LGC AXIO PROFICIENCY TESTING

Food supplements: moving from the 'Wild West' towards quality and compliance

lgcstandards.com/AXIO

Sales of supplements are booming, but are they safe and effective?

A growing body of scientific research suggests that supplementing our diets with vitamins, minerals, botanicals, or fatty acids can have positive effects on various aspects of health - from sports performance and recovery [1] to cardiovascular fitness [2], obesity [3], memory [4] and neurological disorders [5]. This trend is driving a boom in the supplements industry, [6] but recent scrutiny has also called into question the safety and effectiveness of many supplements. These include discrepancies between advertised and actual concentrations of active ingredients, as well as the presence of contaminants and toxic compounds in some products [7-12, 28]. Given the widespread availability of supplements in Europe and the USA through shops and online retailers, combined with the significant safety and quality concerns, this whitepaper explores shortcomings in US and EU regulations [33, 10]. It emphasises the crucial role of Proficiency Testing (PT) in supporting a rigorous and transparent testing programme that enables reputable brands to differentiate themselves from lower quality competitors. Drawing on insights from the LGC AXIO Proficiency Testing team, we examine the breadth and diversity of quality markers and chemical contaminants present in supplements, and consider the significant technical challenges faced by manufacturers.

Still too frequently, dietary supplements are in the spotlight for the wrong reasons

Under the 1994 Dietary Supplement Health and Education Act (DSHEA), dietary supplements in the US are not subject to pre-market approval regarding safety, efficacy, purity, or labelling. In the majority of cases, the Food and Drug Administration (FDA) reacts only in response to serious adverse events, in cases where drug-like claims are made on the label, or if new scientific findings are reported after the goods have gone on sale. Consequently, misleading labelling is common. For example, 30 dietary supplements sold with claims to 'boost the immune system' were purchased from a major US online retailer and tested as part of a 2022 study published in the journal *JAMA Network Open* [7]. It found that more than half had inaccurate labels when compared with the contents of the products, while 13 featured ingredients on the label that were not detected. An FDA news release published in December 2020 also confirmed the presence of undeclared drugs in 50 supplements sold by major online retailers, [8] demonstrating that consumers should be cautious about using certain products, especially those claiming to enhance sexual performance, weight loss, body-building, sleep or pain relief.

Although the FDA is the ultimate authority to regulate the US market, the dietary supplements manufacturer Now Foods launched its own testing programme after becoming frustrated by such persistent reports of the widespread availability of low quality, potentially unsafe products online. In an interview with LGC [9], the company's Senior Director of Quality, Katie Banaszewski, stated that, following six years and 15 rounds of testing of products from lesser known brands, purchased from major US websites, **"All studies performed to date show 50-75% of evaluated brands are non-compliant with their label claims", and that some of those brands "also use deceptive language on their labels, creating the perception that a product is more potent than it is."** She added that the Now Foods' analysis had identified some serial offenders, with one unnamed company "failing all seven rounds of testing we have done".

As of April 2024, Amazon.com has implemented significant updates to strengthen compliance requirements for dietary supplements sold through their website. Sellers must now obtain compliance verification from one of three third-party testing, inspection, and certification organizations: NSF, UL, or Eurofins. While ISO 17025-accredited labs are still acceptable, sellers must submit testing data to one of these companies, which are now responsible for verifying that supplement products adhere to the FDA's Good Manufacturing Practices, are free from harmful contaminants, and have accurate ingredient labelling. Amazon is particularly scrutinising products marketed for sexual enhancement, weight management, and sports nutrition, requiring testing for undeclared active pharmaceutical ingredients (APIs). While supplement suppliers appreciate efforts to improve market integrity, they are still assessing the costs and impact of these rapid changes to their businesses.

In the European Union (EU), food supplements are regulated as foods, and their quality is the responsibility of producers and distributors. Within European law, with the exception of vitamins and minerals, there are no commonly accepted standards for the composition of food supplements [10]. Some EU member states have adopted a list of ingredients allowed or prohibited in food supplements, although the composition of these products is still largely subject to national legislation, resulting in numerous trade barriers even between countries within the EU [10]. Due to the sheer number of supplement products on the market in the EU, and the lack of extensive post-market surveillance, quality standards remain a significant issue. For example, in 2020 Mannino et al. [11] tested 24 supplements that claimed to contain cranberry: only five did so, and the majority of samples also claimed an incorrect amount of bioactive compounds. Another study, published in 2021 by Gaspar et al., reported that 45% of the bilberry food supplements they tested were of unacceptable quality. It also found that some did not even contain bilberry, or had been adulterated with anthocyanin chemicals from other sources [12].

> **'Anytime there is an increased demand for a product there is a very real risk of economically motivated adulteration'**
> *Deleo de Leonardis, CEO of Purity-IQ Inc*

Adulteration can take different forms: for example, by adding extracts or compounds from other plants [13] (as commonly happens with *Gingko biloba*), or by using other parts of the plant [14] (such as Ginseng root adulterated with leaves and/or stem). Meanwhile elderberry, widely used to treat cold and flu symptoms and 'boost the immune system', saw sky-rocketing sales during the COVID pandemic, together with a parallel increase in cases of adulteration [15]. A recent study revealed that over 60% of dietary supplements purporting to contain European elderberry exhibited anthocyanin profiles that differed markedly from those of authentic elderberry anthocyanins - strongly suggesting adulteration with additional ingredients, such as black rice and purple carrot [15].

In a market where adulteration is rampant, manufacturers are increasingly choosing to differentiate themselves by using scientific methods to validate the authenticity of their products. Depending on the supplement in question, testing methods may range from visual microscopy to state-of-the-art Nuclear Magnetic Resonance spectroscopy (NMR) techniques. However, regardless of the measurement method chosen, appropriate quality control (QC) measures to ensure that the method is performing as expected are vital to the quality of the data produced.

LGC Axio proficiency testing provides a range of samples that assist supplement manufacturers in verifying the authenticity, quality, and consistency of commonly adulterated products, including elderberry.

PT Sample	Format	Analyte
PT-PH-19	Supplied as 1g elderberry plant material or plant extract	Phytochemical identity confirmation

Structure/function claims: a non-compliance hotspot

In the US, both conventional foods and dietary supplements commonly feature structure/function claims on their labels which describe the role of a dietary ingredient in affecting the normal structure or function of the human body. For example, a label might state "Calcium builds strong bones" [16]. These claims are exempt from the strict requirements of health claims and do not require pre-market review or approval [16], although manufacturers must be able to verify that the claim is truthful and is not misleading. In addition, the manufacturer must notify the FDA no later than 30 days after the product is introduced to the market, and include a disclaimer that the FDA has not evaluated the claim. However, one study on Ayurvedic herbal supplement blends in the US market revealed significant non-compliance with these regulations, especially with structure/function claims. It found that legally required disclaimers were often absent, and that claims lacked scientific support: for example, statements like "Cinnamon helps maintain healthy blood sugar/sugar metabolism" were non-compliant as they did not align with the scientific consensus [17].

In the EU, manufacturers and importers can promote nutrition and health benefits, provided they are scientifically substantiated and comply with labelling, presentation, and advertising regulations outlined in Regulation (EC) No 1924/2006. This regulation establishes stringent conditions for making nutrition claims, such as the provision of supporting scientific evidence and adherence to specific labelling guidelines. Additionally, the Register of Nutrition and Health Claims provides a comprehensive list of permitted claims and their definitions - offering clarity to manufacturers, as well as additional protection for consumers against unsubstantiated statements.

Confirming label claims

Dietary supplements, often derived from plant-based sources, vary naturally vary in composition. For example, St. John's Wort, commonly used to treat cold and flu symptoms, shows significant changes in active ingredient levels depending on yearly growing conditions and harvest times [18]. It is therefore important that realistic tolerances, which account for this variability, can be applied to the nutritional labelling of these products. A manufacturer can compare the laboratory's testing results with the theoretical composition of the product to determine their similarity. However, the next challenge lies in determining whether the product aligns with regulatory guidelines.

The guidance documents below also set some clear rules on what is considered compliant or not:

- In the EU: *Guidance document for competent authorities for the control of compliance with EU Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers (2012)* [19].
- In the US: *Code of Federal Regulation Title 21 (21 CFR 101.9(g)(3)) and (g)(4)* [20].

Measurement uncertainty

To determine whether a measurement result aligns with a specification and demonstrates compliance with regulations, it is crucial to also consider the associated measurement uncertainty.

The 2021 Eurachem guide Use of uncertainty information in compliance assessment [21] offers the following guidance on incorporating uncertainty when assessing compliance with specified limits:

"*Any analytical measurement is subject to an uncertainty. In practice the uncertainty may arise from many possible sources, including (but not limited to), sampling, matrix effects, uncertainties of masses and volumetric equipment, approximations, etc.*"

And:

"An analytical measurement result is complete only when it is accompanied by a statement of the associated uncertainty." [22]

The need for proficiency testing

Supplement producers and retailers require comprehensive analytical capabilities to assess quality parameters and detect common contaminants. These analytical methods, whether they are chemical or microbiological, must be fit for purpose, and an established means of assessing their effectiveness is proficiency testing.

PT is an essential quality tool for laboratories for a number of reasons, not least of which is that laboratories performing testing which is accredited to ISO/IEC 17025 are required to monitor their performance in comparison to other laboratories. PT involves the distribution of blind samples to participating laboratories, which then analyse the samples and submit their results to a PT provider. These results are evaluated using a performance assessment criteria described in ISO/IEC 17043 and ISO 13528, and feedback is provided to the laboratories, enabling them to identify any areas for improvement in their testing processes.

> **One of the most valued characteristics of PT is the independence of this evaluation: laboratories can, and should, routinely undertake many other forms of quality assurance, but PT is the only one where the 'answer' or desired result is not known by the laboratory beforehand.**

Among the other benefits of PT is that laboratories taking part can receive test materials which are identical or highly similar to their routine samples, while participation also allows an accurate reflection of the accuracy and reliability of their test results, capabilities and resources to emerge. These capabilities encompass a range of factors including the variety of tests conducted, available methodologies, instrumentation, and overall competency.

Proficiency testing can help laboratories assess compliance with labelling

In this unique PT sample, AXIO has provided a means for laboratories to assess the compliance of a supplement product with the claims or information provided on the label.

Sample	Quantity	Supplied as	Target Analyte(s)
PT-PH-21 Potency of multielement	15g	Multielement supplement	Calcium; Zinc; Magnesium; Copper; Manganese; Potassium; Iron; Total Chromium; Selenium; Compliance with labelling.

It challenges laboratories to decide whether they would consider the product compliant or not, based on the label provided in the instruction sheet, their obtained testing results (including the uncertainty of measurement) and the guidance documents.

The PT summary results for two analytes, zinc and potassium (respectively labelled at 5.882 and 0.046 mg/g on the provided label), are shown below.

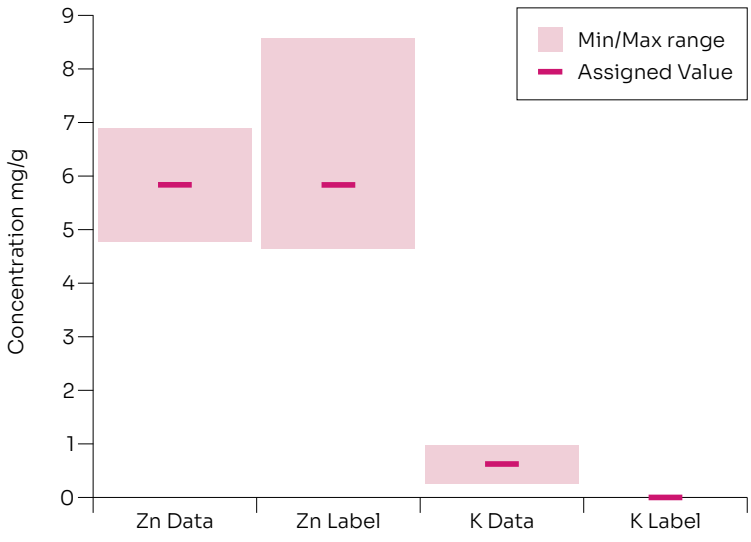
Analyte	Unit	Assigned Value	Uncertainty of Assigned Value	Standard deviation for proficiency assessment (SDPA)	Exp. SDPA	Satisfactory Range
Zinc	mg/g	5.84	0.213	0.482	0.527	4.78 to 6.89
Potassium	mg/g	0.70	0.072	0.163	0.178	0.34 to 1.06

The satisfactory range in a proficiency testing exercise is derived from the Assigned Value and the standard deviation for proficiency assessment (SDPA). In many cases the satisfactory range for proficiency testing is defined as the assigned value +/- 2 times the SDPA. The measurement uncertainty of the assigned value is included in the estimation of the satisfactory range.

The EU guidance document on the control of compliance for minerals in food supplements specifies lower and upper tolerances (including the measurement of uncertainty for the analytical result) of -20% and +45% respectively.

Element	PROFICIENCY TESTING			LABEL		
	Assigned value (AV)	Satisfactory range in the PT		Label (mg per g)	Acceptable range based on the guidance document of -20%, +45%	
		Lower limit	Upper limit		Lower limit	Upper limit
Zinc	5.84	4.78	6.89	5.882	4.706	8.529
Potassium	0.7	0.34	1.06	0.027	0.022	0.039

Zinc concentration was compliant with the labelling, as the measured result and its uncertainty overlap significantly with the label value and its tolerances, while the potassium concentration was not.



Adverse reactions

A significant concern expressed by clinicians relates to the interaction of herbal supplements with a superfamily of drug metabolising proteins known as cytochrome p450 enzymes, which are present mainly in the liver. Six cytochrome p450 enzymes are responsible for metabolising an estimated 80% of prescribed medications [23]. However, ingredients found in some common herbal supplements can interfere with their normal function – leading to altered metabolism of drugs, creation of toxic metabolites or in the worst cases, production of tissue-damaging reactive metabolites such as oxygen free radicals, which can cause organ failure [24]. Multiple compounds in *Gingko biloba*, hyperforin from St. John's Wort, ginsenosides in ginseng, and diallyl sulphide in garlic interfere with the function of cytochrome p450 enzymes, which introduces the possibility of side effects, interactions with medication, or toxicity [24].

Over the past two decades, the utilisation of pre-workout supplements has surged, driven by the quest for weight loss and enhanced sports performance. Among these supplements, those which have naturally high levels of the stimulant synephrine, such as *Citrus aurantium* (Bitter Orange) extracts, have gained significant popularity. Synephrine, a cardiovascular stimulant associated with weight loss, has, however, been linked to a growing number of adverse events. A recent study [25] highlighted 30 case reports of patients experiencing medical issues such as chest pain, palpitations, syncope, and dizziness following the use of synephrine-containing supplements. Shockingly, five patients were left disabled or remained on medication at their last follow-up. The absence of legislation in most countries regarding the permissible amount of synephrine in dietary supplements therefore raises significant concerns about consumer safety.

Adverse reaction monitoring

The potential for dietary supplements to cause adverse effects has prompted the creation of monitoring systems on both sides of the Atlantic. In the US, the FDA's Center for Food Safety and Applied Nutrition (CFSAN) operates the CAERS adverse event reporting system: a database of adverse event and product complaint reports submitted to the FDA about foods, dietary supplements, and cosmetics [26]. Meanwhile, in the EU, EudraVigilance is a system for managing and analysing suspected adverse reactions to medicines which have been authorised or are being studied in clinical trials in the European Economic Area (EEA) [27].

Enhancing safety and compliance using third party certification

When choosing dietary supplements and products, it is important to know they have not been contaminated with unsafe or banned substances. Global quality assurance and third-party supplement certification programmes, such as those provided by LGC's Informed Choice brand, [28] are designed to minimise the risks of dietary supplement products being inadvertently contaminated with prohibited and potentially harmful substances. Certification by Informed Choice is the result of successful participation in a voluntary, third-party, supplement testing programme by companies who wish to become a certified supplement brand, [29] register some (or all) of their products, and carry the Informed mark on them. Their products are then tested by LGC's world-class anti-doping laboratory which screens against more than 250 substances banned in sport, using ISO/IEC 17025 accredited methods. This means that potential buyers who see the Informed logo or on-pack descriptor on a product's packaging can be assured that it has undergone rigorous checks and testing, and is safer to use. While no laboratory's analysis will encompass all of the analytes listed in The World Anti-Doping Agency's prohibited list, LGC is constantly developing new technologies and using its relationships with international anti-doping organizations [30] in order to provide appropriate coverage for new and emerging threats.

Legislation of Dietary Supplements

United States

The United States Food and Drug Administration (FDA) stipulates that dietary supplements are intended to add to, or supplement, the diet and are therefore different from conventional food. The US Congress defines 'dietary supplement' as "a product intended for ingestion that, among other requirements, contains a 'dietary ingredient' intended to supplement the diet." Meanwhile, a product intended to treat, diagnose, cure, or prevent diseases is regarded as a drug in the US, even if it is labelled as a dietary supplement [31].

The FDA regulates both finished dietary supplement products and dietary ingredients under the Dietary Supplement Health and Education Act of 1994 (DSHEA). DSHEA places dietary supplements in a special class within the general categorisation of 'foods', unless the product meets the definition of a drug (e.g. because it is labelled to treat a disease). These are different to the set of regulations that cover conventional food and drug products.

In addition to establishing regulations, the FDA operates a system of official Warning Letters to notify companies of law violations, and instruct them on necessary corrective actions. These have been issued to multiple companies for selling adulterated dietary supplements that contain, in some cases, novel or new dietary ingredients for which the FDA has not received the required notifications or, sometimes, unsafe food additives [32].

DSHEA: Key Points

- Products cannot be represented as "for use as a conventional food or as a sole item of a meal or the diet"
- Products are not required to obtain pre-market approval
- Products do not have to be proven safe or effective prior to being marketed
- To remove supplements from the marketplace, the FDA must demonstrate that a product is related to a "significant or unreasonable risk of illness or injury"
- Establishes labelling rules for the product category (e.g. that dietary supplements cannot make disease prevention or treatment claims)
- Outlines good manufacturing practices that need to be upheld
- Describes the formal adverse event reporting process [33]

European Union

In the General Food Law Regulation (EC) No 178/2002, food supplements are considered as food: meaning that the food business operator placing the product on the market is responsible for its safety. Directive 2002/46/EC establishes both lists of substances permitted as food supplements, and rules for the labelling of vitamins and minerals used in dietary food supplements. [34]

Commission Regulation (EU) 2023/915 regulates the maximum levels of various contaminants which may be present in food supplements (for example, lead at 3 mg/kg, cadmium at 1-3mg/kg, and mercury at 0.1 mg/kg, with polycyclic aromatic hydrocarbons (PAHs) at 10 µg/kg for benzo[a]pyrene and 400-500 µg/kg for pyrrolizidine alkaloids). However, there are aspects of food supplement legislation that are not harmonised across the EU [35].

Testing methods, QC and PT

To safeguard the health of consumers, uphold the reputation of manufacturers and retailers, and mitigate costs associated with product recalls, analytical testing of supplement raw materials and finished products is essential. Since the term 'supplements' can cover an extremely broad range of materials, from herbal medicines and remedies to food additives, the potential range of test analytes is very large, and many analytical techniques can be applied. However, the lack of analytical methods for many ingredients and products in the supplements marketplace presents an ongoing challenge to manufacturers and regulators alike when it comes to proving quality, safety, and consistency [38].

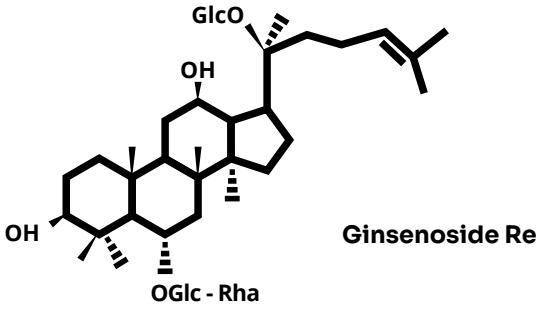
Supplement testing typically falls into two categories, albeit with a significant area of overlap: firstly quality testing for efficacy, and the presence of sufficient or appropriate quantities of components of interest, and secondly contaminant testing for the presence of undesirable compounds, elements or micro-organisms.

Identification of supplements

Herbal supplements are typically plants - or parts of plants, such as flowers, seeds, roots, leaves or bark - in a relatively unprocessed, albeit dried, form. The identification processes for such products are specific to the material in question, and include the evaluation of macroscopic and microscopic characteristics, as well as testing using chromatographic procedures.

The most common herbal supplements often have dedicated monographs in national or international pharmacopeias, outlining tests, acceptance criteria for identification, and contaminant limits. These monographs utilise selected analytical methods developed to identify species-specific metabolites in herbal plants.

Taking ginseng as an example, High Performance-Thin Layer Chromatography (HP-TLC) is an excellent method for 'fingerprinting' the ginsenoside composition in Panax plants, including P. ginseng, P. quinquefolium and P. notoginseng [36]. Fingerprinting involves comparing the phytochemical components of a material with those of a known, authentic standard, providing both qualitative and quantitative insights into the material.



Determination of key secondary metabolites

The determination of key secondary metabolites in herbal supplements involves a variety of methods that have evolved alongside advancements in analytical equipment. Current techniques include thin layer chromatography (TLC), infra-red spectroscopy (IR), near infra-red spectroscopy (NIR), High Performance-Thin Layer Chromatography (HP-TLC), high-performance liquid chromatography (HPLC) with various detectors (ultraviolet, diode array, and mass spectrometry), as well as gas chromatography (GC) coupled with suitable detectors, such as flame ionisation detectors, and mass spectrometry.

Contaminants

Whilst the methods and techniques described previously are widely used to determine components influencing the 'quality' or 'efficacy' of a supplement or medicinal herb, a number of parameters are routinely measured to identify the presence of unacceptable concentrations of a range of contaminants.

The diverse nature of supplements results in a wide range of production processes that can potentially lead to the presence of contaminants, while natural products may also absorb toxic elements from the environment during growth or processing. Microorganisms are another significant concern, especially in herbal supplements as, apart from the direct infection risk, some microorganisms may produce toxins (mycotoxins) that pose both poisoning and carcinogenic hazards.

PT performance in supplements

LGC AXIO Proficiency Testing offers schemes in several different fields of measurement and analysis, including environmental and industrial testing, as well as foods and beverages. AXIO schemes such as PHARMASSURE include samples that are relevant to the supplements industry, including test materials for the identification and quality testing of herbal supplements and preparations, while the CANNABIS scheme is designed for laboratories determining the efficacy and composition of cannabis and cannabis preparations.

The AXIO PHARMASSURE scheme provides dedicated samples for the analysis of cannabidiol (CBD) in supplements, as well as toxic elements in herbal supplements. Several rounds have now been completed for each sample material, typically with good performance recorded by the participants. The most recent round for the determination of CBD in a tincture, effectively an efficacy determination, was a material with a label claim of 5% CBD. Participants exclusively used HPLC methodology for the analysis and reported an average value of 5.06% CBD, with a spread of results, assessed by the reproducibility standard deviation, of 0.056%. Using these criteria to assess the performance of the participant laboratories, the acceptable range of results was 4.94 – 5.17%, within which 83% of the participants were assessed as satisfactory.

Participating laboratories' performance in determining elemental contamination in herbal supplements was similarly good. In this PT, those taking part were required to analyse samples of a herbal supplement for concentrations of the 'big four' toxic elements: arsenic, cadmium, lead and mercury. At concentrations ranging from 0.25 to 1.4 ppm (mg/kg), participant performance was considered satisfactory if the result obtained was within ±20% of the assigned value. Using these criteria, 75%, 86%, 73%, and 73% of the participants were assessed as satisfactory for arsenic, cadmium, lead, and mercury respectively.

The importance of high-quality reference standards

Manufacturers rely on the quality of the laboratories that analyze their products. Contracting a laboratory that holds ISO/IEC 17025 accreditation, covering the compounds that need testing, offers assurance for the manufacturer. These laboratories should use ISO/IEC 17034 accredited reference materials if they are available and participate in PT schemes for compounds within the laboratory's accredited scope [37].

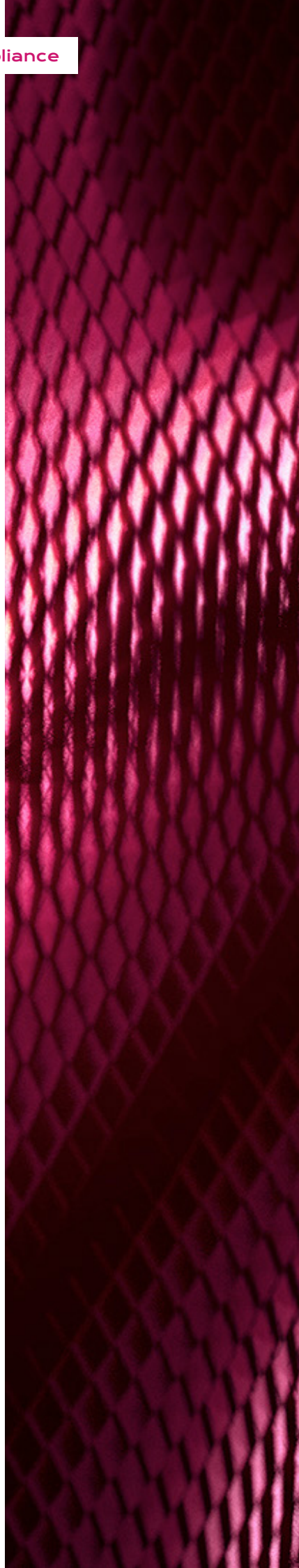
Reference materials play a crucial role in ensuring the accuracy, precision, and recovery of the testing process - encompassing methods, equipment, and staff performance. Beyond this, they are integral to ongoing daily system suitability checks, quality controls, calibration, and training. Therefore, securing high-quality reference standards from a reputable and knowledgeable supplier, such as LGC Standards, is critical. Manufacturers can trust certificates for reference standards that are issued by accredited laboratories, especially those maintaining ISO/IEC 17034 [37].

Conclusions

The supplements market is rapidly expanding [6], resulting in a greater variety of biologically active ingredients, degradation products, and potential contaminants that require measurement and safety assessments [38]. Recent investigations have also emphasised the failure of regulatory frameworks to uphold satisfactory standards for supplements within the major markets of the US and the EU [7-12]. Therefore, renewed investment in method development and validation will be crucial to ensuring the reliable quantification of compounds that enables adequate monitoring of safety and quality [33].

The safety of botanical supplements has become a notable area of concern, due to potential interactions with medications and the risk of side effects [13, 25]. While numerous supplements incorporate potent active ingredients, manufacturers in the US and EU markets are often not bound by the same stringent standards of quality, safety, and efficacy as pharmaceutical products. Consequently, the variability of these parameters persists as a significant issue [33].

The challenges in supplement science and regulation present opportunities for scientists and regulatory bodies to collaborate at national and international levels to share insights and, when appropriate, harmonise approaches to improve public health [39]. Meanwhile, to cater to an increasingly educated customer base, more supplement manufacturers and distributors are differentiating themselves from lower-quality competitors by submitting their products for testing at ISO/IEC 17025 accredited labs enrolled in PT schemes – in order to demonstrate consistent levels of high performance, compliance, and quality in their supplement products.



References

1. Wax B, Kerksick CM, Jagim AR, Mayo JJ, Lyons BC, Kreider RB. Creatine for Exercise and Sports Performance, with Recovery Considerations for Healthy Populations. Nutrients. 2021 Jun 2;13(6):1915.
2. Fernandez ML, Blomquist SA, Hallmark B, Chilton FH. Omega-3 Supplementation and Heart Disease: A Population-Based Diet by Gene Analysis of Clinical Trial Outcomes. Nutrients. 2021 Jun 23;13(7):2154.
3. Xiong H, Wang J, Ran Q, Lou G, Peng C, Gan Q, Hu J, Sun J, Yao R, Huang Q. Hesperidin: A Therapeutic Agent for Obesity. Drug Des Devel Ther. 2019 Nov 12; 13:3855-3866. doi: 10.2147/DDDT.S227499.
4. Hersant H, He S, Maliha P, Grossberg G. Over the Counter Supplements for Memory: A Review of Available Evidence. CNS Drugs. 2023 Sep;37(9):797-817.
5. Yancheva S, Ihl R, Nikolova G, Panayotov P, Schlaefke S, Hoerr R; GINDON Study Group. Ginkgo biloba extract EGb 761(R), donepezil or both combined in the treatment of Alzheimer's disease with neuropsychiatric features: a randomised, double-blind, exploratory trial. Aging Ment Health. 2009 Mar;13(2):183-90.
6. https://www.grandviewresearch.com/industry-analysis/dietary-supplements-market
7. Crawford C, Avula B, Lindsey AT, et al. Analysis of Select Dietary Supplement Products Marketed to Support or Boost the Immune System. JAMA Netw Open. 2022;5(8): e2226040.
8. https://www.fda.gov/news-events/press-announcements/fda-warns-consumers-avoid-certain-male-enhancement-and-weight-loss-products-sold-through-amazon-ebay
9. Interview with natural health company and supplements manufacturer Now Foods, December 2023.
10. Menniti-Ippolito, F., Aiello, E., Arzenton, E. et al. Erice Manifesto 2022: On the Surveillance of Potential Harms Caused by Food Supplements in Europe. Drug Saf 46, 435–437 (2023).
11. Mannino, G.; Di Stefano, V.; Lauria, A.; Pitonzo, R.; Gentile, C. Vaccinium macrocarpon (Cranberry)-Based Dietary Supplements: Variation in Mass Uniformity, Proanthocyanidin Dosage and Anthocyanin Profile Demonstrates Quality Control Standard Needed. Nutrients 2020, 12, 992.
12. Gaspar DP, Lechtenberg M, Hensel A. Quality Assessment of Bilberry Fruits (Vaccinium myrtillus) and Bilberry-Containing Dietary Supplements. J Agric Food Chem. 2021 Feb 24;69(7):2213-2225.
13. Walkowiak A, Wnuk K, Cyrankiewicz M, Kupcewicz B. Discrimination of Adulterated Ginkgo Biloba Products Based on 2T2D Correlation Spectroscopy in UV-Vis Range. Molecules. 2022 Jan 10;27(2):433.

14. Ichim MC, de Boer HJ. A Review of Authenticity and Authentication of Commercial Ginseng Herbal Medicines and Food Supplements. Front Pharmacol. 2021 Jan 11;11:612071.

15. Osman AG, Avula B, Katragunta K, Ali Z, Chittiboyina AG, Khan IA. Elderberry Extracts: Characterization of the Polyphenolic Chemical Composition, Quality Consistency, Safety, Adulteration, and Attenuation of Oxidative Stress- and Inflammation-Induced Health Disorders. Molecules. 2023 Mar 31;28(7):3148.

16. https://www.fda.gov/food/food-labeling-nutrition/label-claims-conventional-foods-and-dietary-supplements

17. Jordan CR, Harris CM, Miranda MI, Kim DY, Hellberg RS. Labeling compliance and online claims for Ayurvedic herbal supplements on the U.S. market associated with the purported treatment of COVID-19. Food Control. 2023 Jun;148:109673.

18. Carrubba A et al Content variability of bioactive secondary metabolites in Hypericum perforatum L., Phytochemistry Letters, Vol 46, 2021, P 71-78, ISSN 1874-3900.

19. https://food.ec.europa.eu/system/files/2016-10/labelling_nutrition-vitamins_minerals-guidance_tolerances_1212_en.pdf

20. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=101.9#:~:text=(g)%20Compliance%20with,of%20the%20act

21. https://www.eurachem.org/index.php/publications/guides/uncertcompliance

22. https://www.eurachem.org/index.php/publications/guides/quam

23. Asher GN, Corbett AH, Hawke RL. Common Herbal Dietary Supplement-Drug Interactions. Am Fam Physician. 2017 Jul 15;96(2):101-107.

24. Brewer CT, Chen T. Hepatotoxicity of Herbal Supplements Mediated by Modulation of Cytochrome P450. Int J Mol Sci. 2017 Nov 8;18(11):2353.

25. de Jonge MLL, Kieviet LC, Sierts M, Egberink LB, van der Heyden MAG. Review of Case Reports on Adverse Events Related to Pre-workout Supplements Containing Synephrine. Cardiovasc Toxicol. 2023 Jan;23(1):1-9.

26. https://www.fda.gov/food/compliance-enforcement-food/cfsan-adverse-event-reporting-system-caers

27. https://www.adrreports.eu/en/index.html

28. https://www.eurachem.org/index.php/publications/guides/quam

29. https://choice.wetestyoutrust.com/informed-choice-certified-brands

30. https://choice.wetestyoutrust.com/education/global-recognition

31. https://www.fda.gov/consumers/consumer-updates/fda-101-dietary-supplements

32. https://www.fda.gov/food/cfsan-constituent-updates/fda-sends-warning-letters-multiple-companies-illegally-selling-adulterated-dietary-supplements

33. Bailey RL. Current regulatory guidelines and resources to support research of dietary supplements in the United States. Crit Rev Food Sci Nutr. 2020;60(2):298-309.

34. https://eur-lex.europa.eu/eli/reg/2023/915/oj

35. https://foodsupplementseurope.org/wp-content/themes/fse-theme/documents/publications-and-guidelines/FSE-Mutual_Recognition-April2021.pdf

36. Baek S-H, Bae O-N, Park JH, Recent methodology in Ginseng analysis, J Ginseng Res. 2012 Apr; 36(2): 119–134.

37. The International Laboratory Accreditation Cooperation (ILAC) maintains a current list of accredited laboratories along with their scope of accreditation. This information can be easily accessed and searched on their website: https://ilac.org/signatory-search/.References

38. Durazzo A, Sorkin BC, Lucarini M, Gusev PA, Kuszak AJ, Crawford C, Boyd C, Deuster PA, Saldanha LG, Gurley BJ, Pehrsson PR, Harnly JM, Turrini A, Andrews KW, Lindsey AT, Heinrich M, Dwyer JT. Analytical Challenges and Metrological Approaches to Ensuring Dietary Supplement Quality: International Perspectives. Front Pharmacol. 2022 Jan 11;12:714434.

39. Dwyer JT, Coates PM, Smith MJ. Dietary Supplements: Regulatory Challenges and Research Resources. Nutrients. 2018 Jan 4;10(1):41.

Order your AXIO Proficiency Testing schemes online

Identify proficiency testing schemes to fit your requirements. Search and order online now at

lgcstandards.com/AXIO

Key features include:

1

Fast Renewals

Use our fast renewals feature to review and place repeat orders at the click of a button.

2

Advanced Search

Allows you to filter for a proficiency testing scheme based on a wide range of analytes and matrices.

3

Up-to-date

You can find our latest schemes, samples, information and instructions online.

You can also browse, search and order the wide range of LGC reference materials at **lgcstandards.com**