



# EU regulation of herbal products, Part 2: Quality, safety and efficacy, and postmarket surveillance

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This article compares and contrasts the regulatory requirements for herbal medicinal products (HMPs), herbal-based medical devices and botanical food supplements in the EU. It is part 2 of a two-part series – [part 1](#) presented the definitions, main regulations, and documentation requirements for placing the products on the market; part 2 addresses quality, the strength of evidence supporting the safety and efficacy, and postmarket surveillance (PMS) requirements across the three product lines. The article provides an overview of the current framework, highlights areas of controversy, and presents recent developments.

## Quality requirements

In contrast to conventional medicines (typically, single chemical entities), herbal medicines are rich, complex mixtures, comprising several constituents. Usually, the active principles responsible for the pharmacological action are unknown and standardization is not easy. Plant constituents are also known to vary, depending on environmental conditions and agricultural practices.<sup>1,2</sup>

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### ***Herbal medicinal products***

HMPs are subject to the same pharmaceutical quality requirements (chemistry, manufacturing, and controls) as the other medicinal products.

The quality and the manufacturing process are secured by adherence to the guidelines for good agricultural and collection practices and good manufacturing practices. The following should be described in the initial application:

Characteristics of the raw herbal materials, plant parts used, compliance with the European or national pharmacopoeia, extraction methods, tests to control for stability of the raw materials and methods to control the concentration of active constituents, and the absence of impurities.

In addition, the following should be described for the finished product:

Components of the medicinal product control for consistency of the final product, validation of analytical procedures, and stability controls. For the complete list of requirements, Directive 2003/63/EC and other EMA guidelines for the production of HMPs should be consulted.<sup>3-5</sup>

### ***Medical devices***

During the conformity assessment, notified bodies evaluate whether medical devices, including those that are herb based, are designed and manufactured so that they are suitable for their intended purpose during normal conditions of use.

EN ISO 13485:2016 is the main quality management system (QMS) standard for medical devices, that leads to the fulfillment of QMS elements under the EU MDR.<sup>6,7</sup> ISO 13485 includes general QMS requirements, management's overall QMS responsibility (both human and physical resources), product realization and measurement, analysis and improvement.<sup>8</sup> Even so, ISO 13485 is not a standard for products and does not define product quality. This is a process-based standard,<sup>9</sup> built on the presumption that, if the process is controlled, the end product should meet the desired results.

Risk assessment, risk analysis, and risk management are critical concepts in all phases of the medical device's lifecycle, that is, design, production, or PMS. Risk management in medical devices should be implemented in accordance with EN ISO 14971, a key standard for medical devices. Currently, manufacturers are reasonably well organized when it comes to generate the initial risk management file. However, these documents are rarely revisited and updated in line with developments in regulations and standards, after product release. Notified bodies are likely to address this question in the context of certificate renewal, every 5 years.<sup>8</sup>

### ***Food supplements***

Botanical food supplements must comply with all relevant aspects of food legislation in terms of composition, manufacture, and control.<sup>10</sup> All horizontal food law applies, including the Regulation (EC) No 853/2004 on food hygiene. This requires use of the hazard analysis and critical control points system as the QMS at all stages of food production, processing, and distribution.<sup>11</sup>

The European Community's microbiological criteria for foodstuffs are laid down in Regulation (EC) No 2073/2005. The micro-organisms commonly found in herbal raw materials include *Salmonella* and bacteria of the *Staphylococcus* species, but *Escherichia coli*, other *Enterobacteria*, *Campylobacter*, *Pseudomonas* and *Listeria* may also be present. Regulation (EC) No 1881/2006 lays down maximum levels for aflatoxins and ochratoxin, which can sometimes contaminate herbal raw materials. Certain levels have also been established for other mycotoxins. The regulation also sets maximum levels for heavy metals (lead, cadmium, mercury, tin).<sup>11</sup>

As the European law does not require a control on quality of food supplements before their marketing, product compliance lies only with the manufacturer.<sup>10</sup>

In fact, on the market, food fraud and adulteration incidents are often related to food supplements. A French study found that, of the 164 examined weight loss food supplements labelled as 100% natural, more than 40% were adulterated with medicinal substances.<sup>12</sup> Adulteration is detected when suspect products are chemically analyzed, or when the user has adverse effects that are serious enough to warrant medical attention.<sup>2</sup> Fortunately, such practices do not characterize the majority of food supplements marketed but it remains a concern.<sup>12</sup>

Some manufacturers may use a standardization of the content for specific active constituents to achieve a more consistent composition. Even so, some products that are claimed to be standardized do not always meet the standards stated on their labels.<sup>2</sup>

### **Safety and efficacy**

For herbal medicines/products, different and often limited levels of evidence are available. Moreover, information is often evaluated with different points of view and filtered by different opinions according to the clinical or traditional experience in the various folk medicines in the country.<sup>13</sup>

### **Herbal medicinal products**

Considering the history of medicinal use of well-established and traditional use HMPs, results of general toxicological (except genotoxicity, for traditional use HMPs) and pharmacological tests or results of clinical trials are not an essential requirement.<sup>5</sup>

Consequently, although feasible, only a few well-controlled, double-blind, placebo-controlled clinical trials have been carried out for few herbal medicines. The current regulatory framework provides little incentive for manufacturers to carry out such tests on their products. It is thus appreciated that there is a paucity of objective information on the safety of many herbal medicines, and there are concerns about the evaluation of efficacy according to the criteria of evidence-based medicine.<sup>1, 2, 13</sup>

However, some herbal drugs, which have also the largest worldwide market, benefit from a large number of different clinical trials. This is the case for herbals as *Ginkgo biloba*, *Hypericum perforatum*, *Panax ginseng*, *Tanacetum parthenium*, *Allium sativum*, *Matricaria Chamomilla*, *Silybinum marianum*, *Valeriana officinalis*, *Piper methysticum*, *Aesculus hippocastanum*, *Cassia acutifolia (Senna)*, *Rhamnus purshiana*, *Echinacea purpurea*, *Arnica montana*, *Serenoa repens*.<sup>1</sup>

Despite the common belief that herbal medicines are safe because of their long history of traditional use and their origin as being derived from natural sources, they do have associated adverse effects, as shown by well-controlled clinical trials and numerous case reports.<sup>13</sup> While the test of time may have identified inherently toxic plants, it cannot, for example, identify delayed adverse effects; effects that can arise from use in patients with illnesses, such as HIV-AIDS; effects in special groups, such as pregnant or breast-feeding women, children, and the elderly; and interactions with conventional medicines.<sup>2,13</sup> These situations require particular consideration.

EU herbal monographs present all the information necessary for the use of the medicinal product containing the herbal substance or preparations.<sup>10,14</sup> These are based on nonclinical and clinical data, documented longstanding use, and experience in the EU and, if available, outside the EU.<sup>5</sup> The monographs have two sections – the well-established use and traditional use – for which type of extracts and doses, interactions, special warnings, and indications are different. Monographs form the basis for the required product information, such as the summary of product characteristics and the package leaflet.<sup>10</sup>

According to Directive 2004/24/EC, the indications for well-established medicinal herbs will be the classical clinical indications requiring medical diagnosis. Traditional HMPs may claim only mild indications that comply with the traditional use. Thus, the indications will be limited to those that can be self-medicated, not requiring medical intervention. The claims of these types of products should contain the following statement into any labelling and leaflet, and advertising materials: “Traditional herbal medicinal product [THMP] for use in specified indication(s), exclusively based upon long standing use.” THMPs are licensed only as over the counter.<sup>13</sup>

Advertising for a medicinal product must not suggest its safety or efficacy is owing to the fact that it is natural (Article 90(h), Directive 2001/83/EC).

### **Medical devices**

A medical device is said to be clinically effective when it exhibits the effect intended by the manufacturer according to the medical condition, for instance, a pain relief medical device should relieve pain. The manufacturer needs to have clear objectives and scientific proof inferring that the pain is relieved when using that device. Both technicality and clinical effectiveness should be considered when it comes to performance measurement of medical devices.<sup>15</sup> Medical devices can claim medical properties and indications.<sup>10</sup>

A clinical evaluation is required for all medical devices, including herb-based, regardless of their classification, to demonstrate safety and performance, as well as the overall positive benefit-risk ratio.<sup>16</sup> The manufacturer must justify the extent of clinical evaluation based on product characteristics and intended purpose (Article 61, MDR). The clinical evaluation must be part of the QMS and is closely connected with the mandatory risk management.<sup>17</sup>

The clinical evaluation involves a defined and methodologically sound procedure based on a critical evaluation of either:

- Relevant scientific literature currently available, where there is demonstration of the device's equivalence to the device to which data relate and the data adequately demonstrate compliance with relevant essential requirements, or
- Results of clinical investigations conducted and combined clinical data.<sup>18</sup>

Clinical investigations or trials need to be performed for all Class III devices, unless reliance on existing clinical data can be justified.<sup>18</sup> When needed, clinical investigations are carried out in accordance with EN ISO 14155 (good clinical practices), EU MDR Annex XV, and applicable MEDDEV guidelines.

The clinical evaluation report (CER), compiled to document the clinical evaluation and its output, is an element of the technical documentation of a medical device and constitutes the clinical evidence for conformity assessment.<sup>19</sup> The CER is updated actively throughout the device's lifecycle as an ongoing process.<sup>20</sup>

Of note, under the MDR, substance-based devices that are introduced into the human body, and that are absorbed by or locally dispersed in the human body, must demonstrate compliance to the relevant requirements laid down in Annex I of Directive 2001/83/EC, for the evaluation of absorption, distribution, metabolism, excretion, local tolerance, toxicity, interactions and potential for adverse reactions.<sup>21</sup> Thus, although these products would still be regulated as medical devices, requirements on the CE mark application would resemble in large parts those of a marketing application of a medicinal product.<sup>22</sup>

It is often pointed out that, given that the new regulation does not grandfather in existing devices, manufacturers need to collect additional clinical evidence for devices already CE marked remain compliant, or the device will need to be re-evaluated to confirm that the data has been collected and analyzed consistently with the MDR requirements.<sup>23</sup>

Annex I of the MDR, chapter III, presents the information to be provided to users/patients with the medical device, and includes provisions on labeling and on instructions for use (IFUs). Specific to substance-based medical devices, information on the overall qualitative composition of the device and quantitative information needs to be stated. The IFUs must contain the device's intended purpose, indications, contra-indications, the patient target group(s), and of the intended users, warnings and precautions, general profile of

interactions, undesirable side-effects and risks relating to overdose. IFUs can be omitted for Class I and Class IIa devices if the manufacturer can ensure they can be used safely without instructions.<sup>21</sup> For Class III medical devices, the manufacturer also draws up summary of safety and clinical performance (SSCP) for users/patients, which should be referenced in the in the labelling or IFUs.<sup>21</sup>

### **Food supplements**

In most cases, food supplements are marketed with a claim that, by definition, is “a message or representation [...] which states, suggests or implies that a food has a particular characteristic.” Foods promoted with claims may be perceived by consumers as having a health advantage over similar or other products to which such substances are not added.<sup>24</sup> It could be reasonably expected that, in most cases, consumers would not buy a food supplement without a claim on it.<sup>25</sup>

Claims are regulated by Regulation (EC) No 1924/2006 on nutrition and health claims made on foods. The Regulation distinguishes two types:

- Nutrition claims describing the foods with regard to the nutrients or energy they contain or do not contain or provide at a reduced or increased rate, for example, low fat, sugars-free, source of fiber, and so on (Annex I, Regulation (EC) No 1924/2006); or
- Health claims stating, suggesting or implying that a relationship exists between a food category, a food or one of its constituents and health,<sup>11</sup> for example, monacolin K from red yeast rice contributes to the maintenance of normal blood cholesterol levels.<sup>26</sup>

All authorized and unauthorized claims are included in the EU Register of nutrition and health claims made on food, which is publicly available.

To be authorized, Regulation (EC) No 1924/2006 provides that health claims must be subject to a scientific assessment of the highest possible standard. From a list of 4,637 claims sent to EFSA for assessment, the final list of permitted health claims, published in 2012, contained only 222 claims, that is, fewer than 10% of those submitted.<sup>27</sup>

From the claims sent to EFSA, 2,078 claims concerned plants and preparations. When EFSA started to carry out the scientific assessment on plants and preparations, the first 530 opinions issued were negative. The reason was that, in many cases, there was not sufficient evidence to substantiate the claims at the highest possible standard. EFSA considered human intervention studies essential to draw a conclusion and clinical data generated in ill patients were not considered suitable to support claims related to conditions in healthy people.<sup>10, 25</sup> Evidence collected solely based on experience over time with the actual consumption (traditional use) alone was not considered sufficient. This led to an inconsistent approach in the treatment of plant substances, particularly the consideration of plants having a traditional use under the legislation of health claims, where claims were not authorized, and that on THMPs, where indications are permitted.

In September 2010, the European Commission requested that EFSA put its assessment of health claims relating to botanical substances on hold. Currently, health claims on the on-hold list, which includes all the 2,078 health claims on plants and preparations, can still be used across the EU under the responsibility of food business operators. Ultimately, this can be misleading to consumers because they may believe the beneficial effects communicated with the on-hold claims have been scientifically assessed (and risk managed) when that is not the case.<sup>25</sup>

In the evaluation of the Regulation (EC) No 1924/2006, published in 2020, 10 years after the decision to put the assessment on hold, the commission recognized that it could be appropriate to explore the notion of “traditional use” in efficacy assessment of health claims on plants and preparations together with the coexistence, on the EU market, of THMP on the same plant substance. It is also noted that classification food versus medicine would remain under the remit of member states.<sup>25</sup>

Nevertheless, to date, there are no timelines communicated for the evaluation process of pending claims on botanicals.

Regulation (EC) No. 1925/2006 (fortified foods) allows for the European Commission to request a safety assessment from EFSA for foods and food ingredients (including ingredients in food supplements) in case of potential risks to human health. It was thought that would make it possible to draw up a list of substances whose use in foods was prohibited, permitted under specific conditions of use, or placed under EU scrutiny if scientific uncertainty persists, and that, over time, a level of harmonization would be achieved for plants and their preparations in food. However, the procedure is not often applied. Two botanicals were thus prohibited, Ephedra herb, previously marketed as performance enhancer, and yohimbe bark, for promoting weight loss.<sup>25</sup>

Labelling specificities for (botanical) food supplements are addressed in the food supplements directive. Among others, the labelling should include a statement that the products should not be used as a substitute for a varied diet and may not mention or imply that a varied diet cannot provide the appropriate quantities of nutrients in general.<sup>28</sup> Medicinal claims (treatment or prevention of diseases) are not allowed for food supplements; bearing medicinal claims would lead to classification as medicine.<sup>3</sup>

### **Postmarket surveillance**

Many herbal products on the market have not been thoroughly tested for their pharmacology and toxicology, so pharmacovigilance has paramount importance in detecting unwanted reactions.<sup>29</sup>

### ***Herbal medicinal products***

As with all medicinal products that have been placed on the market, HMPs are required to comply with the European regulations concerning continuous

monitoring and pharmacovigilance, to assure that aspects impacting the safety profile are detected and assessed and necessary measures are taken.

A range of methods are used for postmarket monitoring of drug safety. The existing system was developed with conventional medicines in mind; adapting these methods to monitoring the safety of herbal medicines presents additional challenges because of their unique characteristics and the ways in which these are regulated, used and perceived.<sup>2</sup>

Spontaneous reporting is currently the main method of detecting signals of safety concerns associated with herbal medicines.<sup>2</sup> Adverse drug reaction (ADR) reports are collated into repositories, the largest being the WHO Collaborating Centre for Monitoring Drug Safety (Uppsala Monitoring Centre, UMC), which gathers information from more than 100 countries. Statistical methods are then used to identify disproportionate reporting rates which can lead to a safety signal.<sup>29</sup> In the EU, EudraVigilance is the platform used to manage information on safety reports. Collected data are being published in the European database of suspected adverse drug reaction reports.<sup>30</sup>

Under-reporting is a known problem with spontaneous reporting systems. It occurs for a range of reasons, such as lack of association between the herb and the adverse event, lack of awareness that herbal ADRs should be reported, and ADRs being managed by the patient alone.<sup>2,29</sup>

Another well-established method for monitoring safety is prescription event monitoring, however, this is of limited use for herbal medicines, given that are rarely prescribed. Pharmacoepidemiological methods, such as case-control and cohort studies, can be used to test hypotheses developed after signals are detected, but these methods have been underused for herbal medicines.<sup>29</sup>

As part of the pharmacovigilance obligations, manufacturers are required to submit to competent authorities periodic safety update reports (PSURs) for every authorized product. This contains an update of the product's worldwide safety experience and critical analysis of the benefit-risk balance. For low-risk or old products, including well-established use medicines and THMPs, PSURs are not routinely required.<sup>31,32</sup> For such products, PSURs must be submitted only on request or where there is a condition in the marketing authorization – for example, for *Hypericum perforatum* L., herba (every 5 years), senna glycosides standardized 60% (every 10 years), diosmin (every 13 years), silibinin, dry extract from Milk Thistle fruit (silymarin; every 13 years), and caffeine (every 28 years).<sup>33,34</sup> The marketing authorization holders of medicinal products exempted from submitting PSURs should use alternative mechanisms to communicate relevant new safety information to regulatory authorities.<sup>35</sup>

### **Medical devices**

Manufacturers are required to monitor the safety profile of medical devices, including herbal-based products, through implementation of a PMS plan. As part of the PMS system, postmarket clinical follow-up (PMCF) data is required for high-risk devices to confirm safety and performance, where long-term



performance and safety information is unknown or where CE marking was based on equivalence. PMCF can be omitted for devices where long-term influence data is available. Data from PMCF will also be used to update the clinical evaluation report (CER) and the summary of safety and clinical performance (SSCP), where applicable.<sup>16,36</sup>

Main PMCF findings must also be included in the periodic safety update report, which is mandatory for Class IIa, IIb and III devices. For Class IIa medical devices, the PSUR is updated every 2 years, and annually for Class IIb and III devices.<sup>8,17</sup> For Class I devices, manufacturers prepare a PMS report.<sup>21</sup>

To fulfill the vigilance or materiovigilance obligations, the manufacturer must report to national competent authorities any serious incidents related to the use their medical devices. If a field safety corrective action, including a recall, is deemed necessary, then the manufacturer must also issue a field safety notice and send copies to the competent authorities and to affected costumers.<sup>8</sup>

Competent authorities, on their end, should take all necessary steps to ensure information concerning serious incidents is centrally recorded and evaluated. This coordination is facilitated by a central database, Eudamed, through which authorities and European Commission exchange vigilance and other legal information.<sup>8,37</sup>

Moreover, manufacturers should have suitable systems in place and proactively scrutinize trends in complaints and incidents occurring with their devices.<sup>8</sup>

### ***Food supplements***

There is no centralized EU system for monitoring food safety–related issues for food supplements. Monitoring is carried out just at the member state level (e.g., in France) on a voluntary basis and to varying extent.<sup>12</sup>

In the context of the EU legislation in place, when risks to public health are detected in the food chain, the RASFF (the Rapid Alert System for Food and Feed) is a key tool for ensuring the flow of information to enable swift reaction, including recalling products from the market. The European Commission notes that, because there is low number of reported incidents involving food supplements containing plant substances and a limited recourse to the RASFF for products containing plant substances, this could suggest an overall effectiveness of the current general regulatory framework.<sup>25</sup>

By way of example, in 2014, there were 208 RASFF notifications in the EU on food supplements (it should be noted this product category also includes dietetic and fortified foods). Of those notifications, 158 concerned the inclusion of unauthorized ingredients in food supplements. In addition, 89 of the 208 RASFF notifications (43%), the food supplements had been manufactured in another member state or were imported through another member state. Incidents were generally found to concern noncompliant products manufactured in third countries, marketed through specific channels, such as online purchases.<sup>25</sup>

## Summary and conclusion

Herbal products, from the medicinal, medical devices or food supplements frameworks, are a diverse group with common specificities and challenges, and different regulatory approaches to address them. Popular demand and industry interests have created a market for such products, where these categories can be competitors. Food supplements and medical devices may have an advantage, having the possibility to circumvent the restricting EU regulatory environment of medicinal products and have lower costs related market launch, quality requirements and postmarket monitoring. Recent developments hold a promise for a certain alignment for efficacy criteria, where medicinal products are taken as reference.

## Abbreviations

**ADR**, adverse drug reaction; **CER**, clinical evaluation report; **EFSA**, European Food Safety Authority; **HMP**, herbal medicinal product; **IFU**, instructions for use; **MDR**, Regulation (EU) 2017/745 on medical devices; **PSUR**, periodic safety update report; **PMCF**, postmarket clinical follow-up; **PMS**, postmarket surveillance; **QMS**, quality management system; **RASFF**, rapid alert system for food and feed; **HMP**; **SSCP**, summary of safety and clinical performance; **THMP**, traditional herbal medicinal product; **UMC**, Uppsala Monitoring Centre.

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**Citation** Armasu A. EU regulation of herbal products, Part 2: Quality, safety and efficacy, and postmarket surveillance. REGULATORY FOCUS. Published online 7 December 2021. [[Link](#)]

## References

*All references were verified on 1 December 2021.*

1. Calixto JB. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). Braz J Med Biol Res. 2000 Feb;33(2):179-89.
2. Barnes J. Adverse drug reactions and pharmacovigilance of herbal medicines. In Stephens' detection and evaluation of adverse drug reactions. 6th ed. Wiley Blackwell; 2012:645-683.
3. Hooyenga P, et al. Herbal products: Marketing strategies and legislation. Int J Green Pharm. [https://www.researchgate.net/publication/42339773\\_Herbal\\_products\\_Marketing\\_strategies\\_and\\_legislation](https://www.researchgate.net/publication/42339773_Herbal_products_Marketing_strategies_and_legislation). Published October 2009.
4. European Parliament and Council. Eur-Lex website. Directive 2004/24/EC ... of 31 March 2004. <https://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX%3A32004L0024>.
5. Qu L, et al. European regulation model for herbal medicine: The assessment of the EU monograph and the safety and efficacy evaluation in marketing authorization or registration in member states. Phytomedicine. 2018;42:219-225.
6. Bos G. Medical device conformity assessment procedure. In: Fundamentals of EU regulatory affairs. 8th ed. Regulatory Affairs Professional Society; 2017:207-220.
7. TUV SUD website. ISO 13485 quality management system for medical devices. <https://www.tuvsud.com/en/industries/healthcare-and-medical-devices/medical-devices-and-ivd/quality-management-and-quality-control-for-medical-devices/iso-13485-quality-management-system-for-medical-devices>. Not dated.
8. Oosterhoff P. Medical device compliance: Postmarket requirements. In: Fundamentals of EU regulatory affairs. 8th ed. Regulatory Affairs Professional Society; 2017:221-231.
9. International Organization for Standardization. ISO 13485:2016(en). <https://www.iso.org/obp/ui#iso:std:iso:13485:ed-3:v1:en>.
10. Bilia AR, Costa MDC. Medicinal plants and their preparations in the European market: Why has the harmonization failed? The cases of St. John's wort, valerian, ginkgo, ginseng, and green tea. Phytomedicine. 2021;81:153421.

11. Association of the European Self-Care Industry. Food supplements data bank. <https://food.aesgp.eu/>.
12. The European Consumer Organisation. Food supplements: Challenges and risks for consumers. [https://www.beuc.eu/publications/beuc-x-2016-092\\_ipa\\_beuc\\_position\\_on\\_food\\_supplements.pdf](https://www.beuc.eu/publications/beuc-x-2016-092_ipa_beuc_position_on_food_supplements.pdf). Published 30 September 2016.
13. Calapai G. European legislation on herbal medicines: a look into the future. *Drug Saf.* 2008;31(5):428-31.
14. European Medicines Agency. European Union monographs and list entries. <https://www.ema.europa.eu/en/human-regulatory/herbal-products/european-union-monographs-list-entries>. Last updated 15 August 2018.
15. Altayyar SS. The essential principles of safety and effectiveness for medical devices and the role of standards. *Med Devices (Auckl)*. 2020;13:49-55.
16. TUV SUD. Clinical data for medical devices. <https://www.tuvsud.com/en/industries/healthcare-and-medical-devices/medical-devices-and-ivd/clinical-services/clinical-data-for-medical-devices>. Not dated.
17. Schloetelburg C. VDE website. Clinical evaluation of medical devices according to MDR. <https://meso.vde.com/clinical-evaluation-of-medical-devices/>. Published 8 December 2020.
18. Bos G. The European medical devices legal system. In: *Fundamentals of EU regulatory affairs*. 8th ed. Regulatory Affairs Professional Society; 2017:137-164.
19. European Commission. MEDDEV 2.7/1 revision 4, Clinical Evaluation: A guide for manufacturers and notified bodies under Directives 93/42/EC and 90/385/EEC. <https://ec.europa.eu/docsroom/documents/17522/attachments/1/translations/en/renderitions/native>. Published June 2016.
20. Pelgrim L. Clinical evaluation and clinical investigations. In: *Fundamentals of EU regulatory affairs*. 8th ed. Regulatory Affairs Professional Society; 2017:201-206.
21. European Parliament and Council. Regulation (EU) 2017/745 ... of 5 April 2017. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0745>.
22. Zeller-Adam R. The European Council's partial general approach to the proposal for a Medical Device Regulation: Its potential implications on demarcation, classification, and conformity assessment of substance-based medical devices. Dissertation. Deutsche Gesellschaft für Regulatory Affairs; 2016. <https://www.dgra.de/deutsch/studiengang/master-thesis/2016-63466?nav=studiengang>.
23. Bos G. The new Medical Device Regulation and In Vitro Diagnostic Device Regulation. In: *Fundamentals of EU regulatory affairs*. 8th ed. Regulatory Affairs Professional Society; 2017:129-136.
24. European Parliament and Council. Regulation (EC) No 1924/2006 ... of 20 December 2006 on nutrition and health claims made on foods. <https://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX%3A32006R1924>.
25. European Commission. Evaluation of the Regulation (EC) No 1924/2006 on nutrition and health claims made on foods with regard to nutrient profiles and health claims made on plants and their preparations and of the general regulatory framework for their use in foods. [https://ec.europa.eu/food/system/files/2020-05/labelling\\_nutrition-claims\\_swd\\_2020-95\\_part-1.pdf](https://ec.europa.eu/food/system/files/2020-05/labelling_nutrition-claims_swd_2020-95_part-1.pdf) Published on 20 May 2020.
26. European Commission. EU Register of nutrition and health claims. [https://ec.europa.eu/food/safety/labelling\\_nutrition/claims/register/public/?event=search](https://ec.europa.eu/food/safety/labelling_nutrition/claims/register/public/?event=search).
27. Adamaszwilli K. Regulation of health and nutrition claims in the European Union. <https://selfcarejournal.com/article/regulation-of-health-and-nutrition-claims-in-the-european-union/>. SelfCare. Published 2014.
28. European Parliament and Council. Directive 2002/46/EC ... 10 June 2002 on the approximation of the laws of the member states relating to food supplements. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32002L0046&from=EN>.
29. Shaw D, et al. Pharmacovigilance of herbal medicine. *J Ethnopharmacol*. 2012;140(3):513-518.
30. EudraVigilance – European database of suspected adverse drug reaction reports. [www.adrreports.eu](http://www.adrreports.eu)
31. Medicines Evaluation Board. Periodic safety update reports (PSUR). <https://english.cbg-meb.nl/topics/mah-periodic-safety-update-reports-psur>. Not dated.

32. Resch I. Austrian Agency for Health and Food Safety website. Update regarding PSUR and RMP for herbal and homeopathical medicinal products [presentation]. [https://www.ages.at/fileadmin/migrated/cal\\_uploads/06\\_Resch.pdf](https://www.ages.at/fileadmin/migrated/cal_uploads/06_Resch.pdf). Dated 11 November 2014.
33. Comparative matrix of EU legislation across product lines [appendix]. In: Fundamentals of EU regulatory affairs. 8th ed. Regulatory Affairs Professional Society; 2017:543-584.
34. European Medicines Agency. List of [EU] reference dates and frequency of submission of periodic safety update reports (PSURs). [https://www.ema.europa.eu/documents/other/list-european-union-reference-dates-frequency-submission-periodic-safety-update-reports-psurs\\_en.xls](https://www.ema.europa.eu/documents/other/list-european-union-reference-dates-frequency-submission-periodic-safety-update-reports-psurs_en.xls).
35. European Medicines Agency. Periodic safety update reports. <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/periodic-safety-update-reports-psurs>. Last updated 17 July 2019.
36. Deloitte. Preparing for the future: The new European Union medical devices regulation. <https://www2.deloitte.com/global/en/pages/life-sciences-and-healthcare/articles/new-european-union-medical-devices-regulation.html>. Published 2016.
37. Gurbeta Pokvic L, et al. European Union medical device legislation, vigilance, and metrology system. Medical device standards, regulations, and the law. In: Clinical engineering handbook. 2nd ed. Elsevier; 2019:753-763.