EIP-AGRI Focus Group

Plant-based medicinal and cosmetic products

MINI PAPER 4. Plant raw materials for herbal-medicinal products, botanical food supplements and frontier products: requirements for quality, safety and efficacy

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1. Introduction

Herbal-medicinal products, medical devices made of herbal substances, botanical food supplements and other frontier products are high value added goods, made of specific plant raw materials, which offer important opportunities for farmers and growers to diversify their crops and to access to high value markets. The intended uses of these final products for medicinal purposes, human health promotion and human welfare, require they comply with the highest standards of quality, which are the basis to ensure the expected efficacy and the required safety in agreement with specific regulations. From the very beginning of the value chain, farmers and growers must be aware on the requirements and challenges to achieve and ensure quality and on the major issues of the regulatory frameworks, which are conditions to understand the opportunities for valorisation of the plant raw materials and to take decisions at different levels. This mini-paper briefly outline the features of the major classes of these products, describes emergent risks and threats that can influence the quality and safety of raw materials and finished products, identifies gaps on knowledge and suggests research opportunities.

2. State of the art

Herbal medicinal products, **Medical Devices**, **Botanical Food Supplements** and other frontier products such as **Natural Cosmetics** are growing market segments linked to increasing opportunities for valorisation of particular plant raw materials. These high added value products are classified according to their intended use (and their mechanisms of action) in compliance with specific quality requirements, guidelines and regulatory frameworks. Due to classification ambiguities, certain of these products can fall into two or more of those segments.

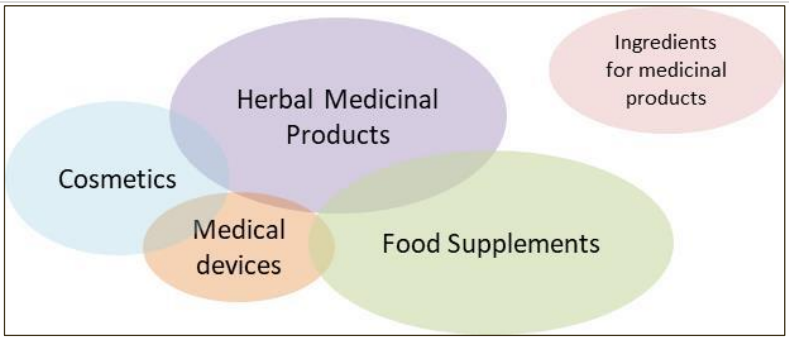

Figure 1. Major segments of marketed finished-products made of particular plant raw materials.

Herbal Medicinal Products

Herbal Medicinal Products (HMP) are plant derived health products exclusively containing as active ingredients one or more herbal substances or herbal preparations aimed to treat or prevent disease in human beings or to restore, correct or modify physiological functions. This definition and the regulatory framework of Herbal Medicinal Products were established by the Directive 2001/83/EC[1] amended by the Directive 2004/24/EC[2].

[1] European Parliament and of the Council. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

[2] European Parliament and of the Council. Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use.

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The access to the market of an HMP depends on a **marketing authorization** granted by a competent authority, briefly, relying on the data provided for demonstration of: the **pharmaceutic quality of the raw materials** and of the finished product, the **efficacy** about specific therapeutic indications and of the **safety** when used under defined conditions.

The standard references for assessment of **pharmaceutic quality** (f.i. the European Pharmacopoeia or the National Pharmacopoeias of the European Member States) only accept and approve raw materials and products that meet the highest quality standards.

The **efficacy** and **safety** of the HMP should be evidenced by obeying one or more of the following procedures: i) the regular procedure for the generality of medicinal products, i.e. providing supportive **preclinical and clinical evidences of efficacy and safety** recorded in agreement with the current scientific knowledge and the international guidelines for **clinical trials;** ii) the simplified procedures, exclusive for HMP, i.e., providing data attesting the **well-established use (WEU)** of the HMP in the basis of a previous existence in the European market long more than ten years; or providing data attesting the **traditional use (TU)** of the Herbal Medicinal Product supported on its long term use, more than thirty years of recognized traditional use, fifteen of which in any of the European member states.

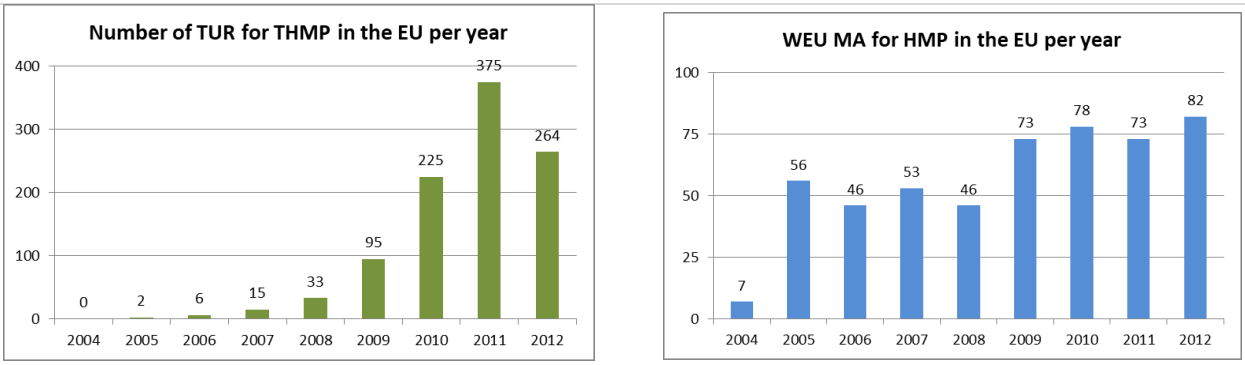

Figure 2. (A) Number of traditional use registrations (TUR) for traditional herbal medicinal products (THMP) in the EU per year (2004 until December 2012). (B) Number of well-established use marketing authorisations (WEU MA) for herbal medicinal products (HMP9 in the EU per year (2004 until December 2012). (Adapted from Peschel, 2014 [3])

A system of manufacturing authorizations and regular inspections ensure that medicinal products on the European market are **exclusively manufactured by authorized manufacturers and that starting materials are traceable** and produced in accordance with the standards of **Good Agriculture and Collection Practices** and **Good Manufacture Practices**.

The majority of the manufacturing companies purchase the raw material and the extracts from **brokers** and **distributors** that play a crucial role in the chain value identifying the market opportunities and giving guidance to growers.

Medical Devices

Medical Devices segment comprises a wide range and different kind of artefacts and substances (from plasters to nasal sprays) intended to be used for diagnosis, monitoring, prediction, prognosis of disease and for prevention treatment or alleviation of disease or injury, since the expected action be not achieved by pharmacological, immunological or metabolic mechanisms, in or on the human body.

[3] Peschel W. The use of community herbal monographs to facilitate registrations and authorisations of herbal medicinal products in the European Union 2004–2012. Journal of Ethnopharmacology 158 (2014) 471–486 doi:10.1016/j.jep.2014.07.015

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Some products made of herbal substances or herbal preparations intended to treat or prevent disease in human beings may be accepted as Medical Devices "composed of substances or of combinations of substances" since proved the mechanisms underlying their action are not pharmacological (Regulation EU 2017/745)[4] .

The market of Medical Devices Made of Substances is growing significantly, representing in some countries more than 20% of the OTC market share. As for herbal medicinal products, the majority of the manufacturing companies purchase the raw material from brokers and distributors, therefore growers may have further opportunities in this sector.

The future development of the sector will depend not only from the consumers' demand, but also on the full implementation of the Regulation 2017/745 that will be applied from 26 May 2020. The new regulation foresees, among others, stricter *ex ante* control for high-risk devices, improved transparency and reinforcement of the rules on clinical evidence and strengthening of post-market requirements[5].

Of specific interest for the growers is a new provision, Rule 21 of the Regulation EU 2017/745, that introduces the category of **medical devices composed of substances or of combination of substances** and their different classes, among them those who comprises **herbal substances and their preparations**. The recognition and inclusion, in the new regulation, of the medical devices made of substances ensures a unique and rigorous respect of certain requirements. To fully exploit the potential of this category of products and to support their development on the European market, **it is important to guarantee the recognition of the specific characteristics of those products** made with herbal substances or herbal preparations and to **adopt a case by case evaluation approach in the regulatory classification.**

Botanical food supplements

The regulatory status of food supplements, botanicals included, was recognised by the Directive 2002/46/EC [6]. Food supplements' are foodstuffs concentrated of nutrients or other substances with a nutritional or physiological effect, marketed in dose form, such as capsules, tablets, sachets of powder, ampoules of liquids and respective similar forms, designed to be taken in measured small unit quantities with the purpose of supplement the normal diet.

Despite the lack of a harmonised EU framework and the difficulties manufacturers met in marketing their products in the different Member States, the botanicals sector still represents a vital economic sector in Europe, due to the increasing demand by the consumers.

The Directive 2002/46/EC does not foresee any central approval and unique procedure at EU level, and it is implemented with differences in the Member States. When it comes to the safety, food supplements, botanicals included have to comply with the requirements of the Regulation of 178/2002 [7] (the general principles and requirements of food law). When it comes to prove the efficacy and obtain the relevant claim, the reference is the Nutrition and Health Claims, the Regulation 1924/2006 [8]. This regulation aims at protecting the consumers while enhancing the development of the business. For the case of botanicals, the

[4] European Parliament and of the Council. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending the Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.

[5] European Commission. Medical Devices: **https://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework_en . Accessed 12/2019**

[6] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements.

[7] European Parliament and of the Council 2002. Regulation (EC) 178/2002 of the European Parliament and of the Council of 28 January 2002, laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety.

[8] European Parliament and of the Council 2006. Regulation (EC) 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods.

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regulation is currently under evaluation for revision.

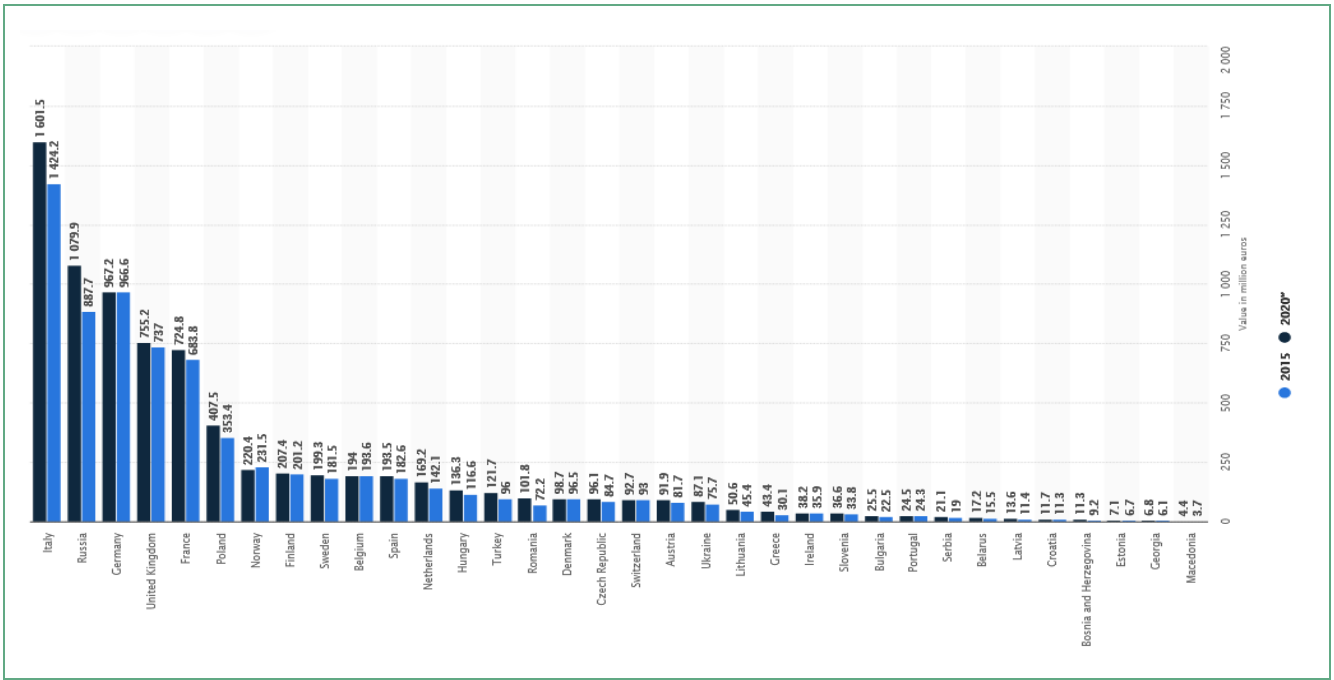

Figure 3. Value of the dietary supplements market in Europe in 2015 and 2020, by country (in million euros).
(Addapted from the original source: Statista Research Department, Jan 17, 2018), https://www.statista.com/statistics/589452/value-dietary-supplements-markets-europe-by-country/

The safety and efficacy of food botanicals is, in the EU, under the jurisdiction the European Food Safety Authority (EFSA). EFSA issued a guidance document on the assessment of the safety of botanical material and preparations[9] and, with reference to the efficacy, published a scientific guidance for stakeholders[10]. Nevertheless, those guidelines do not take into account the specific characteristics of botanicals. It is important to stress that **natural substances, as complex mixtures, do not have to produce the same effects of each one of their isolated constituents**. The matrix effect, the physical and chemical interactions among components, their additive, synergic or antagonistic activities may result in drastically different biological effects. Consequently, the safety and efficacy of botanical food supplements **is guaranteed by the whole complex of natural substances and not by individual ones.** Therefore, the entire matrix needs to be considered. The safety and efficacy assessment should refer to the complex natural matrix and **proper guidelines need to be established**. For instance, the EFSA guidance on the safety assessment refer to OECD guidelines 471 [11] and 487 [12] for the evaluation of mutagenicity and genotoxicity of chemicals *in vitro,* however they are not entirely applicable in case of testing botanical food supplements.

[9] European Food Safety Authority (EFSA) 2009. EFSA Scientific Committee. Scientific Opinion. Guidance on Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements. EFSA Journal 2009; 7(9):1249 https://www.efsa.europa.eu/en/efsajournal/pub/1249

[10] European Food Safety Authority (EFSA) 2016. EFSA Panel on Dietetic Products, Nutrition and Allergies. General scientific guidance for stakeholders on health claim applications. EFSA Journal 2016;14(1):4367 https://www.efsa.europa.eu/it/efsajournal/pub/4367

[11] The Organisation for Economic Co-operation and Development. 1997. OECD Guideline 471 for testing of chemicals. Bacterial Reverse Mutation Test.

[12] The Organisation for Economic Co-operation and Development. 2014. OECD TG 487 Guideline for the testing of chemicals in vitromammalian cell micronucleus test.

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3. Research needs from practice

Emergent concerns regarding the quality of herbal raw materials related to specific contaminants and residues.

The quality of herbal raw materials regarding the eventual contamination with specific substances is a key issue to pursuit the expected safety of the final products for consumers. Potential contaminations with pesticide residues, heavy metals or biological agents (bacteria and their spores, yeasts and moulds, viruses, protozoa, insects) are currently addressed as at the level of the good agriculture practices and post-harvest processing, as at the level of the intermediate and final assessment of the raw materials and finished products. Suitable recommendations for crop management and laboratorial requirements were issued both by agriculture, food safety and pharmaceutical authorities.

Nevertheless, emergent concerns and challenges must be taken in account in consequence of recent scientific evidences. Contamination with low-molecular-mass compounds, metabolites from moulds, **mycotoxins**, specially aflatoxins and ochratoxin A[13], or metabolites of particular weeds, such as the **pyrrolizidine alkaloids (PAs)**, must be in mind and took seriously regarding the safety of the consumers.

Aflatoxins and ochratoxin A

Aflatoxins and **ochratoxin A** are harmful substances produced by certain kinds of moulds that develop under favourable conditions. In the case of the plant-materials used in herbal-medicinal or welfare products, the contamination mainly results from improper post-harvesting processing, inappropriate storage, drying and stabilization procedures. Large **doses of these mycotoxins lead to acute poisoning, but the real risk for consumers is the long term exposure by the of carcinogenesis and immunologic impairment**. The major contribution for the long term exposure comes from some food crops (maize, wheat, rice, peanuts …), but the contribution of other contamination sources should not be neglected. In the case of health products (HMP or MD) or welfare-products this kind of contamination is absolutely unacceptable.

Pyrrolizidine alkaloids

Pyrrolizidine alkaloids (PAs) are nitrogen containing compounds produced by plants of certain plant families (*Borraginaceae*, *Asteraceae* and *Fabaceae)*. **Many of the species included are common weeds**. Among PAs those of a particular group (the 1,2-unsaturated PAs) are relevant concerning the safety assessment of raw-materials and finished products. Their genotoxic and carcinogenic potential are generally accepted. Studies have shown that 1,2-unsaturated PAs are able to **induce damage to macromolecules, including DNA, leading to acute and chronic effects that include disruption of the hepatic microcirculation and subsequent liver failure and malignancy**. It has also been shown that PA-producing weeds are the source of the contamination with PAs, not only in foods (vegetables, cereals, honey, and dairy products) but in also botanic materials used in the production of health products and supplements. The European Food Safety Authority and the European Medicines Agency expressed their concerns in this regard and established limits to the PAs contamination in finished products considering the consumer exposure and safety [14,15,16].

[13] Word Health Organization. Department of Food Safety and Zoonoses. 2018. Food Safety Digest. Aflatoxins. Available at : https://www.who.int/foodsafety/FSDigest_Aflatoxins_EN.pdf accessed in 12/2019

[14] EFSA Scientific Opinion on Pyrrolizidine alkaloids in food and feed. EFSA Panel on Contaminants in the Food Chain (CONTAM). EFSA Journal 2011, 9(11) : 2406:1-134. Accessed on 12/2019 available at: http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/2406.pdf

[15] European Comission. European Medicines Agency. 2014. Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs). EMA/HMPC/893108/2011. 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2014/12/WC500179559.pdf . Accessed 12/2019

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4. Ideas for research and innovation

In line with the scientific evidences and with the concerns regarding consumers for safety, the quality of herbal medicinal and welfare products, including the corresponding raw materials, claim for additional requirements and adaptations, imposing new challenges not only at all levels of the chain value, but also at the regulatory and risk management levels. In this context specific responses from fundamental and applied research will be welcome, specifically addressed to:

Consolidation of the basic knowledge on the risks:

- toxicological research on the mechanisms of toxicity of PAs and other toxic plant metabolites;
- establishment of safety limits of contaminants (mycotoxins, PAs, etc.) in raw materials and finished products;
- research on mechanisms underlying crops and soils´ PAs contamination.
- classification of weeds according the effective risk of contamination,

Weed management:

- establishment of characters for immediate identification and recognition of specific weeds on field: macroscopic characters; chemical features supporting the recognition by optical or other physico-chemical sensors;
- development of new and sustainable plant breeding practices;
- development of machinery supported on new technologies and artificial intelligence for detection of weeds on field;
- development of tailor-made machinery for selective weeding and selective harvesting.

Post-harvest processing:

- crop management methods and development of specific equipment for suitable post-harvesting processing of medicinal and aromatic plants;
- best practices to prevent microbial contamination of raw materials and finished products (moulds, bacteria).

Risk assessment and management:

- development of free access databases compiling relevant information for risk assessment and management;
- development of standard methods of analysis for screening and quantification of contaminants;
- validation and accreditation of laboratories for phytochemical analysis;
- development of specific guidelines specific to assess genotoxicity and carcinogenicity of botanicals.
- development of expertise (knowledge and training) adapted to the specific needs of the assessment of safety of botanicals and botanic mixtures.

5. Idea for a new Operational Group

An Operational Group to promote the quality and certification of MAP will contribute decisively for the translation of the research and to support the actors of the different levels of the chain value.

Operational Group Theme	Description

[16] European Comission. European Medicines Agency, 2016. Public statement on contamination of herbal medicinal products/traditional herbal medicinal products with pyrrolizidine alkaloids. EMA/HMPC/328782/2016.. Available at: https://www.ema.europa.eu/en/documents/public-statement/public-statement-contamination-herbal-medicinal-products/traditional-herbal-medicinal-products-pyrrolizidine-alkaloids_en.pdf Accessed 12/2019

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Quality and certification of plant materials	Network of laboratorial facilities able to: • on field monitor the quality of plant materials; • assess the compliance with quality standards; • develop and propose certified labelling • ensure proper standards for traceability.

6. Conclusion

The consumer's demand of herbal medicinal products, medical devices composed of substances, supplements and other frontier products is increasing and consequently the request of raw material represents an interesting opportunity for growers. Expectations for market development lays on the consolidation and development of the supportive regulatory framework taking into account the potential and the specific characteristics of botanicals, as well on the support of research specifically addressed to the improvement of the quality of herbal raw-materials and finished products for safety of consumers.

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The European Innovation Partnership 'Agricultural Productivity and Sustainability' (EIP-AGRI) is one of five EIPs launched by the European Commission in a bid to promote rapid modernisation by stepping up innovation efforts.

The **EIP-AGRI** aims to catalyse the innovation process in the **agricultural and forestry sectors** by bringing **research and practice closer together** – in research and innovation projects as well as *through* the EIP-AGRI network.

EIPs aim to streamline, simplify and better coordinate existing instruments and initiatives and complement them with actions where necessary. Two specific funding sources are particularly important for the EIP-AGRI:

- ✓ the EU Research and Innovation framework, Horizon 2020,
- ✓ the EU Rural Development Policy.

An EIP AGRI Focus Group* is one of several different building blocks of the EIP-AGRI network, which is funded under the EU Rural Development policy. Working on a narrowly defined issue, Focus Groups temporarily bring together around 20 experts (such as farmers, advisers, researchers, up- and downstream businesses and NGOs) to map and develop solutions within their field.

The concrete objectives of a Focus Group are:

- ✓ to take stock of the state of art of practice and research in its field, listing problems and opportunities;
- ✓ to identify needs from practice and propose directions for further research;
- ✓ to propose priorities for innovative actions by suggesting potential projects for Operational Groups working under Rural Development or other project formats to test solutions and opportunities, including ways to disseminate the practical knowledge gathered.

Results are normally published in a report within 12-18 months of the launch of a given Focus Group.

Experts are selected based on an open call for interest. Each expert is appointed based on his or her personal knowledge and experience in the particular field and therefore does not represent an organisation or a Member State.

*More details on EIP-AGRI Focus Group aims and process are given in its charter on:
http://ec.europa.eu/agriculture/eip/focus-groups/charter_en.pdf

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