised conditions of sale. [1,23]

The reasoning is unusually important. Italy had provided a confirmation in **February 2016** stating that this stabilised salt was not novel in food supplements and was a common source of SAMe in Italian supplements. In later consultations Member States considered the alternative word orders "tosylate disulfate" and "disulfate tosylate" to refer to the same substance. Italy subsequently contributed technical and historical documentation on the development of stabilised salt forms and their supplementary use. Much of the commercial evidence was **post-15 May 1997**: the October document openly acknowledges that such documents do not, by themselves, prove significant pre-1997 use. Nevertheless, taken together with Italy's earlier confirmation and the discussions of the Working Group on **17 September 2026**, they persuaded Lithuania to reconsider its initial assessment. [23]

This is a materially different legal narrative from saying that "Europe has approved SAMe." What happened was an administrative reassessment of documentary evidence and of the identification of the substance for the **history-of-consumption test**. The revised conclusion is explicitly limited to that salt and food supplements; the document expressly warns against automatic extrapolation to **other SAMe salts**. Since the October determination is not an Article 10 novel-food authorisation, it should not be described as an EFSA safety opinion, a Union-list authorisation or an EU-wide licence to claim health benefits.

The case also demonstrates that evidentiary assessment is not strictly mechanical. Whether a pre-1997 historical reference to a generic ingredient name can be linked to a later-defined stabilised salt depends on contextual records, trade practices, chemical nomenclature, manufacturing descriptions and the credibility of the Member State's historical evidence. The fact that the underlying documentation includes post-cut-off records is not proof of a new post-1997 ingredient; neither, conversely, is any modern use of the brand name "SAMe" sufficient evidence for all salt forms. Appropriate due diligence would preserve a copy of the public outcome, match the proposed raw material to its identity, retain supplier specifications and keep an auditable statement of intended use.

From a procedural perspective, Article 4 of Regulation (EU) 2015/2283 places the initial burden of checking status on the operator. Commission Implementing Regulation (EU) 2018/456 sets out the dossier, evidence and consultation framework. A change of classification follows a particular documentary record, not a general principle that intrinsically occurring human metabolites escape novel-food scrutiny. The same 1997 threshold continues to apply where novel status is uncertain. [2,24]

Practical legal consequence: for the identified salt in food supplements, the public Article 4 outcome is strong and directly relevant evidence of non-novel status. It is not a substitute for a composition/safety assessment, a national market-entry review or verification of marketing claims. Nor does it remove the separate issue of classification as a medicinal product by presentation or function in specific circumstances.

16. Methionine-cycle biochemistry beyond the methyl-donor slogan

16.1 The cycle is a network, not a one-way pipe

The familiar representation "**methionine + ATP → SAMe → SAH → homocysteine**" is a useful teaching shorthand, but mechanistically incomplete. Methionine adenosyltransferases catalyse an energetically demanding activation step in which ATP is consumed and the adenosyl group becomes connected to methionine's sulfur. SAMe then participates in many enzyme-dependent transfer reactions. Once a methyl group is donated, **S-adenosylhomocysteine (SAH)** is formed. SAH hydrolase catalyses a reversible reaction yielding adenosine and homocysteine; the reaction's direction in living cells is influenced by removal of its products. Thus a rising pool of SAMe cannot be interpreted without considering SAH, adenosine and homocysteine handling. [8,9,25]

Homocysteine has at least two principal metabolic destinies. **Remethylation** regenerates methionine, using methionine synthase in a reaction linked to vitamin B12 and 5-methyltetrahydrofolate, or using betaine-homocysteine methyltransferase in tissues such as liver and kidney. **Transsulfuration** channels sulfur toward cystathionine and cysteine through cystathionine beta-synthase and cystathionine gamma-lyase; vitamin B6 status matters to this pathway. Cysteine may then support glutathione synthesis, subject to substrate supply, enzymatic regulation and cellular demand. The system therefore has multiple feedback points. [8,25]

SAMe also influences regulatory decisions within the cycle: under some physiological conditions SAMe activates cystathionine beta-synthase and restrains methylenetetrahydrofolate reductase, directing homocysteine handling away from continued remethylation and toward disposal via transsulfuration. These are context-dependent enzymatic regulatory effects, not guarantees that an oral supplement lowers homocysteine or increases glutathione in all humans. Dietary folate, B12, B6 and choline/betaine deficiencies can change the response to additional methyl-donor inputs. The correct clinical question is not simply "does the individual need more SAMe?" but "what is the limiting factor in the relevant metabolic network, and will external SAMe correct it?"

16.2 The methylation potential is not an epigenetic score

Methyltransferase activity depends on local concentrations and catalytic properties, and many enzymes are competitively inhibited by SAH. The **SAMe:SAH ratio**, sometimes called methylation potential, can be informative in experimental systems. It should not be sold as a universal numerical scale of health. Methylation is inherently site-specific: a histone lysine mark, a CpG site in a regulatory region, an RNA nucleotide, a neurotransmitter metabolite and phosphatidylethanolamine are not interchangeable targets. Moreover, epigenetic states arise from a dialogue among writers, erasers, readers, chromatin access, cell division and environmental signals. More precursor in blood does not prove a favourable, selective chromatin effect in a given brain or liver cell. [9]

A technically credible intervention would measure more than serum SAMe alone. Depending on the hypothesis it may need SAMe, SAH, total homocysteine, folate, B12, methylmalonic acid, methionine, relevant glutathione species, tissue-specific functional outcomes and, in research settings, precisely defined methylation markers. Even then, a biochemical shift constitutes **target engagement**, not proof of clinical efficacy. Proposed biomarker panels must also contend with circadian timing, food intake, renal function and sample-processing artefacts.

16.3 Compartmentation and hepatic specificity

The liver is not a passive storage site for methyl groups. Methionine adenosyltransferase genes show tissue and disease-related patterns: **MAT1A** is characteristically expressed in differentiated hepatocytes; **MAT2A** and regulatory **MAT2B** participate in other cellular contexts. Changes in these patterns accompany hepatic injury, proliferation and malignant transformation, as described in mechanistic literature. This offers an explanation for research interest in liver pathology but simultaneously highlights a limitation of supplementation: adding substrate cannot be assumed to restore abnormal expression of particular MAT isoforms or tissue architecture. [25]

One important conceptual implication follows. A metabolite may be **essential for the functioning of a pathway** without being a nutrient that has a defined dietary requirement. Human SAMe is normally synthesised endogenously. No established reference intake or conventional SAMe-deficiency syndrome analogous to folate or B12 deficiency was identified in the sources reviewed. This should temper arguments that all consumers need to "top up" SAMe levels and encourage selective rather than mass-market research hypotheses.

17. Chemical identity, stereochemical activity and the economics of a milligram

17.1 Salt mass, parent ion and truthful dose comparisons

A disulfate–tosylate salt is chosen in part because the parent sulfonium species is chemically challenging to handle. Counterions are not merely typographical annotations; they contribute materially to molecular mass. The USP preview gives the formula **C22H34N6O16S4**, molecular mass **766.80 g/mol**, for this salt, and identifies the SAMe cation as **C15H23N6O5S+**. Accordingly, the theoretical proportion of SAMe cation is roughly **399.45/766.80 = 52.1% by mass** for the anhydrous ideal composition. This arithmetic clarifies why "400 mg of the salt" and "400 mg SAMe (as its salt)" need not mean the same thing. [11,26]

A manufacturing case illustrates the commercial consequences without endorsing any intake. If a hypothetical product specification requires **400 mg SAMe cation per unit**, approximately **768 mg pure anhydrous disulfate–tosylate** is needed *before* correction for water, nonactive material, process loss and assay tolerance. If the hypothetical active-moiety assay were 50% by actual received weight, **800 mg of received material** would be required to supply 400 mg cation. A supplier offering material at a lower price per kilogram could therefore be more expensive per delivered milligram of chemically verified SAMe. These are analytical calculations, not instructions for clinical dosage or labelling; formulations must be assessed against applicable national law.

17.2 Stereochemistry is not a marketing ornament

The SAMe sulfonium centre is stereogenic. The native **(S,S)** configuration has historically been regarded as the principal functionally active cofactor for canonical methyltransferase-mediated reactions, whereas **(R,S)** material can arise by epimerisation. A 2015 analytical study explicitly developed HPLC separation of the two forms and emphasised the relevance of native stereochemistry. A 2026 biochemical perspective has, however, nuanced any absolute assertion of inactivity by showing that some enzyme systems tolerate alternative configurations and that stereochemical flexibility can matter in specialised biosynthetic pathways. Both statements can be true: alternative diastereomers may be biochemically relevant in some contexts while a mixture remains **non-equivalent to a validated clinical preparation** until specific exposure and efficacy are demonstrated. [12,13,27]

The company evaluating a product should therefore ask whether "purity" means total salt, total SAMe cation, native (S,S) SAMe, or some unspecified spectroscopic response. A single assay peak measured under unvalidated conditions may fail to separate diastereomers or closely related degradants. It is entirely possible for a batch to have a reassuring gross mass or nitrogen value while differing in biological and pharmacotechnical quality.

17.3 From production route to a finished-product quality dossier

Fermentation and chemical synthesis can both yield chemically defined material, as the Lithuanian consultation states; their industrial hazard profiles nonetheless differ. Fermentation requires control of organism identity, media, process-related metabolites, purification and microbiological quality; chemical synthesis involves attention to reaction by-products, solvents and stereochemical outcomes. Neither route should be assumed superior without batch data. A suitable risk assessment uses the actual process and impurity profile, not a generic claim of "natural fermentation." [23]

For the active ingredient, a defensible technical specification would include a traceable identity method (for example orthogonal chromatographic and spectrometric evidence), expression of active-moiety assay, diastereomeric profile, validated detection of selected degradants, water content, relevant residual solvents,

contaminants and an appropriate microbiological specification. For the finished supplement it must also address uniformity, dissolution or disintegration as appropriate, packaging moisture barrier, exposure to heat and humidity, shelf-life assay and in-use stability. Stability-indicating methods should demonstrate specificity against relevant degradation mechanisms. Supplier certificates are necessary documentation, but periodically verified, independent testing is prudent for commercially critical attributes.

The concept of **quality by design** is therefore applicable without pretending that dietary supplements are automatically pharmaceutical products: define the intended quality target, identify critical material attributes, map formulation sensitivities, test protective packaging and build real-time data that support expiry. A proposed "SAMe 400" position becomes meaningful only after the label's mathematical basis and analytical evidence are unambiguous.

18. From ingestion to tissues: a full translational pharmacokinetic framework

The pharmacological pathway between a swallowed tablet and a change in brain or joint physiology comprises dissolution, intestinal stability, uptake, presystemic metabolism, systemic transport, distribution, intracellular penetration, metabolism and elimination. A relative rise in plasma SAMe is one part of this chain. Each step can introduce variability and affect interpretation of a clinical trial. The oral route is especially challenging for a polar, reactive molecule, making formulation and handling important potential effect modifiers.

In the **MSI-195** phase-I programme, investigators used a cross-over comparison of their proprietary oral enteric-coated tablet with a named US commercial formulation. When exposure was normalised for declared milligrams in that study, the investigational product delivered roughly **2.8-fold higher AUC**. Food delayed its **Tmax from approximately 4.5 to 13 hours** and reduced observed AUC over the measured interval to about **55%** of the fasting value. Those figures demonstrate how strongly a particular product's delivery can depend on formulation and administration conditions. The trial was small and industry funded; its value is as proof of pharmacokinetic variability, not as validation of a general superiority claim or proof of a health outcome. [14,28]

One subtlety often missed in commercial interpretation is the distinction among **AUC**, **Cmax**, **Tmax** and **clinical pharmacodynamic benefit**. AUC represents integrated systemic exposure over time; Cmax is the observed peak concentration; Tmax describes the time of peak. A product can increase AUC without proportionately increasing pharmacological activity if tissue uptake saturates, if the principal relevant action is intracellular and tightly regulated, or if concentrations already exceed those required for a particular biochemical reaction. Conversely, a short-lived plasma increase might be clinically relevant if it affects a target with durable downstream effects. These scenarios cannot be resolved by comparing supplement labels.

Study design priority: standardise the actual SAMe moiety delivered rather than gross salt weight; measure pre-dose endogenous concentrations; control food intake and circadian sampling; use validated LC–MS/MS analyses; report both absolute and dose-normalised exposure; evaluate intraindividual variability; assess the product at beginning and end of shelf life; record relevant co-medications; and, where possible, connect exposure metrics with a prospectively specified biological or clinical outcome. This is the logical basis for testing whether a different formulation changes an intervention's benefit–risk balance.

There is no scientifically defensible universal conversion factor between oral supplements and intravenous or intramuscular regimens on the basis of the public sources reviewed. Historical studies using different routes should be assessed by route, dose expression and era, rather than merged as if they were the same intervention. Similarly, the observation that fasted MSI-195 performed differently from fed MSI-195 does not establish a blanket instruction for taking every SAMe product without food; such instructions need product-specific evidence and a safety evaluation.

19. Depression: reconstructing the evidence trial by trial

19.1 Why the favourable signal exists

A six-week randomised, double-blind trial published by **Papakostas and colleagues in 2010** investigated adjunctive SAMe among **73 patients** with major depressive disorder who had not responded adequately to serotonin-reuptake inhibitors. The target oral regimen was **800 mg twice daily** on top of stable antidepressant therapy. HAM-D response occurred in **36.1%** receiving adjunctive SAMe versus **17.6%** on adjunctive placebo; remission figures were **25.8% versus 11.7%**, respectively. These are clinically interesting differences, and the authors appropriately framed them as preliminary findings requiring replication. The study does not establish safe consumer use with antidepressants outside medical supervision. [29]

Why is this result attractive? It investigated a well-defined unmet clinical need, used a placebo-controlled design and reported outcomes that patients and clinicians can understand. Why is it insufficient? It was modest in size, short in duration, used a pharmacological target dose and a population already receiving prescription drugs, and could not establish robust long-term risks including mood switching. It also represented one trial within a much larger and heterogeneous literature.

19.2 What the larger negative trial contributes

In a **2014** multi-arm, double-blind study, **189 outpatients** were assigned to oral SAMe (**1,600–3,200 mg/day**), escitalopram (**10–20 mg/day**) or placebo over **12 weeks**. Mean HAM-D improvements were observed across all three groups, but **the overall between-group treatment difference was not statistically significant**. Intent-to-treat response rates were approximately **36%, 34% and 30%**, respectively. Attrition was substantial: only 97 patients completed treatment. These facts do not show that escitalopram and SAMe are therapeutically equivalent; rather, the design failed to distinguish the active arms adequately from placebo in that sample. High dropout and expectancy effects complicate interpretation, but they do not authorise the reader to discard an unfavourable trial. [30]

A subsequent reanalysis reported an apparent sex-specific signal in a subgroup. Such post-hoc analyses may generate hypotheses but are **not** proof of a biologically stable male-only response, especially in the presence of limited subgroup numbers and multiplicity. Likewise, analyses of higher doses in nonresponders must be viewed as exploratory rather than direct evidence that escalating SAMe is necessarily beneficial. [31,32]

19.3 Later adjunctive trial and conflicting meta-analyses

A further **2018** eight-week double-blind adjunctive study enrolled **107** antidepressant non-remitting outpatients. Both arms improved over time, but there was **no significant between-group difference** on the Montgomery–Åsberg Depression Rating Scale (**$p = 0.51$**); response rates at week eight were **54.3% with SAMe and 50.0% with placebo**, with no established advantage across secondary outcomes. This directly tempers inferences from the earlier 73-person trial. [33]

The 2024 meta-analysis by **Limveeraprajak et al.** pooled **23 RCTs, 2,183 participants**; it found a favourable placebo-controlled **monotherapy** signal of **SMD −0.58**, with **$I^2 = 68\%$**, but not a statistically significant adjunctive effect (**SMD −0.22, 95% CI −0.63 to 0.19**). The comparison with antidepressants (**SMD 0.06, 95% CI −0.06 to 0.18**) should not be converted into a noninferiority conclusion, because the studies were not designed to establish equivalence against a prespecified margin. Another 2024 systematic review reached a more cautious interpretation. [15,16]

Important methodological questions concern allocation concealment in older studies, potential influence of route of administration, product heterogeneity, study size, baseline depression severity, placebo response, endpoint selection, publication bias and the unequal contribution of positive and negative trials. Pooling a parenteral preparation from one clinical era with a modern oral supplement may be useful for a broad pharmacological hypothesis yet inadequate for predicting what a European retail product will accomplish. A scientifically disciplined review should be prepared to report a moderate point estimate and serious uncertainty simultaneously.

19.4 What can reasonably be concluded in 2026?

There is a **signal worth pursuing**, particularly for SAMe monotherapy in selected populations, but no consistent evidence base sufficient to displace standard care. For adjunctive use, well-conducted negative studies and statistically inconclusive pooling remain important. The risk of mania/hypomania and potential interaction with serotonergic drugs demand trial-level safety surveillance. A next-generation study would use one chemically characterised formulation, preregister clinical and functional outcomes, allow long enough to investigate maintenance and relapse, and stratify only by adequately justified biological hypotheses rather than opportunistic subgroup mining.

The public-health distinction is absolute: **research on a molecule in depressive illness is not a claim permission for a food supplement.** Consumers with persistent depressive symptoms, suicidal thoughts or suspected bipolar-spectrum illness require appropriate clinical assessment, not advertising that rebrands a commercial methyl donor as an antidepressant.

20. Osteoarthritis and the false equivalence between analgesia and structural osteo-regeneration

A rationale for joint research might involve synovial inflammation, cartilage matrix turnover, oxidative stress and cellular methylation. However, the path from such processes to a better outcome in a person with knee or hip osteoarthritis is indirect. Pain in osteoarthritis is multifactorial; it may arise from synovium, subchondral bone, surrounding tissues and central pain processing as well as structural abnormalities. A proposed intervention could conceivably change discomfort without rebuilding cartilage, and the absence of cartilage repair would not itself exclude a modest symptomatic effect.

The most useful conservative benchmark is the Cochrane synthesis of **four placebo-controlled trials, 656 patients**. For pain the pooled standardised mean difference was **−0.17** (95% CI **−0.34 to 0.01**), equivalent to approximately **0.4 cm on a 10-cm visual analogue scale**. The direction favoured SAMe but the confidence interval included no effect; function did not improve convincingly. The review criticised methodological quality and advised against routine use pending better studies. Its interpretation must not be eclipsed by older head-to-head comparisons with non-steroidal anti-inflammatory drugs, which often lacked the power and design required to establish equivalence. [18]

The benefit–risk calculation in osteoarthritis must be comparative. A modest pain reduction may still matter to some patients if replicated with acceptable tolerability; yet real-world benefit must exceed placebo and measurement noise, and affordability should be considered. An appropriate modern trial would include predefined responder thresholds, WOMAC or a comparable validated index, analgesic-rescue recording, intention-to-treat analysis, relevant age and comorbidity representation, and robust harms ascertainment. **Structural or disease-modifying** claims would require separate structural endpoints, longitudinal imaging and clinical corroboration. A laboratory mechanism involving sulfur, methylation or collagen metabolism alone cannot justify “cartilage rebuilding” copy.

The conventional choice is not “SAMe versus nothing.” Exercise-based treatment, weight management where appropriate, physical therapy, symptom-guided medicines and clinician-led assessment already form part of standard osteoarthritis care. Scientific evaluation of an ingredient should examine *incremental* efficacy relative to an appropriate comparator and make no implication that it can replace effective interventions without direct evidence.

21. Liver disease: compartment-specific biology and clinically meaningful endpoints

A legitimate hepatological case for SAMe begins with the high importance of hepatic methionine adenosyltransferase activity, membrane phospholipid metabolism and glutathione-related pathways. Experimental data connect reduced hepatic SAMe availability and disturbed MAT expression to injury and altered cell regulation. The weak step in the promotional chain is the assumption that oral supplementation reverses these mechanisms sufficiently to prevent cirrhosis, portal hypertension, hepatic decompensation, hepatocellular carcinoma or mortality. [8,25]

A placebo-controlled **24-week trial in alcohol-related liver disease**, enrolling **37 patients**, administered approximately **1,200 mg oral SAMe per day** and studied clinical, biochemical and histological variables in the context of alcohol abstinence. There was **no demonstrated between-group improvement** in the studied clinical or histological outcomes. This result illustrates why a treatment may look mechanistically attractive yet fail to produce benefit beyond essential standard interventions. Older studies and reviews are heterogeneous, and the evidence on outcomes important to patients´ survival, transplantation, decompensation and quality of life, all remains inadequate. [10,19,20]

The distinction between **cholestasis, alcohol-associated disease, metabolic dysfunction-associated steatotic liver disease, viral hepatitis and decompensated cirrhosis** is essential. A response observed in a laboratory marker of biliary dysfunction cannot be transported automatically to fibrosis reversal in metabolic liver disease. Similarly, short-term reductions in aminotransferase concentrations may reflect biological activity or background clinical management; without a validated disease-specific relationship, they do not establish prevention of advanced liver outcomes. Trials should predefine whether they seek relief of a symptom, improvement of an accepted surrogate or reduction in hard outcomes.

Pregnancy-associated intrahepatic cholestasis demands a particularly strict standard. Cochrane's review of treatments concluded that evidence was insufficient to establish that SAMe, alone or combined with other studied interventions, effectively treats the condition. The balance must consider both maternal symptoms and fetal outcomes. It would be unsafe to cite older pregnancy research as evidence that supplement use in pregnancy is generally established as safe. [34]

At the translational level, an appropriate liver study would distinguish baseline liver function, degree of fibrosis, etiology, concurrent standard treatment, alcohol use, metabolic risk factors and relevant drug interactions. Where liver-specific biomarkers are explored, investigators should decide in advance which are mechanisms of action and which are clinically validated endpoints. A positive glutathione measure in a small trial would support target engagement; it could not support a claim that the supplement “detoxifies the liver,” a phrase too imprecise to be scientifically meaningful and often problematic under food-claim rules.

22. Methylation, psychiatry and ageing: evaluating the seductive hypotheses

Commercial narratives often conflate **methylation**, **epigenetic rejuvenation**, **mood**, **detoxification** and **healthy ageing** as if all were outputs of a single biochemical switch. They are not. SAMe is involved in methyl transfer, but the methylated targets, relevant compartments and regulatory feedback systems differ by tissue, age, genetic background and disease context. Increased methyl-donor availability might raise the flux through some pathways, fail to affect others, or alter ratios through SAH accumulation. A biological change must be demonstrated; it cannot be inferred from taking a capsule.

For neuropsychiatric translation, SAMe's relationship to phospholipid methylation and monoamine-associated biochemistry is an interesting mechanistic framework. However, central nervous system physiology involves blood–brain barrier transport, neuron–glia metabolic exchange, receptor signalling, synaptic plasticity and network-level adaptation. Even if plasma SAMe rises after supplementation, the extent to which it changes central methylation at relevant targets in patients with depression remains an empirical question. The concept of “normalising neurotransmitters” is therefore an attractive but scientifically unearned simplification.

In **epigenetic ageing**, DNA methylation clocks can be powerful predictive or descriptive research tools, yet changes in clock values are not automatically valid surrogate endpoints for longevity or reduced disease incidence. An intervention that perturbs methylation in peripheral blood without tissue-specific causal evidence may move a biomarker without altering a person's health trajectory. In oncology, the same caution applies even more strongly: tumour formation involves both aberrant hypermethylation and hypomethylation, metabolic reprogramming and shifts in MAT isoforms. The direction of a desirable intervention cannot be assumed to be “more methylation.” [9,25]

Claims concerning **physical or cognitive performance, fertility, immunity, muscle growth, liver cleansing and universal fatigue reduction** would need separate evidence. The fact that SAMe is present in cellular growth and differentiation pathways is not proof that external SAMe produces a favourable anabolic

or cognitive effect. Nor can evidence of a pharmacological effect in people with depression be automatically generalised to healthy adults seeking wellbeing.

A fruitful research programme could instead test **a narrow mechanistic hypothesis**: define the tissue, baseline phenotype and target, verify that a specified formulation produces relevant exposure, demonstrate a prespecified biomarker response, then investigate a patient-important clinical outcome in a controlled study. The goal should be a reproducible causal chain rather than a catalogue of biologically plausible benefits.

23. Safety science: what short-term tolerability does not tell us

23.1 Stratifying foreseeable risks

Pooled clinical trials usually suggest that SAMe is tolerated reasonably well over short periods, with gastrointestinal discomfort, nausea, sleep disturbance or activation-type complaints among events reported. Such observations cannot establish safety for **years of exposure** or for every population. Most trials are too short or too small to exclude uncommon harms, and serious adverse events are not uniformly ascertained in older studies. In the absence of a convincing upper-intake evaluation, food operators should avoid presenting an arbitrary commercial dose as a universally safe threshold. [17,21]

The clinically most consequential precaution is **bipolar-spectrum vulnerability**. If a substance can affect mood in some subjects, manic or hypomanic switching is an outcome worth proactively monitoring. This risk is not eliminated by describing the product as endogenous or natural. Individuals with diagnosed bipolar disorder or a history of mania/hypomania should not self-treat mood symptoms with SAMe. Published and institutional guidance also flags potential interactions with serotonin-enhancing medicines and supplements; study results involving physician-supervised antidepressant augmentation are not safety clearance for unsupervised combinations. [17,35]

Other contexts require evaluation: use with **levodopa** for Parkinson's disease; pregnancy and lactation, where robust exposure and safety information remains limited; children and adolescents; advanced renal or hepatic disease; and complex polypharmacy. The NIH discusses a theoretical concern about *Pneumocystis* growth in immunocompromised populations; this should be reported explicitly as a **theoretical** concern rather than as a proven common adverse event. Breastfeeding resources distinguish expected infant exposure from direct clinical outcome evidence; they should not be recast as general proof of safety for pregnant women. [17,36]

23.2 Homocysteine and the danger of one-direction narratives

Because SAMe is metabolically upstream of SAH and homocysteine, an investigator could hypothesise higher homocysteine under certain conditions. Equally, the regulatory interplay with remethylation and transsulfuration makes it inappropriate to assume that every individual experiences an elevation. One small biochemical substudy embedded in a depression trial measured plasma SAMe, SAH, homocysteine, methionine and folate-related parameters, illustrating how the question can be studied empirically rather than settled by argument. It was not large enough to establish long-term cardiovascular safety. [37]

A research safety plan should, where biologically justified, record baseline nutritional status, renal function, total homocysteine and medications; systematically capture mood activation, sleep disturbance, serious adverse events and discontinuation; and follow participants after treatment where relapse or withdrawal may matter. A manufacturer should separately assess toxicological impurities and counterion exposure. SAMe's clinical adverse-effect profile cannot substitute for the **ingredient-specific chemical safety assessment** required for the actual commercial preparation.

23.3 Safety statements belong to a population and exposure

“Safe” is never a property of the molecular name in isolation. It is conditional on **dose, route, duration, identity, formulation, vulnerable populations, interactions and observation period**. Similarly, “no serious adverse events observed” in 30 or 70 subjects does not mean the probability of an uncommon serious event is zero. An author who wants to describe safety precisely should identify the study population and what its size makes it able -and unable- to detect.

24. A food supplement, a medicine and a claim: four different regulatory questions

The 2026 outcome addresses novelty; lawful development requires at least four additional reviews. First, verify the identity and exact scope of the ingredient: **this specified disulfate–tosylate salt used in food supplements**, not every ademetionine preparation. Second, assess the intended composition and daily exposure as a food-safety issue under Regulation (EC) No 178/2002 and the food-supplement framework in Directive 2002/46/EC. Third, analyse national rules governing substances other than harmonised vitamins and minerals, including any notified or prohibited ingredients, maximum or advisory levels, notification requirements and administrative practice. Fourth, review every website, label, brochure and professional-facing communication for its likely regulatory character. [2,4–7,23,38]

Novel-food status and **authorised health claims** are separate tracks. Regulation (EC) No 1924/2006 regulates nutrition and health claims; a scientifically plausible or even clinically observed effect does not by itself create an authorised health claim. The exact wording, nutrient/constituent, conditions of use and regulatory status must be checked in the EU register and the legal acts that determine the claim. Claims to treat major depression, repair cartilage, prevent fibrosis or reverse ageing cannot be justified by pointing to the October 2026 Article 4 statement.

Product classification is another question. Under Directive 2001/83/EC, a product may fall within the medicinal framework by presentation or by function when the relevant legal conditions are satisfied. Its assessed positioning matters: capsule format alone does not settle the question, but advertising it as an antidepressant, anti-inflammatory treatment or liver medicine raises obvious medicinal-product risks. No scientific author should confuse the ability to discuss clinical investigations with permission to sell a treatment claim as a food claim. [39]

For Spain, competent-authority guidance from **AESAN** reiterates that food supplements are concentrated food sources marketed in dose form and are not medicines intended to prevent or treat disease. A Spain-facing regulatory file should assess Royal Decree 1487/2009 and subsequent amendments where applicable, current AESAN interpretation, notification obligations and the identity of the operator placing the product on the market; no universal permissible SAMe intake in Spain should be invented without a current authoritative basis. Other EU Member States may apply different lawful conditions to substances outside harmonised lists. [40]

Suggested launch decision rule: do not proceed to promotional copy until technical identity and stability are demonstrated, safety and market-entry conditions have been checked country by country, and every substantive claim is mapped to its legal basis. “Not novel” is an important first step, not the final signature on a label.

25. Designing the dossier that would separate a real ingredient platform from an opportunistic trend

An independent scientific developer can use the regulatory opening to raise rather than lower the market's standard of proof. A **research-grade dossier** should begin with a clear question and a hierarchy of evidence. It would connect the ingredient's verified identity with clinically meaningful exposure and then with a measured outcome in a defined population. Its documents should be sufficiently complete that another qualified laboratory could test the same material and another investigator could reproduce the regimen.

Stage 1 - Molecular and manufacturing identity. Record CAS and unambiguous substance nomenclature, salt stoichiometry, manufacturing route, raw material origin, test methods, impurity profile, native diastereomer fraction, microbiological controls and process-specific risks. Do not represent an ingredient as identical merely because it shares the parent SAMe acronym with another product. [11,12,23]

Stage 2 - Stability and dose truthfulness. Develop a stability-indicating procedure; specify the relationship between gross salt weight and active-moiety declaration; validate dosage-unit consistency; measure storage and shipping effects; and ensure that the amount supported by the label is available at the *end* of shelf life. An attractive potency at batch release is not sufficient if the molecule degrades before consumption.

Stage 3 - Human exposure comparability. Where claims of superior bioavailability are commercially important, perform a suitable direct human comparison using equimolar active SAMe, ideally crossover design with prespecified sampling. Account for fasting/feeding and endogenous baseline. State explicitly whether results are relative or absolute bioavailability and whether they extend beyond the particular comparator and population tested. [14]

Stage 4 - Clinical efficacy and safety. Select one realistic indication and a population with a demonstrable unmet need; use a placebo-controlled design when ethically appropriate; choose an accepted patient-important endpoint; define meaningful effect size and sample-size assumptions prospectively; pre-register statistical analysis and handle missingness transparently. Monitor adverse events and interactions sufficiently to support the proposed exposure period. Positive biochemical results alone should not be repurposed as proof of clinical outcomes.

Stage 5 - Health-economics and commercial viability. Cost per kilogram is a poor metric if the delivered active content differs. Model cost per assay-confirmed milligram, stability losses, packaging, quality-control costs, realistic daily intake where legally permissible, target-market constraints and distribution margins. Where clinical trials are required to substantiate a commercially useful authorised claim, the expected cost and evidentiary threshold should enter the business plan rather than being treated as a later marketing exercise.

Stage 6 - Legal translation and post-market stewardship. Create a documented claims matrix; establish notification and traceability procedures where relevant; collect and assess complaints and suspected adverse events; maintain batch traceability; monitor scientific and regulatory changes; and update communication materials when evidence evolves. The objective is not to turn a supplement company into a medicinal manufacturer by rhetorical fiat. It is to apply proportionate, auditable controls to an ingredient with complex chemistry and clinically sensitive suggested uses.

26. Critical appraisal checklist: questions the next SAMe paper or supplier must answer

A rigorous editorial or industrial review can be organised around a dozen questions. **Identity:** was the salt specified or was the material merely called SAMe? **Dose:** did milligrams denote the salt, SAMe cation or an unspecified proprietary blend? **Quality:** were native stereochemistry, degradation products and expiry potency known? **Route:** oral, intravenous or intramuscular, and can the exposure be compared? **Population:** healthy adults, patients with a diagnosed illness, medicated patients or vulnerable groups? **Comparator:** placebo, an active drug or historical control? **Duration:** enough to detect a plausible effect and relevant harms? **Outcome:** biological surrogate, questionnaire score, function, relapse or hard clinical event? **Statistics:** prespecified endpoint, multiplicity and robust handling of withdrawals? **Transparency:** sample-size calculation, registration, conflicts and complete reporting? **Generalisability:** would the actual commercial formulation reach comparable exposures? **Regulatory translation:** does the suggested claim have an authorisation and does the target country allow the product as configured?

This checklist prevents four recurrent errors. The first is the **biochemical fallacy**: a molecule has a function in normal physiology, therefore consuming more improves that function. The second is the **pharmacokinetic fallacy**: better absorption proves a better clinical outcome. The third is the **meta-analytic fallacy**: the favourable pooled estimate settles disagreements among heterogeneous and often small studies. The fourth is the **regulatory fallacy**: one favourable classification in one legal domain amounts to permission for an entire catalogue of health or disease claims.

The same list is also constructive. A manufacturer able to answer these questions well may differentiate its product legitimately, propose reproducible studies and provide better information to professionals. A reader can be enthusiastic about translational research while remaining exacting about what has been demonstrated. This is a stronger scientific position than either reflexive scepticism or promotional certainty.

27. A final verdict: an opportunity made more serious by restraint

The most important aspect of the October 2026 event is not that SAMe has suddenly become a new biochemical discovery. It has not. Nor has Europe pronounced it therapeutically effective. What changed is a status determination concerning a **specified stabilised chemical form in a specified food category**, after a contested assessment of historical use. [1–3]

SAMe remains genuinely remarkable: an endogenous metabolite linking methyl transfer, membrane biochemistry, redox regulation and cellular adaptation. That fact justifies research enthusiasm. It does not abolish the ordinary disciplines of pharmaceutical analysis, clinical epidemiology or food law. The evidence for antidepressant effects is promising but heterogeneous; the osteoarthritis signal is limited; meaningful benefits in chronic liver disease are not established; and the safety of indiscriminate or prolonged use cannot be assumed. [15–21]

The future of SAMe in Europe should therefore be determined less by the language of nutritional fashion and more by six questions: **Which molecular form? What active dose? Which formulation and exposure? Which population? What clinically important outcome? Which lawful claim?**

If these questions are answered with measurable evidence, SAMe may evolve from a fascinating metabolic cofactor and contested supplement ingredient into a precisely characterised platform for targeted interventions. If they are not, the 2026 regulatory reversal risks being mistaken for a scientific validation it never was.

The right conclusion is neither "miracle molecule" nor "marketing illusion." It is a serious biochemical candidate whose real value depends on the quality of the evidence that accompanies it.

References and primary sources

[1] European Commission, DG SANTE. *Consultation process on novel food status.* Public entry: "S-adenosyl-L-methionine disulfate tosylate", 14 October 2026, "Not Novel in food supplements". https://food.ec.europa.eu/food-safety/novel-food/consultation-process-novel-food-status_en

[2] Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, particularly Articles 3–6. https://eur-lex.europa.eu/eli/reg/2015/2283/oj/eng

[3] Haslam O. EU reverses novel food decision on healthy aging ingredient SAMe. *NutraIngredients*, 20 October 2026. Secondary account of 2026 consultation chronology. https://www.nutraingredients.com/Article/2026/10/20/eu-reclassifies-same-ingredient-as-non-novel/

[4] European Food Safety Authority. *Food supplements — EU framework.* https://www.efsa.europa.eu/en/topics/topic/food-supplements

[5] Directive 2002/46/EC on the approximation of the laws of Member States relating to food supplements; and Regulation (EC) No 178/2002 (general food law). https://eur-lex.europa.eu/eli/dir/2002/46/oj/eng ; https://eur-lex.europa.eu/eli/reg/2002/178/oj/eng

[6] Regulation (EC) No 1924/2006 on nutrition and health claims made on foods, especially Articles 3, 5, 6 and 10. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:32006R1924

[7] European Commission, DG SANTE. *EU register of nutrition and health claims* and guidance on health claims. https://food.ec.europa.eu/food-safety/labelling-and-nutrition/nutrition-and-health-claims/eu-register-health-claims_en

[8] *One-Carbon Metabolism and S-Adenosylmethionine in Non-Alcoholic Fatty Liver Disease Pathogenesis and Subtypes.* Review. PubMed PMID: 37123053. https://pubmed.ncbi.nlm.nih.gov/37123053/

[9] *Subcellular one carbon metabolism in cancer, aging and epigenetics.* Review, 2024. https://pmc.ncbi.nlm.nih.gov/articles/PMC11375787/

[10] Medici V et al. S-adenosyl-L-methionine treatment for alcoholic liver disease: a double-blinded randomised placebo-controlled trial; biochemical pathway discussion. *Alcohol Clin Exp Res*, 2011. PMID: 22044287. https://pubmed.ncbi.nlm.nih.gov/22044287/

[11] United States Pharmacopeia. *S-Adenosyl-L-methionine Disulfate Tosylate*, USP–NF monograph preview. https://doi.usp.org/USPNF/USPNF_M704_04_01.html

[12] *HPLC Separation of the (S,S)- and (R,S)-forms of S-Adenosyl-L-methionine.* https://pmc.ncbi.nlm.nih.gov/articles/PMC4398633/

[13] Bartels A, Germer P, Andexer JN. *SAM is not the SAM(e): diastereomers of an important cofactor. Natural Product Reports*, 2026. PMID: 42454449. https://pubmed.ncbi.nlm.nih.gov/42454449/

[14] Cameron BR, Ferreira L, MacDonald ID. Pharmacokinetic study of a novel oral formulation of S-adenosylmethionine (MSI-195) in healthy subjects. *BMC Pharmacol Toxicol*, 2020;21:88. doi:10.1186/s40360-020-00466-7. https://pubmed.ncbi.nlm.nih.gov/33317621/

[15] Limveeraprajak N et al. Efficacy and acceptability of S-adenosyl-L-methionine (SAMe) for depressed patients: a systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*, 2024;132:110985. doi:10.1016/j.pnpbp.2024.110985. https://pubmed.ncbi.nlm.nih.gov/38423354/

[16] Peng T-R, Cheng H-Y, Wu T-W. S-adenosylmethionine as an adjuvant therapy for patients with depression: an updated systematic review and meta-analysis. *Gen Hosp Psychiatry*, 2024;86:118–126. doi:10.1016/j.genhosppsych.2024.01.001. https://pubmed.ncbi.nlm.nih.gov/38199136/

[17] US National Institutes of Health, NCCIH. *S-Adenosyl-L-Methionine (SAMe): In Depth.* https://www.nccih.nih.gov/health/sadenosyllmethionine-same-in-depth

[18] Rutjes AWS, Nüesch E, Reichenbach S, Jüni P. S-adenosylmethionine for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev*, 2022;4:CD007321. doi:10.1002/14651858.CD007321.pub2. https://www.cochrane.org/evidence/CD007321_s-adenosylmethionine-same-osteoarthritis

[19] Medici V et al. Randomised 24-week trial in alcohol-related liver disease. *Alcohol Clin Exp Res*, 2011. https://pubmed.ncbi.nlm.nih.gov/22044287/

[20] Rambaldi A, Gluud C. S-adenosyl-L-methionine for alcoholic liver diseases. *Cochrane Database Syst Rev*, 2006;CD002235 (historical review; consult subsequent review history). doi:10.1002/14651858.CD002235.pub2. https://pubmed.ncbi.nlm.nih.gov/16625556/

[21] Norwegian Scientific Committee for Food Safety (VKM). *Risk assessment of histidine, methionine, S-adenosylmethionine and tryptophan.* Report 2013:10. https://vkm.no/english/riskassessments/allpublications/riskassessmentofhistidinemethioninesadenosylmethionineandtryptophan.4.27ef9ca915e07938c3b2c02a.html

[22] EFSA NDA Panel. Scientific Opinion on substantiation of claims concerning maintenance of joints (including ID 1973), bone and muscles. *EFSA Journal*, 2010;8(2):1493. doi:10.2903/j.efsa.2010.1493. https://www.efsa.europa.eu/en/efsajournal/pub/1493

[23] Lithuania, Institute of Hygiene; European Commission publication. *Article 4 consultation: S-adenosyl-L-methionine disulfate tosylate*, dated 14 October 2026, two-page primary administrative record (Lithuanian reassessment; Italian 2016 confirmation; Working Group of 17 September 2026). https://food.ec.europa.eu/document/download/aecca872-9446-4f5b-a522-59530dc19a88_en?filename=novel-food_consult-status_same.pdf

[24] Commission Implementing Regulation (EU) 2018/456 of 19 March 2018 on the procedural steps of the consultation process for determination of novel-food status. https://eur-lex.europa.eu/eli/reg_impl/2018/456/oj/eng

[25] Ramani K, Lu SC. Methionine adenosyltransferases in liver health and diseases. *Liver Research*, 2017;1(2):103–111. doi:10.1016/j.livres.2017.07.002. https://pubmed.ncbi.nlm.nih.gov/29170720/

[26] PubChem. S-Adenosyl-L-methionine (disulfate tosylate), CID 9875462; mass and constituent identification. https://pubchem.ncbi.nlm.nih.gov/compound/9875462

[27] Bartels A, Germer P, Andexer JN. SAM is not the SAM(e): diastereomers of an important cofactor. *Natural Product Reports*, published 15 July 2026. doi:10.1039/D6NP00059B. https://pubmed.ncbi.nlm.nih.gov/42454449/

[28] Cameron BR, Ferreira L, MacDonald ID. Pharmacokinetic study of a novel oral formulation of S-adenosylmethionine (MSI-195) in healthy subjects: dose escalation, food effect and comparison to a commercial nutritional supplement product. *BMC Pharmacology and Toxicology*, 2020;21:88. doi:10.1186/s40360-020-00466-7. https://pmc.ncbi.nlm.nih.gov/articles/PMC7734772/

[29] Papakostas GI, Mischoulon D, Shyu I, Alpert JE, Fava M. S-adenosyl methionine augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: a double-blind, randomized clinical trial. *American Journal of Psychiatry*, 2010;167:942–948. doi:10.1176/appi.ajp.2009.09081198. https://pubmed.ncbi.nlm.nih.gov/20595412/

[30] Mischoulon D et al. A double-blind, randomized, placebo-controlled clinical trial of S-adenosyl-L-methionine versus escitalopram in major depressive disorder. *Journal of Clinical Psychiatry*, 2014;75:370–376. doi:10.4088/JCP.13m08591. https://pmc.ncbi.nlm.nih.gov/articles/PMC5360105/

[31] Sarris J et al. Is S-adenosyl methionine (SAMe) for depression only effective in males? A re-analysis of data from a randomized clinical trial. 2015. PMID:26011569. https://pubmed.ncbi.nlm.nih.gov/26011569/

[32] Mischoulon D et al. Dose increase of S-adenosyl-methionine and escitalopram in a randomized clinical trial for major depressive disorder. Secondary analysis of 2014 RCT. https://pmc.ncbi.nlm.nih.gov/articles/PMC6917851/

[33] Sarris J et al. Adjunctive S-adenosylmethionine (SAMe) in treating non-remittent major depressive disorder: an 8-week double-blind, randomized, controlled trial. 2018. PMID:30115553. https://pubmed.ncbi.nlm.nih.gov/30115553/

[34] Cochrane Pregnancy and Childbirth. *Interventions for treating intrahepatic cholestasis of pregnancy.* Evidence review including SAMe, search to December 2019. https://www.cochrane.org/evidence/CD000493_interventions-treating-intrahepatic-cholestasis-pregnancy-icp

[35] Mayo Clinic. *S-adenosylmethionine (SAMe): Safety and interactions.* Expert consumer summary; accessed October 2026. https://www.mayoclinic.org/drugs-supplements-same/art-20364924

[36] US National Library of Medicine. *SAM-e.* Drugs and Lactation Database (LactMed); updated 15 February 2025. https://www.ncbi.nlm.nih.gov/books/NBK501870/

[37] Mischoulon D et al. Bioavailability of S-adenosyl methionine and impact on response in a randomized, double-blind, placebo-controlled trial in major depressive disorder. *Journal of Clinical Psychiatry*, 2012;73:843–848. doi:10.4088/JCP.11m07139. https://pubmed.ncbi.nlm.nih.gov/22687580/

[38] Regulation (EU) No 1169/2011 on food information to consumers (consolidated law should be consulted for implementation). https://eur-lex.europa.eu/eli/reg/2011/1169/oj/eng

[39] Directive 2001/83/EC on the Community code relating to medicinal products for human use; consult current consolidated Article 1(2). https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02001L0083-20250101

[40] AESAN. *Complementos alimenticios* (food supplements), including legal requirements and notification guidance; see also Spain's Royal Decree 1487/2009, as amended. https://aesan.gob.es/seguridad-alimentaria/alimentos-especificos/complementos-alimenticios ; https://www.boe.es/eli/es/rd/2009/09/26/1487/con

Editorial and methodological note

This research monograph is a critical narrative synthesis, not a new systematic review, medicinal product assessment or clinical practice guideline. Searches and regulatory checks were performed against accessible public sources on 26 October 2026. Primary EU legislation, the Commission's public consultation table, recognised compendial material, published clinical studies and public-health guidance were prioritised. The complete two-page Lithuanian Article 4 reassessment published by the Commission on 14 October 2026 has been reviewed directly; references to the earlier May 2026 conclusion are additionally supported by the accessible public record and contemporary reporting. The October primary document is privileged over secondary press accounts when describing the grounds for reconsideration. No inference is made that an Article 4 status outcome is a positive safety evaluation or a clinical efficacy approval. The analysis is for scientific, regulatory and industry discussion and is not individual medical advice.

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