Comparative analysis of the EU regulatory requirements for essential oils as ingredients for the pharmaceutical, cosmetic products and feed additives

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Свобода

Правда

Милосердие

Liberty

Truth

Mercy

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List of Abbreviations

API	Active Pharmaceutical Ingredient
AP	Applicant's Part
ASMF	Active Substance Master File
BSE/TSE	Bovine spongiform encephalopathy / Transmissible Sponigforme Encephalopathie
CAS	Chemical Abstracts Service
CEP	Certificate of Suitability to the Pharm. Eur. Monograph
CMDh	Co-ordination Group for Mutual Recognition and Decentralised procedures – Human
CPNP	Cosmetic Products Notification Portal
CTD	Common Technical Document
CSA	Chemical Safety Assessment
EC	European Commission
ECHA	European Chemicals Agency
EDQM	European Directorate for the Quality of Medicines & HealthCare
EINECS	European INventory of Existing Commercial chemical Substances
ELINCS	European LIst of Notified Chemical Substances
EMA	European Medicines Agency
EO	Essential Oil
EU	European Union
EEA	European Economic Area
EEC	European Economic Community
EFSA	European Food Safety Authority
FFAC	Feed Flavoring Authorisation Consortium
EFfCI	European Federation for Cosmetic Ingredients
FEEDAP	Panel on Additives and Products or Substances used in Animal Feed
FEFANA	Fédération Européenne des Fabricants d'Adjuvants pour la Nutrition Animal (EU Association of Specialty Feed Ingredients and their Mixtures)
JECFA	Joint FAO/WHO Expert Committee on Food Additives

GACP	Guideline on good agricultural and collection practice for starting materials of herbal origin
GC	Gas Chromatography
GMO	Genetically Modified Organism
CLP	Regulation EC No. 1272/2008 on Classification, Labelling and Packaging
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis and Critical Control Points
HMP	Herbal Medicinal Product
HMPC	Committee on Herbal Medicinal Products
HPLC	High-Performance Liquid Chromatography
IBS	Irritable Bowel Syndrome
IFRA	International Fragrance Association
INCI	International Nomenclature of Cosmetic Ingredients
ISO	International Organization for Standardization
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
NCA	National Competent Authority
NMR	Nuclear Magnetic Resonance
OTC	Over-The-Counter
Ph. Eur.	European Pharmacopoeia
PIF	Product Information File
ppm	Parts Per Million
RP	Restricted Part
PSR	Product Safety Report
REACH	Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
SCCS	Scientific Committee on Consumer Safety
SDS	Safety Data Sheet
SIEF	Substance Information Exchange Forum
SME	Small and Medium-Sized Enterprises
TLC	Thin-Layer Chromatography
THMP	Traditional Herbal Medicinal Product

TUR	Traditional Use Registration
QOS	Quality Overall Summary
WEU	Well-Established Use

1. Introduction

For over 5000 years essential oils (EOs) have been used for a variety of different purposes, including personal care (*i.e.* perfumes and cosmetics), foods, home care, repellents for humans and animals (livestock and domestic animals), and health-promoting agents for the treatment of various diseases (1). Until now, more than 3000 essential oils have been described, of which about one tenth are relevant for pharmaceutical, nutritional, or cosmetic industries (1).

Essential oils are hydrophobic liquids containing complex mixture of volatile chemical compounds with low molecular weight and variable concentrations. Depending on the concentration, the individual substances can be divided into main (20–95 %), secondary (1–20 %) and trace components (less than 1 %) (2). In general, monoterpenes and sesquiterpenes are the main components of essential oils, though diterpenes, phenylpropanoids, aldehydes, ketones, ethers and esters, alcohols and hydrocarbons can be present to a different extent (1). Many of these molecules are found in low concentrations, while few of them are the main component(s) that can represent up to 90 % of the total oil. The chemical composition of essential oils obtained from one botanical species can vary depending on several factors like the time of harvest, the geographical location of the crop, growing conditions, the part of the plant, as well as the manufacturing conditions.

Essential oils could be isolated from different parts of the plant. Some of them could be found in leaves (oregano), seeds (almond), flowers (jasmine), peel (bergamot), berries (juniper), rhizome (galangal ginger), roots (angelica), bark (sassafras), wood (agar wood), resin (frankincense), and petals (rose) (3).

EOs are produced by glandular trichomes and other secretory structures, specialized secretory tissues mainly diffused onto the surface of plant organs, particularly flowers and leaves, thus exerting a pivotal ecological role in plant (1). These secondary metabolic products perform important functions in the plant life, *e.g.* they are responsible for allelopathy, adaptation to abiotic stresses, intra- and inter-plant signalling, direct and indirect defence against herbivores and pathogens. Based on the plant source, the

essential oil gets its name, such as the essential oil obtained from Peppermint plant is known as peppermint oil or *Menthae piperitae aetheroleum*.

The International Organization for Standardization (ISO) defines an EO as "a product made by distillation with either water or steam or by mechanical processing of citrus rinds or by dry distillation of natural materials. Following the distillation, the essential oil is physically separated from the water phase" (4). The European Pharmacopoeia (Ph. Eur.) applies the following definition to essential oil: "Odorous product, usually of complex composition, obtained from a botanically defined herbal drug by steam distillation, dry distillation, or a suitable mechanical process without heating. If an aqueous phase is present, the essential oils are separated from it by a physical process that does not significantly affect their composition" (5). Both definitions include the natural (herbal) origin of EO and the method of extraction. Hence it follows that the products extracted from plant material by methods other than distillation or cold pressing are not essential oils. For example, the products obtained from plant material with solvents such as hexane, ethanol, or supercritical fluids (*e.g.* CO_2), which are then partly or totally removed, do not apply to essential oils. The oils of synthetic origin but with identic to natural oils composition do also not belong to essential oils. They called "nature identical essential oils" (6).

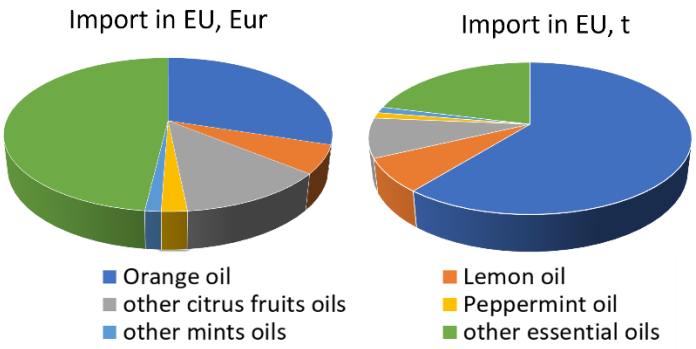
According to data from Access2Markets (7), the European essential oils market size was valued at 593.3* million EUR in 2022. The highest share of 30 % in EUR and 61 % in tonnage belongs to the orange essential oil (**Figure 1**) because of its availability, low cost, and properties. Orange essential oil is a by-product of orange juice production and is obtained from the orange peel through the cold-pressed method. This oil is widely used not only to improve the flavour and taste of food, but also as natural agent for food preservation because of their antimicrobial properties. Moreover, orange oil has found great application in cosmetic products and aromatherapy.

The second biggest group after citrus fruits oils (48.4 % in EUR) is mints oils with value of 3.5 % in EUR and 9.7 % in tonnage (**Figure 1**). The most commonly used essential oil in this group is peppermint oil (2.1 % in EUR) (**Figure 1**). Thanks to its cool, refreshing odour and taste peppermint oil is extensively utilized as a flavouring agent in chewing gums,

*Resinoid, terpenic by-products, extracted oleoresins and category "other" were excluded.

toothpaste, aftershaves, and mouthwashes. Moreover, peppermint oil occupies an important position in medicine. Peppermint oil has shown to be effective in the treatment of Irritable Bowel Syndrome (IBS) symptoms, for the symptomatic relief of muscle pain, intact skin, headache, coughs, and colds.

Figure 1 *EU Essential oils market distribution in EUR and tonnage*



1.1 Applications and Uses of Essential Oils in Medical Products

Because of their biological activities the essential oils have been used, since ancient times, in many different traditional healing systems all over the world, *e.g.* in Traditional Chinese Medicine, Arabian Traditional Medicine, Traditional Aboriginal Australian Medicines, Ayurvedic Medicine, Traditional Korean Medicine, antic Greek Medicine. Although further drug development predominantly expanded in the direction of chemically synthesized drugs and later biologic drugs, the herbal medicinal products containing essential oils keep an important place in the modern health care system especially in non-prescription (over-the-counter (OTC)) segment. Essential oils as active ingredient are used as herbal preparation in herbal medicinal products (HMPs) both for human and veterinary use and in traditional herbal medicinal products (THMPs) for human use. With respect to the spread use of essential oils as API the related monographs have been published in European union (EU) to assure quality, efficacy, and safety of the final medicinal products.

The Ph. Eur. is a single reference work for the quality control of medicines and their ingredients in EU. Ph. Eur. includes a general chapter 5.30 “Monographs on essential oils” (information chapter), a general monograph “Essential oils” (Ph. Eur. 04/2022:2098) and

32 individual monographs on essential oils (**Table 1**), which are describing legally binding quality standards for them. These monographs contain detailed analytical methods for identification and quality control of essential oils.

Parallel to the Ph. Eur. monographs, which define the basic requirements for quality, 14 EU herbal monographs for essential oils (12 final, one is under assessment, and one is withdrawn, **Table 1**) have been developed by the Committee on Herbal Medicinal Products (HMPC) (8). The EU herbal monographs (formerly known as Community herbal monographs) contain the HMPC's scientific opinion on safety and efficacy of a herbal substance or preparations intended for medicinal use based on evaluation of available scientific data and/or historical evidence. These monographs are used as the safety and efficacy reference material and assessment standard by applicants and National Competent Authorities (NCAs) and plays a supportive function by the well-established use (WEU) marketing authorisation and traditional use registration (TUR) (9). The EU herbals monographs for tea tree oil, thyme oil and peppermint oil are included in the EU list entries (14 in total) (10). Unlike EU herbal monographs, EU list entries are legally binding on applicants and national competent authorities in the Member States in respect to TUR.

Table 1 *Essential oils extracted from a variety of plants listed in Ph. Eur.*

Essential Oil	Botanical Name	Plant Part Used	Ph. Eur. monograph	EU herbal monographs	EU list entries
Anise oil	*Pimpinella anisum* L.	ripe fruit	01/2008:0804 corrected 7.0	EMA/HMPC/321185/2012	/
Bitter-fennel fruit oil	*Foeniculum vulgare* Mill., spp. *vulgare* var. *vulgare*	ripe fruit	01/2008:1826	EMEA/HMPC/137428/2006 (withdrawn)	/
Bitter-fennel herb oil	*Foeniculum vulgare* Mill., spp. *vulgare* var. *vulgare*	aerial parts	07/2009:2380 corrected 7.0	/	/
Caraway oil	*Carum carvi* L.	dry fruit	01/2008:1817	EMA/HMPC/715094/2013	/
Cassia oil	*Cinnamomum aromaticum* Nees	leave and young branches	01/2008:1496 corrected 10.0	/	/
Cinnamon bark oil, ceylon	*Ceylon Cinnamomum zeylanicum* Nees	bark of the shoot	04/2011:1501 corrected 10.0	/	/
Cinnamon leaf oil, ceylon	*Ceylon Cinnamomum zeylanicum* Nees	leaves	01/2008:1608 corrected 7.0	EMA/HMPC/706229/2009	/
Citronella oil	*Cymbopogon*	fresh or	01/2008:1609	/	/

Essential Oil	Botanical Name	Plant Part Used	Ph. Eur. monograph	EU herbal monographs	EU list entries
	winterianus Jowitt ex Bor	partially dried aerial parts	corrected 7.0		
Clary sage oil	*Salvia sclarea* L.	fresh or dried flowering stem	01/2008:1850 corrected 7.0	/	/
Clove oil	*Syzygium aromaticum* (L.) Merr. & L.M.Perry	dried flower buds	01/2008:1091 corrected 7.6	EMA/HMPC/534924/2010	/
Coriander oil	*Coriandrum sativum* L.	fruits	04/2023:1820	/	/
Dwarf pine oil	*Pinus mugo* Turra	fresh leaves and twigs	07/2019:2377	/	/
Eucalyptus oil	*Eucalyptus globulus* Labill.; *Eucalyptus smithii* R.T.Baker; *Eucalyptus polybractea* R.T. Baker	fresh leaves or fresh terminal branches of various species of Eucalyptus rich in 1,8-cineole	07/2021:0390	EMA/HMPC/307781/2012	
Juniper oil	*Juniperus communis* L.	ripe, non-fermented berry cones	07/2013:1832 corrected 10.0	EMA/HMPC/12402/2010	
Lavender oil	*Lavandula angustifolia* Mill.	flowering tops	04/2023:1338	EMA/HMPC/143181/2010	
Lemon oil	*Citrus limon* L.	fresh peel	04/2022:0620	/	/
Mandarin oil	*Citrus reticulata* Blanco	fresh peel	04/2022:2355		
Matricaria oil	*Matricaria recutita* L.	fresh or dried flower-heads or flowering tops	01/2008:1836	EMA/HMPC/278814/2010	
Mint oil, partly dementholised	*Mentha canadensis* L.	fresh, flowering aerial parts	01/2008:1838	/	/
Neroli oil	*Citrus aurantium* L.	fresh flowers	01/2008:1175	/	/
Niaouli oil, cineole type	*Melaleuca quinquenervia* (Cav.) S.T.Blake	young leafy branches	07/2012:2468	/	/
Nutmeg oil	*Myristica fragrans* Houtt.	dried and crushed kernels	01/2008:1552 corrected 10.0		

Essential Oil	Botanical Name	Plant Part Used	Ph. Eur. monograph	EU herbal monographs	EU list entries
Peppermint oil	*Mentha x piperita* L.	fresh aerial parts of the flowering plant	04/2019:0405	EMA/HMPC/522410/2013	Yes
Pine sylvestris oil	*Pinus sylvestris* L.	fresh leaves and branches	01/2008:1842	/	/
Rosemary oil	*Rosmarinus officinalis* L.	flowering aerial parts	01/2008:1846	EMA/HMPC/513893/2021 (draft)	
Spanish sage oil	*Salvia lavandulifolia* Vahl	flowering aerial parts	07/2008:1849 corrected 7.0	/	/
Spike lavender oil	*Lavandula latifolia* Medik	flowering tops	07/2018:2419	/	/
Star anise oil	*Illicium verum* Hook	dry ripe fruits	01/2008:2108 corrected 7.0	/	/
Sweet orange oil	*Citrus sinensis* (L.) Osbeck	fresh peel	04/2022:1811	/	/
Tea tree oil	genus *Melaleuca*	foliage and terminal branches	01/2008:1837 corrected 7.0	EMA/HMPC/320930/2012	Yes
Thyme oil, thymol type	*Thymus vulgaris* L. or *Thymus zygis* L.	fresh flowering aerial parts	01/2012:1374 corrected 10.0	EMA/HMPC/59032/2017	Yes
Turpentine oil	*Pinus pinaster* Aiton and/or *Pinus massoniana* D.Don.	oleoresin obtained by tapping	07/2014:1627 corrected 9.4	/	/
Valerian essential oil	*Valeriana officinalis L.*	valerian root	/	EMA/HMPC/278053/2015	/

According to public data from Article 57 database (11) the mostly used essential oils (active substance) in mono-herbal component products or combination products are *eucalyptus oil* with 182 items, *peppermint oil* with 102 items, *turpentine oil* with 68 items, and rosemary oil with 52 items. Unfortunately, there is no publicly available information about the distribution by tonnage or total revenue between medical products containing essential oils.

1.2 Applications and Uses of Essential Oils in Feed

Since ancient times, essential oils have been used not only on humans but also on animals due their positive effects on the health and welfare of animals. The effects can vary depending on factors such as the type and quality composition of the essential oil, the species of the animal, the feed diet, and environmental conditions. Commercially, essential oils are commonly used as feed additives categorized as flavouring compounds to improve the quality of animal feed. However, essential oils have a broader impact than just improving the sensorics of the feed. Essential oils show antibiotic, antioxidant, anti-quorum sensing, anti-inflammatory, and digestive fluids stimulating activities, that have positive effects on animal health and the performance of animal products. Thus, the strict classification into the single group of flavouring feed additive is not exhaustively.

Essential oils attracted increased interest in the livestock industry when the use of antibiotics as growth promoters was banned by European Commission (EC) on January 1, 2006. Antibiotics were widely used in animal production as antimicrobial growth promoters for decades worldwide. Added in low doses to the feed of farm animals, they improve their growth performance (12) and have a prophylactic role against infectious diseases (13). The problem of increasing resistance in bacteria to antibiotics led to the restriction or even ban for the use of antibiotics as feed additives in many countries and search for new alternatives. Such possible alternative could be essential oils. The growth-promoting feature of essential oils is associated mainly with effects on the gastro-intestinal tract to increase the palatability of feed, stimulate secretion of digestive fluids, improve intestinal morphology, stabilize intestinal microbiome, and reduce inflammation (14). It is important to note that the mechanism of essential oils action is not always clear, and this issue should be subject to further research. It is needed to fully understand the mechanisms of action and potential long-term effects of using essential oils as feed additive.

The antioxidant properties of essential oils have also been linked to improved stability of eggs and meat during storage, as they help reduce lipid oxidation (13). Moreover, literature data have documented that using essential oil in animal feeding reduce the emissions of ammonia into the atmosphere from pig production, and methane from

fermentation in the rumen. That decrease the environmental impact of the livestock industry and improve animal welfare (13, 14).

In conclusion, while essential oils are commonly used as flavouring compounds in animal feed, their impact goes beyond just improving the flavour and palatability of feed. They improve animal health and the quality of animal products. At the same time, they reduce the negative influence on environment and could be used in “green” concept of livestock farming.

1.3 Applications and Uses of Essential Oils in Cosmetic

The shift towards an environmentally aware and resource-friendly lifestyle has had a significant impact on various industries, including the cosmetic market. The demand for natural cosmetics has been steadily increasing, with consumers becoming more conscious of the ingredients used in their personal care products (15). The market for natural cosmetics has seen substantial growth in recent years, in 2021 it reached approximately 40 billion USD, which corresponds to roughly 10% of the global cosmetics and toiletries market (16). Essential oils have gained significant popularity in the cosmetic industry, particularly in the production of natural cosmetics, because they combine the properties of active ingredient, fragrance and preservative and can be used as natural alternatives to synthetic ones, which are commonly found in conventional cosmetics.

Essential oils are used in various cosmetic products in:

- skin care such as moisturizers, lotions, soaps and cleansers;
- hair care such as conditioners, masks, or anti-dandruff products;
- make-up such as lipsticks;
- perfumery as perfumes.

The one of the main reasons for usage of essential oils in cosmetics is their pleasant odour. Essential oils can effectively mask any unpleasant scents associated with fatty acids, fatty oils, and surfactants used in the production of personal care products. As result such products can be labelled as “fragrance-free”, “contains no perfume” or “scented-free”, because they do not contain chemical fragrance (6).

The manufacturing of cosmetic products requires the use of preservatives which are added to reduce the risk of microbial contamination of the product and to ensure the product remains suitable and safe during shelf-life and the period of its use by consumers (17). Due to antimicrobial properties essential oils and their individual components can be used instead of preservatives to protect the cosmetic products against bacteria and fungi.

At the same time essential oils and their individual components may have specific pharmacological impact, *e.g.* antioxidant, anti-inflammatory, antimicrobial, and anxiolytic activity, thus offer benefits for skin and hair. The unique chemical profile of each individual essential oil is associated with different benefits. **Table 2** summarizes some of the potential applications of EOs in the design of cosmetic formulations.

Table 2 *Potential application of some EOs in the design of different cosmetic formulations. Reproduced from Guzmán et al.(16)*

Application	Essential Oil	Plant	Main Components	Properties	Function
Skin care	Chamomile	*Matricaria chamomilla*	α-bisabolol; bisabolol oxide; bisabolon oxide; chamazulene; 1,8-Cineole; β-farnesene; α-Terpineol	anti-inflammatory wound healing	anti-acne anti-aging
	Sandalwood	*Santalum spicatum*	α-bisabolol; (*E*)-farnesol; nuciferol; α-santalol; α-santalol	antiseptic antioxidant	anti-aging
	Evening primrose	*Oenothera biennis*	β-amyrin; 1-hexacosanol; linoleic acid; γ-linolenic acid; 1-tetracosanol; squalene	antibacterial antioxidant	anti-wrinkles moisturizer anti-acne
	Camellia	*Camellia japonica*	β-amyrin; cycloartenol; lanosterol; lupeol; γ-sitosterol; squalene	antibacterial antioxidant	anti-aging moisturizer
	Rosemary	*Rosmarinus officinalis*	borneol; camphene; camphor; β-caryophyllene; 1,8-cineole; p-cymene; limonene; linalool; myrcene; α-pinene; β-pinene; α-terpineol	antibacterial antioxidant	anti-acne
Hair care	Sweet orange	*Citrus sinensis*	limonene; myrcene; α-pinene; β-pinene; sabinene	antibacterial antioxidant	antidandruff
	Lavender	*Lavandula officinalis*	borneol; caryophyllene; lavandulol; lavandulol acetate; linalool; linalyl acetate; α-terpineol; terpinene-4-ol	antibacterial antioxidant	hair growth conditioning
	Peppermint	*Mentha piperita*	carveone; 1,8-cineole; limonene; menthol; menthone; methyl acetate; neomenthol	antibacterial antioxidant	hair growth conditioning
	Thyme	*Thymus vulgaris*	α-cadinene; γ-cadinene; δ-cadinene; α-cadinol; α-cadinol; δ-caryophyllene; p-cymene; elemol; β-eudesmol; germacrene; limonene; γ-muurulene; myrcene; trans-β-ocimene; β-pinene; γ-terpinene; α-terpineol	antibacterial antioxidant	antidandruff hair growth
	Bergamot	*Citrus bergamia*	bergamottin; bergapten; citropten; limonene; linalool; linalyl acetate; α-pinene; β-pinene; γ-terpinene	antibacterial anti-inflammatory	antidandruff hair growth

Additionally, certain essential oils have been shown to have mood-enhancing properties. For instance, citrus oils like lemon and orange can uplift and energize, while chamomile and lavender oils can promote relaxation and stress relief (18).

While there are numerous benefits to using essential oils in cosmetic products, there are also some drawbacks, including their high volatility, poor solubility in water, and their thermal and chemical labilities, which makes their handling difficult for a rational design of cosmetic products (16).

Moreover, it is important to note that essential oils and their compounds could cause some adverse reactions, *e.g.* allergies, chronic toxicity in human cells, and photosensitisation. The toxicity of essential oils is associated not only with the concentration, but also with their physicochemical properties. Therefore, it is crucial for cosmetic manufacturers to perform the risk assessment of essential oils and the potential implications when including them in cosmetic products (6, 19).

2. Results

2.1 Essential oils as ingredients for medical products

Essential oils could be included in medical product as an active ingredient, also known as active substance or active pharmaceutical ingredient (API), or as inactive ingredients, also known as excipients. According to the European Medicines Agency (EMA) the active substance is indicated as "substance responsible for the activity of a medicine" (20) and the excipient as "a constituent of a medicine other than the active substance" (for example, essential oils often used as flavours) (21). Because the essential oils are produced from the plant material, or to be in line with European Pharmacopoeia from drug substance*, they belong to the group of herbal drug preparations†. The term *herbal drug preparation* is synonymous with the term *herbal preparation* used in European Community legislation on herbal medicinal products (22). Herbal preparations used as active substance in herbal medicinal products (HMPs) both for human and veterinary use and in traditional herbal medicinal products (THMPs) for human use.

2.1.1 Essential oils as active substance

According to the Article 6 of the Directive 2001/83/EC "no medicinal product may be placed on the market of a Member State unless a marketing authorisation (MA) has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EEC) No 2309/93". To obtain the MA for the medical product the intended MA holder (MAH) must submit to the competent authority the MA dossier to prove the quality, efficacy, and safety of its product. The content and structure of this dossier is worldwide harmonized (23) and established in EU legislation (24, 25). For more details about marketing authorisation dossier and procedures for marketing authorisation please refer to the Directive 2001/83/EC and Regulation (EEC) No 2309/93, and to official EMA and CMDh (Co-ordination Group for Mutual Recognition and Decentralised procedures - Human) websites where the specific guidelines can be found. In this work we focus on the EU

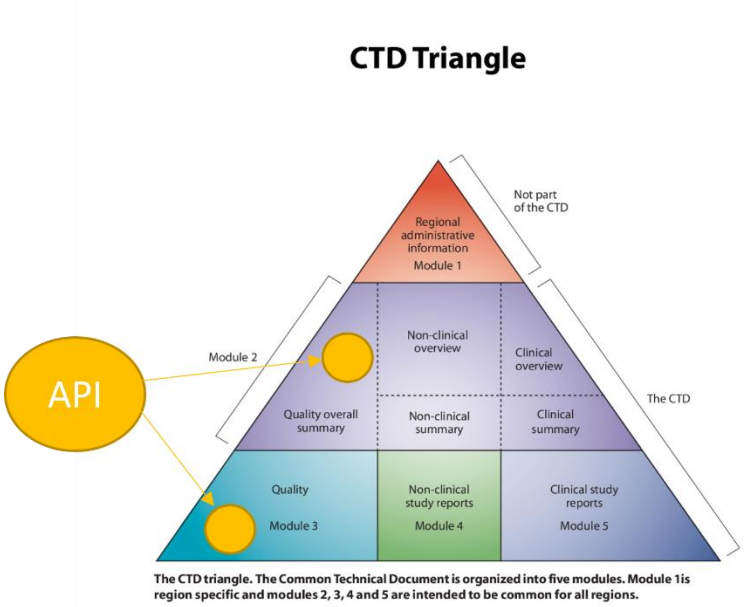
* Herbal drugs are mainly whole, fragmented or broken plants or parts of plants in an unprocessed state, usually in dried form but sometimes fresh (Ph. Eur. 07/2017:1433).

† Herbal drug preparations are homogeneous products obtained by subjecting herbal drugs to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation (Ph. Eur. 07/2010:1434).

regulatory requirement for active substance, especially for essential oils, in medical products.

The quality of active substance is an integral part of the marketing authorisation dossier for medical product and must be presented in Module 3 in Section "3.2.S Drug Substance" and as part of Quality Overall Summary in Module 2 (**Figure 2**).

Figure 2 Common Technical Document (CTD) Triangle on an MA dossier with API part



2.1.1.1 Regulatory pathways

There are the three options for integrating the document relating to quality of essential oils as API in the finished medicinal product dossier:

- **Complete API documentation**

The essential oil manufacturer provides the complete active substance documentation to the MAH and the MAH integrates the documents into their dossier. The quality of essential oil is assessed by the competent authority as a part of MA dossier and the applicant for MA is responsible to answer all raised questions related to active substance.

- **Active Substance Master File (ASMF)**

The essential oils manufacturer or an authorized agent prepares the Active Substance Master File (ASMF) by themselves and became ASMF Holder. ASMF has the CTD/eCTD as well and represents an excerpt of section from MA dossier related to quality of active substance. The ASMF should be physically divided into two separate parts, namely the

Applicant's Part (AP) and the Restricted Part (RP). The AP contains the information that the ASMF holder regards as non-confidential to the Applicant/MA holder, whereas the RP contains the information that the ASMF holder regards as confidential. In addition to the AP and RP, the ASMF should contain a table of contents, and separate summaries for both the AP and the RP as a Quality Overall Summary (QOS). The ASMF holder should submit to the Applicant/MA holder a copy of the latest version of the AP, a copy of the QOS or detailed and critical summary and a copy of the Letter of Access. The NCAs/EMA involved in the MA application procedure receives from ASMF Holder the ASMF, accompanied by a Submission Letter and Administrative Details, and the Letter of Access (26).

During the assessment phase the questions concerning the AP are sent to the applicant and the ASMF holder and the questions concerning the RP receives only the ASMF holder. In case questions can be formulated without revealing any confidential information, the List of Questions concerning the RP can also be sent to the applicant (27). With ASMF procedure the confidential intellectual property of the manufacturer of the essential oil is protected.

However, the ASMF procedure has one critical drawback. The same ASMF can be used within multiple MA applications through the different MA procedures and consequently requires individual assessment by different NCAs or EMA by every application. This leads to the duplication of work, inconsistent decisions being made on the same data and frequent and numerous updating of the ASMF. To solve this problem the Working Group on Active Substance Master File Procedures has established a work-sharing procedure for the assessment of ASMFs, including a centralised EU numbering system for ASMFs and a centralised repository for the ASMF assessment reports (28-30).

- **Certificate of Suitability to the Ph. Eur. Monograph (CEP)**

If the essential oil has the individual monograph in Ph. Eur. (31) the essential oils manufacturer or supplier, or their duly authorized representatives can submit the dossier (32) in CTD/eCTD format written in English or French to European Directorate for the Quality of Medicines & HealthCare (EDQM) to apply for a Certificate of Suitability to the Ph. Eur. Monograph (CEP). The EDQM evaluates the dossier to ensure that the essential oil meets the requirements specified in the relevant Ph. Eur. monograph.

If the assessors and, if necessary, the relevant technical advisory board conclude that:

i. the monograph is able to control the quality of the substance *or*
ii. the monograph is not able fully to control the quality of the substance, but the information provided (new, validated, analytical method and/or additional tests) nevertheless guarantees that the quality of the substance is adequately controlled

the CEP is granted (33).

CEP certifies that the quality of a substance (essential oil) can be suitably controlled by the Ph. Eur. monograph, *i.e.* that the quality of a substance corresponds to the quality defined in the Ph. Eur. monograph and according to the Directive 2001/83/EC (34) the substance is suitable for use in pharmaceutical applications within EU. Moreover, CEPs are recognized by other member of the Convention on the Elaboration of the Ph. Eur. and some countries such as Canada, Australia, New Zealand, Tunisia and Morocco (35).

CEP can replace the documentation for an active substance in MA dossier for medical product and in contrast to ASMF do not require the addition assessment through NCA/EMA. Thus, CEP procedure simplifies the management of regulatory documentation for the MA applicant, active substance producer as well competent authorities. The MA applicant submits the dossier with reduced 3.2.S part that saves its time and resources. The agency does not need to evaluate the part of the dossiers related to information on the quality of the active substance because CEP based on a centralized assessment by EDQM. The active substance manufacturer has single dossier, single assessment, and single approval which is independent from marketing applications and recognized by broad range of countries.

Here is the short overview of three options to integrate the documentation regarding essential oils in the dossier of final medical product (**Table 3**).

The MA for medical products and the Certificate of suitability are valid for five years from the date of granting. The MAH or CEP holder shall ask for the renewal nine months prior to expiry date in case of MA and six months prior in case of CEP. Usually, after successful renewal the MA and CEP will be granted unlimited validity.

Table 3 Short overview of three regulatory pathways to integrate the documentation regarding essential oils in the MA dossier

Complete API documentation	ASMF*	CEP
for all essential oils	for all essential oils	only for essential oils described in Pharm. Eur. (32 monographs)
the confidential information is not protected	the confidential information is protected	the confidential information is protected
individual documents	single dossier with frequent and numerous updating	single dossier
individual submission within every MA application	individual submission within every MA application	single submission to EDQM
part of MA dossier	linked to MA dossier	independent from MA dossier but with responsibilities towards MAHs used CEP
individual assessment by various authorities with different requirements	individual assessment by various authorities with different requirements	single assessment by EDQM
individual Life-Cycle-Management within MA	individual Life-Cycle-Management within MA	harmonized Life-Cycle-Management through EDQM

2.1.1.2 Content of regulatory documentation

Regardless the way used to integrate the information on the quality of the essential oil in the MA dossier the content remains the same for every option and corresponds to the CTD structure, namely 3.2.S part.

Taking into account all current relevant guidelines concerning herbal preparation from both EU authorities EDQM (32) and the EMA (36), as well as the requirements of the Ph. Eur. (specific monographs, general monographs and general chapters) I tried to describe the necessary information which should be provided by manufacturer or authorized agent to build successful CTD part 3.2.S for essential oil. It should be noted that in the existing quality guidelines the requirements are not fully addressed for essential oils (37) and the general requirements for herbal preparation, that are developed firstly for extracts, could not be applied to essential oil or some of them are too strict and could be excluded if it is justified.

* The ASMF worksharing procedure was not considered

3.2.S.1 GENERAL INFORMATION

3.2.S.1.1 Nomenclature

Information on the nomenclature of the essential oil should be provided:

- Binomial scientific name of plant (genus, species, variety and author), and chemotype used for production of essential oil.
- Parts of the plants (*e.g.* leaves, branches, tops, seeds, roots etc.), form (dried or fresh) and vegetable state (*e.g.* flowering) used for production of essential oil.
- Name of essential oil: Ph. Eur. name if the corresponding monograph exists, or the name from another Pharmacopoeia (*e.g.* Pharmacopoea Helvetica, Deutsches Arzneibuch), or name based on the botanical name of plant.

  If necessary, the name of essential oil can be supplemented by an indication of the chemotype (*e.g. Thyme oil, thymol type*).

  Any significant modification is usually indicated in the name of the essential oil:

  - *Rectified essential oil*: an essential oil from which part of the constituents has been partially or totally removed by rectification; rectification can also be used to enrich an essential oil in a particular component (*e.g.* 1,8-cineole in Eucalyptus oil (0390));
  - *Deterpenated essential oil*: an essential oil from which monoterpene hydrocarbons have been partially or totally removed by rectification or any other suitable process;
  - *Deterpenated* and *desesquiterpenated essential oil*: an essential oil from which monoterpene and sesquiterpene hydrocarbons have been partially or totally removed by rectification or any other suitable process.

  At the same time, certain rectified essential oils sometimes may keep a 'traditional' name that does not include the word 'rectified' (*e.g.* Eucalyptus oil or peppermint oil) (38).
- Definition of the herbal preparation: for essential oils described in Ph. Eur. should correspond to individual monograph. If not, the alternative Pharmacopoeia could be used.

- Ratio of the herbal substance to the herbal preparation: the ratio between the quantity of herbal substance used in the manufacture of a herbal preparation and the quantity of herbal preparation obtained.
- Extraction solvent(s): not relevant for essential oil
- Other names (synonyms mentioned in other Pharmacopoeias)
- Laboratory code: any laboratory code used in the dossier if applicable
- Possible addition of excipients: in exceptional cases the antioxidant may be added (*e.g.* to Pine Sylvestris Oil or Dwarf Pine Oil). The name and the quantity of this antioxidant must be defined.

3.2.S.1.2 Structure

- Physical form: liquid
- Description of the constituents of essential oil with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass)
- Other constituent(s)

3.2.S.1.3 General Properties

A list should be provided of organoleptic and physic-chemical characters (*e.g*. solubility, boiling point, relative density, refractive index, optical rotation) and other relevant properties of the essential oil.

3.2.S.2 MANUFACTURE

3.2.S.2.1 Manufacturer(s)

For herbal substances (starting material)

The name, address, and responsibility of each supplier, including contractors, and each proposed site or facility involved in cultivation/harvesting/collection and testing of the herbal substance as starting material should be provided.

For herbal preparations (essential oil)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the essential oil should be provided.

3.2.S.2.2 Description of Manufacturing Process and Process Control

For herbal substances as starting material

Detailed information on the site of cultivation/collection, the time of harvesting and stage of growth, treatment during growth with pesticides *etc.*, and drying and storage conditions should be included. It should be confirmed that an adequate quality assurance system for the collection and/or cultivation, harvest and primary processing according to the "Guideline on good agricultural and collection practice for starting materials of herbal origin" (GACP) (39) is verified to be in place. A written GACP declaration for the herbal substance should be provided by every herbal substance supplier (farmers or collectors).

The HMPC emphasizes that the GACP rules apply not only to cultivation and harvesting of herbal drugs but to collection and processing of wild growing plants as well. The collectors should be trained and controlled by a local supervisor with a higher botanical/scientific education (40).

For essential oil

Information should be provided to adequately describe the manufacturing process of the essential oil as follows.

- Description of processing (including flow diagram).

Brief outline flow chart, starting from introduction of the herbal drug used as starting material and covering all further steps including intermediates.

Detailed description of each stage of the manufacturing process of the essential oil (cold expression, steam distillation, rectification, fractional distillation, washing, blending, or reprocessing), including information on preliminary treatment (grinding or drying). Critical steps should be mentioned and discussed (duration, temperature, *etc.*).

A maximum batch size should be stipulated, corresponding to batches already manufactured and referred to in the dossier.

In case of alternative processes, associated, for example, with different manufacturers, each of these should be clearly defined and described and shown to be equivalent, *i.e.* resulting in an essential oil of equal quality and complying with the same specification.

- Water, materials (*e.g.* Argon, NaOH, Na_2SO_4 *etc.*)

Materials used in the manufacture of the essential oil should be listed, identifying the stage at which each material is used in the process.

- Purification stages

All purification steps (rectification, filtration, washing *etc.*) performed on the intermediates and on the essential oil should be described in the application.

- Batch size

3.2.S.2.3 Control of Materials

Information on the quality and control of materials used in the manufacture of an essential oil (*e.g.* starting material, water, excipients) should be provided and that such materials meet the appropriate standards for their intended use.

Herbal drug

The specification of the herbal drug should be in compliance with the current general (Herbal drugs Ph. Eur. 07/2017:1433) and specific Ph. Eur. monographs, if it is available. Since the fresh herbal substances are used to produce the most of essential oils, the extensive analysis described in specific Ph. Eur. monographs for dried herbal drug is not appropriate but could be used as supporting information. The general Ph. Eur. monograph for “Herbal drugs” offers three opportunities to prepare the specification for fresh herbal drug:

1. For a cultivated fresh herbal drug whose origin and traceability can be demonstrated from seed to harvesting, only the macroscopic identification and test for foreign matter could be included in the specification.
2. For a cultivated fresh herbal drug where the information on life cycle from seed to harvesting is incomplete, the macroscopic identification, test for foreign matter as well as any additional tests to exclude any potential or known quality issues should be included in the specification.

3. For a wild-collected fresh herbal drug the analytical requirements should be assessed on a case-by-case basis depending on the ease of identification or characterisation of plant and potential adulterants, the method of processing or type of herbal drug preparation to be manufactured. For example, a wild-crafted fresh flower requires fewer analytical control parameters than wild-crafted fresh root because it could be easier identified. Analytical requirements as described under [1] may be acceptable as well for wild-collected fresh herbal drug when fully justified.

The “EMA Guideline on quality of herbal medicinal products/traditional herbal medicinal products” also allows only identification tests for fresh herbal drug provided that other tests will be transferred to the essential oil (36).

Batch results from at least two batches of the herbal drug should be submitted. If more than one supplier of herbal drug is declared, then batch analytical data on the herbal drug obtained from all declared suppliers should be provided.

Water

Appropriate specification for water should be supplied.

The Ph. Eur. general monograph “Essential oils” (04/2022:2098) requires for water used in the production of essential oils as a minimum compliance “with local drinking water standards or, in their absence, with World Health Organization drinking water standards”. Nevertheless, in the EMA “Questions & answers on quality of herbal medicinal products/traditional herbal medicinal products” laid down that the water used for steam distillation of essential oils should be in line with the Ph. Eur. monograph Water for Preparation of Extracts (04/2012:2249). That means, it should be water intended for human consumption of a quality equivalent to that defined in Directive 98/83/EC which is monitored at regular intervals for conductivity, nitrate, and microbiology.

In many cases the distillation of oil from fresh plant material is performed in the fields. In these situations, the water used for distillations could originate from wells or directly from a local river. Nevertheless, according to HMPC this water should be in line with the Ph. Eur. 2249. Thus, the specification can be based on “the limits applied to drinking water and a database evaluation of historical data following a risk-based approach. Testing should also include parameters that represent a potential risk regarding

contamination of the water because of former agricultural or other uses of the area. The frequency of the testing should be established following Good Manufacturing Practice (GMP) guidelines. The specification should be approved by the Competent Authority" (40).

Other materials

Appropriate specifications for all materials used in manufacturing process should be supplied.

3.2.S.2.4 Controls of Critical Steps and Intermediates

Critical Steps

Any critical steps should be identified, and in-process tests and acceptance criteria should be described.

Intermediates

Information on the quality and control of intermediates during the process should be provided (*e.g.* specification of crude essential oil).

3.2.S.2.5 Process Validation and/or Evaluation

The manufacturing process of essential oils is usually a standard process. No process validation and/or evaluation in this case is needed.

3.2.S.2.6 Manufacturing Process Development

A brief summary describing the development of the herbal preparation where applicable should be provided, taking into consideration the proposed route of administration and usage. The comparability of the phytochemical composition of the essential oil used in supporting bibliographic data and the herbal preparation described in 3.2.S.1.2 should be discussed as appropriate.

3.2.S.3 CHARACTERISATION

3.2.S.3.1 Elucidation of Structure and other Characteristics

<u>For herbal substances as starting material</u>

Information on the botanical, macroscopic, microscopic, phytochemical characterisation should be provided.

For essential oil

Information on the phyto- and physicochemical characterisation should be provided.

The phytochemical characterisation consisting of chromatographic profiles (thin-layer chromatography (TLC), High-performance liquid chromatography (HPLC), gas chromatography (GC)) or spectroscopic technique (Nuclear magnetic resonance (NMR) spectroscopy) is important to define the essential oil.

3.2.S.3.2 Impurities

Potential contaminants originating from the herbal substance production and post-harvesting treatments such as pesticides and fumigants residues, toxic metals, aflatoxins, (and ochratoxin A for herbal drugs subject to contamination), microbial contamination as well as potential adulterants should be discussed. For essential oils produced by steam distillation or dry distillation such impurities/contaminations are not or less critical because these compounds cannot be over-distilled in a distillation process. For the essential oils produced by a mechanical process without any heating (cold-pressed oils) the presence of such impurities must be critically assessed and if necessary controlled.

Since no chemical reactions are performed during manufacturing of essential oils and no organic solvents are used, the impurities like the side products, or reagent residues, or solvents are out of the question for essential oils production.

Possible impurities originating from degradation or from contamination through packaging material should be listed and discussed with an indication of their origin (*e.g.* potential degradants formed on storage or those that might arise as a result of decontamination treatments).

Another one impurity which is generally not usual for herbal preparation but is required by competent authorities is nitrosamines. Every manufacturer of essential oil must prepare risk assessment on nitrosamine and include the conclusions[*] in this section.

[*] Similar as described for (traditional) herbal medical products in „CMDh practical guidance for MAHs of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5(3) Referral on Nitrosamines“

3.2.S.4 CONTROL OF DRUG SUBSTANCE

3.2.S.4.1 Specification

For essential oils described in the Ph. Eur. or in the pharmacopoeia of an EU the specification would generally be in accordance with this monograph, taking into account the provisions of Ph. Eur. 5.30 (Monographs on essential oils (Information Chapter)) and Ph. Eur. 2098 (Essential oils (General Monograph)).

Where essential oil is neither described in the Ph. Eur. nor in the pharmacopoeia of a MS, compliance with the monograph of a third country pharmacopoeia (*e.g.* United States Pharmacopoeia/National Formulary and Japanese Pharmacopoeia) can be accepted.

If the essential oil is not described in any pharmacopoeia a comprehensive specification for the herbal preparation must be developed also taking into account the provisions of Ph. Eur. 5.30 (Monographs on essential oils (Information Chapter)), Ph. Eur. 2098 (Essential oils (General Monograph)) and guideline on specifications (41). This comprehensive specification should be established on the basis of recent scientific data and should, in general, give particulars of the characteristics, identification tests, assay and purity tests. Chromatographic fingerprinting should be used based on appropriate chromatographic methods.

For potentially toxic constituents (estragole, pulegone (42), menthofuran (42)), impurities (e.g. pyrrolizidine alkaloids, heavy metals, aflatoxins), and microbiological contaminants the maximum limits should be defined together with the analytical procedures.

3.2.S.4.2 Analytical Procedures

This section includes the description of any tests applied to ensure the quality of the essential oil. If the analytical procedure corresponds to one described in Ph. Eur., the reference to the relevant monograph is enough. In case the method is described in another Pharmacopoeia, a copy of the monograph should be included. All other analytical procedures should be described in detail.

3.2.S.4.3 Validation of Analytical Procedures

Analytical validation information including experimental data for non-pharmacopeial procedure used for testing the essential oil should be provided. Validation of the tests

performed according to Ph. Eur. monographs is not necessary, only the suitability of these methods should be demonstrated.

In case of application for CEP the test methods different from Ph. Eur. methods must be validated against Ph. Eur. methods and should be in line with the requirements of the current version of the Ph. Eur. general monograph on Essential oils (2098). It may be possible to propose excluding certain tests of the monograph on this basis if a justified rationale is provided.

For impurities, quantitative analysis of pesticides residues must be validated on a suitable herbal matrix (according to the indication given in European Pharmacopoeia in 2.8.13). For aflatoxins determination (and ochratoxin A determination for herbal drugs subject to contamination), the suitability of the Ph. Eur. methods (2.8.18 and 2.8.22, respectively) to the herbal matrix tested must be performed. For microbiological examination, the suitability of the method must be performed (according to the indication given in 2.6.31).

3.2.S.4.4 Batch Analyses

The results of testing of at least two representative batches with their description (batch size, date of production, date of analysis) should be provided. When alternatives/different sites are described in the dossier, the results of the analysis of the batches shall be provided for each. The certificates of analysis should cover the declared in 3.2.S.2.2 batch size.

The results of the analysis are given as actual figures whenever possible instead of statements such as “conforms”, “complies” etc. In cases of use of TLC, a coloured photographic picture should illustrate the results.

3.2.S.4.5 Justification of Specification

A justification for the specification of the essential oil should be provided unless it is based on a Ph. Eur. monograph or one in the Pharmacopoeia of a Member State.

The manufacturer should provide the rationale and justification for including and/or excluding testing for specific quality attributes. If available, historical experimental data should be taken into account to set the acceptance criteria. It is known for essential oils that the risk for some contaminants, *e.g.* microbial contamination, is very low and in such instances absence or reduced testing may be justified.

3.2.S.5 REFERENCE STANDARDS OR MATERIALS

Information on the reference standards or reference materials used for testing the essential oil should be provided. The Ph. Eur. chemical reference standard and/or Ph. Eur. essential oil standard should be used whenever possible.

The composition of non-pharmacopeial reference standards intended for use in assays should be adequately controlled and the purity should be measured by validated quantitative procedures. For these non-pharmacopeial standards, the supplier's name and the standard reference number should be provided, and storage conditions should be stated.

3.2.S.6 CONTAINER CLOSURE SYSTEM

For herbal substances as starting material

A description of the container closure system(s) should be included. In addition, at least certificates of food compatibility should be provided.

For essential oil

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate. In the absence of European Pharmacopoeia guidance, a certificate of food compatibility should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the essential oil. Where relevant, conformity to current regulations on plastic packaging should be demonstrated (43, 44).

3.2.S.7 STABILITY

It should also be demonstrated that the essential oil remains in the same quality in the proposed packaging and under proposed conditions.

3.2.S.7.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized (45, 46). The summary should include conclusions with respect to storage conditions and re-test date or shelf-life, as appropriate. Stress tests are unnecessary for essential oils.

The stability studies should be performed on least two batches of the essential oil. When alternatives manufacturing sites are described in the dossier or the herbal substance is used from different region, the design of stability studies should consider these differences and if it is necessary the stability information shall be provided for each alternative.

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

3.2.S.7.3 Stability Data

Results of the stability studies should be presented in an appropriate format such as tabular, graphical, or narrative. The description of batches (batch size, date of production, date of analysis manufacturer of intermediate, if more than one declared in dossier) should be provided. Information on the analytical procedures used to generate the data and validation of these procedures should be included. Chromatographic profiles should be provided.

2.1.1.3 GMP requirements

According to Article 46 of the Directive 2001/83/EC the active substances, used in medical products must be manufactured in line with the detailed guidelines on GMP for active substances used as starting materials (47). Anex 7 (48) to the EU GMP Guideline specify application of GMP provisions for active substances used as starting materials for the manufacture of herbal medicinal products (**Table 4**). It requires to implement the GACP principles (39) for the cultivation, collection, harvesting, cutting, and drying of herbal drugs (starting material). Since many essential oils are manufactured by farmers or very small companies in the traditional way – directly from fresh plant material by steam distillation on the field, the Annex 7 allow to regard this step as an integral part of harvesting and to perform it under GACP as well. This exceptional circumstance should be

"justified in the relevant marketing authorisation/ registration documentation. For activities carried out in the field, appropriate documentation, control, and validation according to the GMP principles should be assured". For steam distillation/cold expression performed on production site and for following purification steps the GMP standards for active substances must be applied.

Table 4 illustrating the application of Good Practices to the manufacture of herbal medicinal products. Reproduced from Annex 7 to the EU GMP.

Activity	**Good Agricultural and Collection Practice (GACP)**	**Part II of the GMP Guide**	**Part I of the GMP Guide**
Cultivation, collection and harvesting of plants, algae, fungi and lichens, and collection of exudates			
Cutting, and drying of plants, algae, fungi, lichens and exudates			
Expression from plants and distillation			
Comminution, processing of exudates, extraction from plants, fractionation, purification, concentration or fermentation of herbal substances			
Further processing into a dosage form including packaging as a medicinal product			

2.1.2 Essential oils as excipients

As mentioned above the essential oil can be used in medical products as excipients. The general regulatory requirements for excipient in medical products are laid down in the corresponding EU Guideline (49). Information on the excipients used in a medicinal product should be provided in part 3.2.P.1 (Description and Composition of the Drug Product), 3.2.P.2 (Pharmaceutical Development), 3.2.P.4 (Control of Excipients) and appendix 3.2.A.3 (Excipients) of the dossier. To ensure the suitable quality of essential oil

as excipient the corresponding data should be provided to the manufacturer of the herbal medicinal product:

- The common name, the composition, and a reference to a relevant standard. Because of the complexity of essential oil composition, it is only necessary to describe the general qualitative composition mentioning the main constituents with an appropriate process of identification to ensure the consistency of the composition (in particular, identification of the main constituents). For flavouring agents, it is allowed to state the qualitative composition only.
- The specifications for essential oil*
- The analytical procedures used for testing the essential oil*
- Analytical validation information for the analytical procedures used for testing the essential oil*
- Justification for the proposed excipient specifications essential oil*

* Please refer to the same parts described for essential oil as active substance

If the essential oil manufacturer has already developed the ASMF or CEP granted for essential oil in question the medicinal product manufacturer could use this documentation to fulfil MA dossier.

Like in cosmetic products the essential oils are often added as flavouring agents to mask the unpleasant odour of medicinal products caused by some active ingredients and/or to make the smell of finish product more enjoyable for the patient. The EU Regulation 1223/2009 on cosmetic products together with Commission Implementing Decision 2013/674/EU define a list of fragrances which are currently designated by the EC as allergens requiring labelling in cosmetic and detergent products if the concentration of the designated ingredient exceeds 100 parts per million (ppm) for a rinse-off product and 10 ppm for a leave-on product. Some essential oils are included in this list and a lot of essential oils contain substances identified as allergens.[*] To warn the sensitized patients the topically applied medicinal products (*e.g.* ointments and creams) containing such ingredients must be labelled regardless of concentration (zero threshold) in the product information. Since the medicinal products may be applied on a more sensitive skin (if

[*] For details please refer to the part “Essential oils as ingredients for cosmetics” of this work

damaged). The International Nomenclature of Cosmetic Ingredients (INCI) is also considered to be applicable to medicines (50).

2.2 Essential oils as feed additives

The European legislation concerning feed additives is governed by "Regulation (EC) No 1831/2003 on additives for use in animal nutrition" published in the Official Journal of the EU in October 2003. This legal act sets out the requirements and procedures for the authorisation, labelling, and control of additives for use in animal nutrition. This Regulation replaced the Directive 70/524/EEC concerning additives in feeding-stuffs from 23 November 1970.

Regulation 1831/2003 defines the feed additives as "substances, micro-organisms or preparations, other than feed material and premixtures, which are intentionally added to feed or water in order to perform, in particular, one or more of the functions" (51):

a. favourably affect the characteristics of feed,
b. favourably affect the characteristics of animal products,
c. favourably affect the colour of ornamental fish and birds,
d. satisfy the nutritional needs of animals,
e. favourably affect the environmental consequences of animal production,
f. favourably affect animal production, performance or welfare, particularly by affecting the gastro-intestinal flora or digestibility of feedingstuffs, or
g. have a coccidiostatic or histomonostatic effect (52).

Five main categories of feed additives are recognized under current EU law:

1. technological additives: any substance added to feed for a technological purpose;
2. sensory additives: any substance, the addition of which to feed improves or changes the organoleptic properties of the feed, or the visual characteristics of the food derived from animals;
3. nutritional additives;
4. zootechnical additives: any additive used to affect favourably the performance of animals in good health or used to affect favourably the environment;
5. coccidiostats and histomonostats (53).

Essential oils fall under the **Category "2" (Sensory Additives)** and **Functional Group "b" (flavouring compounds)**. The flavouring compounds (2.b.) are substances the inclusion of which in feeding stuffs increases feed smell or palatability. According to the old classification (Directive 70/524/EEC) essential oils was included in the common group "Natural products – botanically defined".

To protect the animal and human health as well as the environment feed additives may not be put on the market unless authorisation has been given following a scientific evaluation demonstrating that the additive has no harmful effects (54). The application procedure for authorisation is described in Regulation 1831/2003. Further scientific and technical requirements and instructions are provided in Commission Regulation 429/2008 as well as in the administrative and scientific EFSA Guidance documents (55). EFSA is European Food Safety Authority which plays a crucial role in the regulation of feed additives. The Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) is a department within the EFSA which is responsible for conducting risk assessments and providing scientific output on the safety and efficacy of feed additives. Based on EFSA's scientific opinion, the European Commission makes decisions regarding the authorisation and use of feed additives.

For zootechnical additives, coccidiostats, and histomonostats, as well as additives consisting of, containing or produced from genetically modified organisms (GMOs) the authorisation holder have to apply for authorisation and authorisation will be granted to a specific holder. The technological, **sensory** and nutritional additives should be evaluated by EFSA and authorized by European Commission as well, but such authorisations are not issued to a defined holder. These are so called non-holder-specific authorisation. Any person who imports or manufactures those products or any other interested party may submit the application. In case of feed flavourings (2b), which include essential oils, the Feed Flavouring Authorisation Consortium (FFAC) took responsibility to manage the authorisations (56), although every other interested party can initiate authorisation procedure for essential oil as feed additive if necessary. FFAC is an European industry initiative within FEFANA (Fédération Européenne des Fabricants d'Adjuvants pour la Nutrition Animal, EU Association of Specialty Feed Ingredients and their Mixtures). The consortium is responsible for collecting and reviewing existing scientific data, as well as

managing of new studies if some information is missing. FFAC develops common authorisation dossiers and works closely with EFSA to support the evaluation and authorisation procedure.

It should be noted that the feed additives placed on the market pursuant to the Directive 70/524/EEC could be placed on the market and used in accordance with the conditions specified in this Directives after the entry into force of the Regulation 1831/2003 (08.11.2003) but after the transition period they should be re-evaluated respectively (57). Essential oils were authorized without a time limit in accordance with Directive 70/524/EEC as feed additives for all animal species (**Figure 3**) (58). These products should have been re-evaluated during the transition period of a maximum of seven years (deadline of 08.11.2010) (57).

Figure 3 *Excerpt from CHAPTER III: List of other additives authorized for an unlimited period of (59)*

EC No	Additive	Chemical formula, description	Species or category of animal	Maximum age	Minimum content	Maximum content	Other provisions	End of period of authorisation
					mg/kg of complete feedingstuff			
Flavouring and appetising substances								
	1. *All natural products and corresponding synthetic products*	—	All species or categories of animals	—	—	—	—	Without a time limit

Moreover, Regulation 1831/2003 enacted the creation of Commission's European Union Register of Feed Additives (60) which contains information on feed additives that have been authorized for use in animal feed within the European Union (61). This register was established on 07.11.2005 and adopted all feed additives registered according to the Directive 70/524/EEC (58) and then has been updated based on new authorisation, re-evaluation, or withdrawals after transition period. The register provides detailed information on each authorized feed additive, including its name, function, category, species for which it is authorized, and maximum levels of use. It also includes the date of authorisation, any conditions or restrictions that may apply, and in case authorisation holder-specific the information on the applicant who submitted the authorisation request. At the time of this writing the Commission's European Union Register of Feed Additives includes 73 items for essential oil, only 14 of them have been completely authorized within the Regulation 1831/2003 (**Table 5**). For other oils a dossier has been already submitted to EC but evaluation process is ongoing. The reason for this is the

limited resources of the EFSA, so the Agency with the agreement of EC has given priority to the assessment of the chemically defined feed flavourings.* Such oils are still on the register and could be used as feed additives in EU and European Economic Area (EEA). Moreover, 29 essential oils were deleted from the register because no application for re-evaluation has been submitted or the application has been withdrawn.†

Table 5 *Essential oils authorized as feed additive according to Regulation 1831/2003*

Essential Oil	Botanical Name	Code in Register	Animal category(ies)	Reference(s) of Community legal act	Authorisation date
Buchu leaf essential oil	*Agathosma betulina* (P.J. Bergius) Pillans	2b85c-eo	All animal species	OJ L 218, 23.08.2022, p. 12	12/09/2022
Camphor white essential oil	*Cinnamomum camphora* (L.) J. Presl.	2b130-eo	All animal species	OJ L 228, 02.09.2022, p. 10	22/09/2022
Oregano oil	*Origanum vulgare* L., subsp. hirtum, (Link) letsw.	2b317-e-o-i	Chickens for fattening; laying hens; turkeys for fattening; piglets; pigs for fattening; sows; dairy cows; calves; cattle for fattening, sheep, goats and horses; rabbits; dogs; cats; salmonids; ornamental fish	OJ L 191, 20.07.2022, p. 7	09/08/2022
Oregano oil	*Origanum vulgare* L., subsp. hirtum, (Link) letsw. Var. Vulkan (DOS 00001)	2b317eo	All animal species	OJ L 137, 22.04.2021, p. 16	12/05/2021
Cardamom essential oil	*Elettaria cardamomum* (L.) Maton	2b180	All animal species	OJ L 241, 27.07.2020, p. 28	16/08/2020
Expressed lemon essential oil	*Citrus limon* (L.) Osbeck	2b139-eo	Chickens for fattening; turkeys for fattening; salmonids; laying hens; pigs for fattening; piglets; sows; calves (milk replacers); cattle for fattening; dairy cows; horses;	OJ L 234, 09.09.2022, p. 1	29/09/2022

* In case of expressed ogange essential oil the dossier was submitted on 05/11/2010 and the scientific assessment was started on 19/03/2018.

† For details, please refer to Annex 2

Essential Oil	Botanical Name	Code in Register	Animal category(ies)	Reference(s) of Community legal act	Authorisation date
			sheep/goats; rabbits;		
Distilled (steam) lime essential oil	*Citrus aurantiifolia (Christm.) Swingle*	2b141-eo	Chickens for fattening; turkeys for fattening; salmonids; laying hens; pigs for fattening; piglets; sows; lactating sows; cattle for fattening; calves (milk replacers); dairy cows; sheep/goats/horses; rabbits; salmonids; ornamental fish	OJ L 234, 09.09.2022, p. 1	29/09/2022
Expressed mandarin essential oil	Citrus reticulata Blanco	2b142-eo	Poultry; rabbits; salmonids; pigs; ruminants; horses.	OJ L 55, 28.02.2022, p. 41	20/03/2022
Expressed orange essential oil	*Citrus sinensis* (L.) Osbeck (*Citrus sinensis* (L.) Pers., *Citrus aurantium* (L.) Dulcis.)	2b143-eo	Chickens for fattening and other minor poultry species for fattening; laying hens and other minor poultry species for laying and breeding purposes; turkeys for fattening; all *Suidae* for fattening; piglets of all *Suidae* species; sows; ruminants; horses; rabbits; fish except ornamental fish; other species	OJ L 218 23.08.2022, p. 27	12/09/2022
Litsea berry essential oil	*Litsea cubeba* (Lour.) Pers.	2b491-eo	Chickens for fattening; laying hens; turkeys for fattening; pigs for fattening; piglets; Lactating sows; calves; dairy cows; cattle for fattening; sheep/goats; horses; rabbits; salmonids; dogs; cats; ornamental fish	OJ L 114, 12.04.2022, p. 44	02/05/2022
Petitgrain bigarade essential oil	*Citrus aurantium* L.	2b136-eo	Chickens for fattening; laying hens; turkeys for fattening; pigs for	OJ L 64, 02.03.2022, p. 1; OJ L 119 SL, 21.04.2022, p. 116	22/03/2022

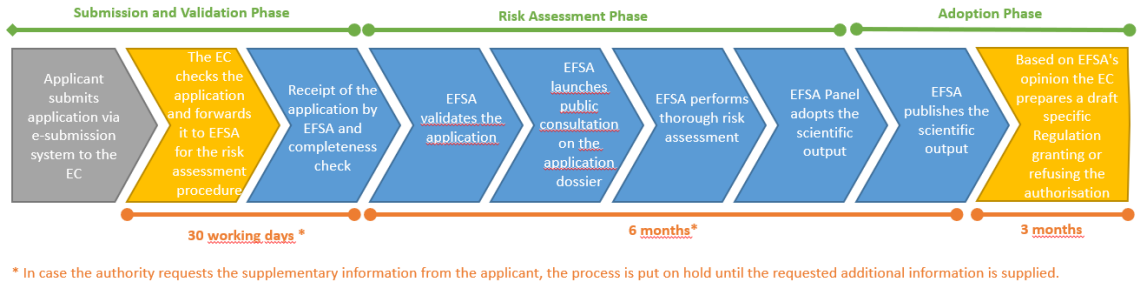
Essential Oil	Botanical Name	Code in Register	Animal category(ies)	Reference(s) of Community legal act	Authorisation date
			fattening; piglets; Lactating sows; calves; dairy cows; cattle for fattening; sheep/goats; horses; rabbits; salmonids; dogs; cats; ornamental fish		
Turmeric essential oil	Curcuma longa L.	2b163-eo	All animal species	OJ L 111, 31.03.2021, p. 3; OJ L 78, 08.03.2022, p. 21	20/04/2021
Ylang ylang essential oil	*Cananga odorata* (Lam) Hook f. & Thomson	2b103-eo	All animal species	OJ L 217, 22.08.2022, p. 1	11/09/2022
Ginger essential oil	*Zingiber officinale* Roscoe	2b489-eo	All animal species	OJ L100, 23.03.2021, p. 3; OJ L 78, 08.03.2022, p. 21	12/03/2021

2.2.1 Authorisation procedure

According to Article 7(1) of Regulation (EC) No 1831/2003, the application for authorisation under Article 4(1) (authorisation of a feed additive or new use of a feed additive) or under Article 10(2) (re-evaluation of an authorised feed additive) should be submitted to the European Commission, which forwards this to the EFSA. EFSA receives directly from the applicant the technical dossier in support of the application. When the particulars and documents are considered valid, EFSA shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. Based on the EFSA opinion the European Commission decides whether or not to authorise the feed additive. The authorised feed additive shall be entered in the Register of authorised feed additives. For the flow chart and the legally required timetable please refer to **Figure 4**.

Simultaneous to the submission of the documentation the applicant must send three samples of the feed additive directly to the Community reference laboratory, which test, evaluate, validate the method for detection, evaluate the data provided by the applicant and provide full evaluation reports to EFSA.

Figure 4. The Flow chart of application procedure for feed additives with timetable. Reproduced and adopted from (55)



The technical dossier for feed additives consists of 5 sections:

Section I: summary of the dossier

1.1 Public summary according to Article 7(3)(h) of Regulation (EC) No 1831/2003

1.2 Scientific summary of the dossier

1.3 List of documents and other particulars

1.4 List of parts of the dossier requested to be treated as confidential, where necessary

Section II: identity, characterisation, and conditions of use of the additive; methods of analysis

2.1 Identity of the additive

2.2. Characterisation of the active substance(s)/agent(s)

2.3. Manufacturing process, including any specific processing procedures

2.4 Physic-chemical and technological properties of the additive

2.5 Conditions of use of the additive

2.6 Methods of analysis and reference samples

Section III: studies concerning the safety of the additives

3.1. Studies concerning the safety of use of the additive for target animals

3.2. Studies concerning the safety of use of the additive for consumers

3.3. Studies concerning the safety of use of the additive for users/workers

3.4. Studies concerning the safety of use of the additive for the environment

Section IV: studies concerning the efficacy of the additive

4.1 In vitro studies

4.2 Short term efficacy studies with animals

4.3 Long term efficacy studies with animals

4.4 Duration of long term efficacy studies with target animals

4.5 Efficacy requirements for additive categories and functional groups

4.6 Studies on the quality of animal products where this is not the effect claimed

Section V: post-market monitoring plan

The Commission Regulation 429/2008 describes the requirements to the technical dossier for certain categories of additives or certain particular situation. In case of essential oils, the requirements for Sensory additives (2) must be taken into account. Moreover, this regulation allows substances already approved for use in human food (8) to be assessed with a more limited procedure than for other feed additives. Although there is no specific EU authorisation for any essential oil as a flavour in food, many of the components of the essential oils have been already evaluated by the FEEDAP Panel as chemically defined flavourings for use in feed and food. Moreover, according to Regulation (EC) No 1334/2008(62), flavouring preparations produced from food, may be used without an evaluation and approval as long as “they do not, on the basis of the scientific evidence available, pose a safety risk to the health of the consumer, and their use does not mislead the consumer”. Therefore, the technical dossier for essential oils could be shorted in section II, III and IV respectively.

For the detailed structure and requirements for the technical dossier for feed additives please refer to Regulation (EC) No 429/2008 and the relevant guidance documents (63-73).

Authorisations under this Regulation are valid for 10 years after granting unless an application for renewal is submitted no later than one year prior to the expiry date. The renewal of feed additives is granted for the next 10 years on the basis of Article 14 of Regulation (EC) No 1831/2003. In the case of non-holder-specific authorisation any person who first places the additive on the market or any other interested party may submit the application to the Commission and shall be considered as the applicant.

2.2.2 Labelling

The Article 16 of Regulation (EC) No 1831/2003 laid down the provisions on the labelling of feed additives and their premixtures which must be adhered to. Additives must be labelled in a conspicuous, clearly, legible, and indelible manner. Below the requirements and their application by example for Expressed orange essential oil (74) are demonstrated.

The specific name given to the additives upon authorisation, the functional group to which they belong, and their identification number	***Expressed orange essential oil*** ***Category:*** *Sensory additives* ***Functional group:*** *Flavouring compounds* ***Identification number:*** *2b143-eo*
The name and address or registered place of the person responsible for these particulars	*Not applicable*
The net weight or net volume of the additives	*xxx kg*
Where appropriate the approval number of the establishment manufacturing the additive or placing it on the market	*Not applicable*
Directions for use and, where applicable, any safety recommendations regarding use	*Expressed orange oil is safe up to the maximum proposed use levels in complete feed of 80 mg/kg for chickens for fattening and other minor poultry species for fattening; laying hens and other minor poultry species for laying and breeding purposes; and turkeys for fattening, 172 mg/kg for all Suidae for fattening, 144 mg/kg for piglets of all Suidae species, 200 mg/kg for sows, 130 mg/kg for ruminants, 230 mg/kg for horses, 50 mg/kg rabbit, fish except ornamental fish and other species.*
The specific requirements mentioned in the authorisation	*1. The additive shall be incorporated into the feed in the form of a premixture.* *2. Mixture with other botanical additives is permitted provided that the amounts of perillaldehyde added to*

	feedingstuffs by such mixtures is lower than the one resulting from the use of a single additive at the maximum or recommended level for the species or category of animal. *3. For users of the additive and premixtures, feed business operators shall establish operational procedures and organisational measures to address potential risks by inhalation, dermal contact or eyes contact. Where those risks cannot be eliminated or reduced to a minimum by such procedures and measures, the additive and premixtures shall be used with personal protective equipment, including skin, eye and breathing protection.*
The batch reference number and date of manufacture	***Batch number:*** *xxxxxx* ***Date of manufacture:*** *xx.yy.zzzz* *Manufacturer name and address*

2.3 Essential oils as ingredients for cosmetics

2.3.1 Cosmetics Regulation (EC) No 1223/2009

In the European Union, cosmetic products and their ingredients are regulated by the Cosmetics Regulation (EC) No. 1223/2009. This legislation is aimed directly at companies that place cosmetic products on the European market and only indirectly to the suppliers of the substances used as a cosmetic ingredient. In contrast to feed additives and medical products, that could not be placed on the market before authorisation, cosmetics products do not require pre-market approval in EU. Instead, they undergo a notification process where the manufacturer or importer must notify the Commission via Cosmetic Products Notification Portal (CPNP) about the cosmetic product before placing it on the market. To understand the requirements for essential oils as cosmetic ingredients the notification process of cosmetic products should be shortly summarized here.

The Regulation (EC) No. 1223/2009 lays down that each cosmetic product should be linked to a “responsible person” (legal or natural) established within the Community who

will ensure compliance with the regulations and act as a point of contact with the authorities.

Prior to placing the cosmetic product on the market, the responsible person informs the Commission about the name and the category of product, name and address of the responsible person, the country of origin, the Member State where product is to be placed on the market, information about nanoparticles and substances classified as carcinogenic, mutagenic or toxic, and the frame formulation.

When the cosmetic product is placed on the market, the responsible person shall notify to the Commission the original labelling and keep a product information file for the product.

When the cosmetic product is placed on another Member State market, the responsible person submits the corresponding information to the Commission.

The Product Information File (PIF) is a comprehensive document that contains in-depth details about the final product, its ingredients, packaging, manufacturing process, and labelling. It serves as a crucial legal requirement for introducing a product into the European market. In contract to medical product dossier or feed additive technical dossier, the PIF is not submitted to the competent authority for assessment but is open for inspection. The product information file content is described in article 11 of EU Cosmetics Regulation 1223/2009:

1. **Description of the cosmetic product** – The description part establishes a clear relation between the cosmetic product and its PIF. It includes the name of the product, product's formula, identification, and code, all the names in the national language of European Union, if the product must be commercialized in the EU member countries etc.
2. **Product Safety Report** – The aim of the product safety report is to evaluate the safety of the cosmetic product. It consists of two parts:

   Part A – It contains all the necessary data required to conduct the safety assessment. For example, microbiological quality of the product, toxicological profile, exposure to the substance and cosmetic products, physical/chemical properties etc.

Part B – Contains the conclusion of the product safety report based on the safety assessments. It includes references of the person in charge, scientific reasoning, conclusion of the safety assessment, instructions displayed on the label.

3. **Manufacturing Method** – This part contains manufacturing methods of the cosmetic product and a declaration to the GMP of the product's compliance.
4. **Proof of the claimed effect** – This part contains information which can support the claims of the product.
5. **Data related to animal testing** – If no animal testing has been performed, it should be clearly mentioned in the PIF.

One of the most critical parts of PIF is the Product Safety Report (PSR) which demonstrates that a cosmetic product is "safe for human health when used under normal or reasonably foreseeable conditions of use" (75). In cosmetic industry the responsible person is obligated to prepare the safety assessment and ensure the safety of their product on its own responsibility without additional assessment from the site of competent authority. The cosmetic product safety report shall include the following information concerning substances contained in the cosmetic product (highlighted in bold) (76):

PART A – Cosmetic product safety information

1. Quantitative and qualitative composition of the cosmetic product

   Chemical identity of the substances (incl. chemical name, INCI, CAS, EINECS/ELINCS, where possible) and their intended function. In the case of perfume and aromatic compositions, description of the name and code number of the composition and the identity of the supplier.
2. Physical/chemical characteristics and stability of the cosmetic product

   The physical and chemical characteristics of the substances or mixtures.
3. Microbiological quality

   The microbiological specifications of the substance or mixture.
4. Impurities, traces, information about the packaging material

   The purity of the substances and mixtures.

   In the case of traces of prohibited substances, evidence for their technical unavoidability.

5. Normal and reasonably foreseeable use
6. Exposure to the cosmetic product
7. Exposure to the substances

   Data on the exposure to the substances for the relevant toxicological endpoints.
8. Toxicological profile of the substances

   Toxicological profile of substances for all relevant toxicological endpoints. A particular focus on local toxicity evaluation (skin and eye irritation), skin sensitisation and, in the case of UV absorption, photo-induced toxicity shall be made.
9. Undesirable effects and serious undesirable effects
10. Information on the cosmetic product

PART B – Cosmetic product safety assessment

1. Assessment conclusion
2. Labelled warnings and instructions of use
3. Reasoning
4. Assessor's credentials and approval of part B

For more details about PSR please refer to Annex I of the Cosmetic Regulation (EC) No. 1223/2009 and the Guidelines on Annex I according to the Commission Implementing Decision 2013/647/EU (77).

The safety of finished cosmetic products can already be ensured on the basis of knowledge of the safety of the ingredients that they contain. Thus, the detailed information about the full chemical composition of essential oil, including any impurities, is critical for the safety assessment. Understanding the chemical composition of a cosmetic ingredient is a fundamental principal of the industry. Moreover, the essential oil supplier should support the responsible person with all available information about toxicological data to make decisions on safe use of the ingredient.

Although essential oils are often considered as very safe cosmetic ingredient because they are obtained from plant raw materials and have been used for a long time, certain constituents from essential oils can cause some adverse reactions, *e.g.* allergic reactions, irritate the eyes and mucous membranes, or photosensitisation. The essential oils using in

cosmetics should be checked for presence and content of substance mentioned in Annex II and Annex III of Cosmetic Regulation No. 1223/2009. Annex II lists substances which are prohibited for use in cosmetic products. Among listed substances there are some plants and its preparations *e.g.* essential oils from *Chenopodium ambrosioides* L. and *Juniperus sabina* L. In addition, the prohibited substances can be found as contaminants in legally permitted essential oils. For example, the cold-pressed unrefined sesame seed oil might contain lead (Pb) which belongs to prohibited group of heavy metals (78).

Annex III lists substances that cosmetic products must not contain except subject to the restrictions laid down. Initially this annex contained 26 fragrance allergens, derived from synthetic fragrances, as well as natural essential oils and extracts. In practice, it means their presence in cosmetics must be mentioned in the list of ingredients (individually labelled) [*] when a given allergen exceeds 0.01 % in a rinse-off cosmetic (*e.g.* soap, shower gel, shampoo) or 0.001 % in a leave-on cosmetic (*e.g.* cream, lotion, tonic). In light of the scientific committee on consumer safety (SCCS) opinion (SCCS/1459/11) identifying 56 additional substances caused allergies (79), the list of fragrance allergens has been expanded and updated for certain existing entries through Commission Implementing Decision 2013/674/EU (80). The list includes substances found in most essential oils such as Citronellol, Eugenol, Linalool, Menthol, Terpineol, Isoeugenol, Limonene, Linalyl Acetate, Camphor, Vanillin, Geranial and Geranyl Acetate etc., as well as 25 essential oils, *e.g.* ylang-ylang oil (Cananga Odorata Flower Oil), cinnamon oil (Cinnamomum Zeylanicum Bark Oil), or eucalyptus oil (Eucalyptus Globulus Oi).

The essential oils are used in cosmetic products not only as fragrances but also as active substance. To help cosmetics producers to assess the safety of natural ingredients the Council of Europe has published three volumes of recommendations concerning plants and plant preparations (*i.a.* essential oils) used as ingredients for cosmetic products (81-83). The volumes contain datasheets on plant and plant preparations including the safety assessments which have been evaluated by the Council of Europe's Committee of Experts on Cosmetic Products. The first volume covers entries which do not present a health hazard such as Roman Chamomile oil, Chamomile oil, Pine Sylvestris oil, Rosemary oil,

[*] Article 19 (1) of Regulation (EC) No. 1223/2009 specifies that perfume and aromatic compositions and their raw material not listed in Annex III are to be referred to by the terms 'parfum' or 'aroma' in the list of ingredients.

Sage oil, Thyme oil. The second volume includes plants which may pose a health risk. The last one of the trilogy concerns potentially harmful components which occur naturally in some plants the ingredients of which could likely be used in cosmetic products such as thymol, camphor, eucalyptol (known as 1,8-cineol), and menthol. The last three substances are mentioned as active ingredients which give raise to toxicological concerns in cosmetic products for infants (84) and older consumers (85). From this reason it is recommended that the use of these ingredients should be avoided in cosmetic products intended for infants. It has to be stressed that a lot of essential oils contain camphor, eucalyptol and/or menthol as constituent(s): *Artemisia* ssp, *Basilicum*, *Calamintha nepeta*, *Chrysanthemum balsamita*, *Chrysanthemum parthenium*, *Cinnamomum camphora*, *Elettaria cardamomum*, *Eucalyptus* ssp, *Lavandula* ssp, *Mentha* ssp, *Ocimum*, *Rosmarinus officinalis*, *Salvia* ssp, *Santolina chamaecyparissus*, *Tanacetum vulgare* and *Thymus mastichina* (84).

Along with European there are specific national recommendation for these substances:

- The German Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung) recommends maximum concentration of 1 % eucalyptus oil, camphor or menthol for products which remain on the skin and a maximum level of 5 % camphor and 4 % menthol for products which are washed off (86).
- The French Health Products Safety Agency deemed it acceptable to have low concentrations of camphor, eucalyptol, or menthol in perfume compositions, as long as they fell within the specified limits (87):
  - camphor: 0.015 % (150 ppm)
  - eucalyptol: 0.1 % (1 000 ppm)
  - menthol: 0.45 % (4 500 ppm)

  This recommendation does not apply to oral hygiene products.

Thus, the essential oils as cosmetic ingredients are in the focus of European and national agencies and committees. The widely used essential oils are well described and there are official recommendations which could be used for development of cosmetic products and their safety assessment. In addition to that, the cosmetic industry has developed on their own initiative a system to manage the safe use of fragrance: the IFRA Standards, that ban, limit or set criteria for the use of certain ingredients (88). The **Certificates of Conformity**

to the IFRA Standards for essential oils as cosmetic ingredient for both application as fragrance and as active substance became an essential part of documentation although it is not legally required.

IFRA stands for the International Fragrance Association. It is a global trade association representing the fragrance industry. In close collaboration with the authorities and based on scientific evidence IFRA has developed IFRA Standards that impose a quantitative limit on the use of fragrance ingredients are expressed as a Maximum Acceptable Concentration of fragrance ingredients in the finished consumer product. The fragrance mixtures have usually a very complex composition, and their recipe is a company secret. To be able to protect perfumer's creativity on the one hand, and, to ensure the safety use of fragrance on the other hand, the fragrance suppliers perform a calculation based on IFRA Standards to determine safe use levels of its fragrance in different categories of cosmetic products[*]. With the Certificate of Conformity to the IFRA Standards the companies creating fragrance mixtures declares compliance with the requirements expressed in the IFRA Standards and confirms that a specific fragrance mixture up to a certain concentration can be used in a specified consumer product in compliance with up to and including a specific Amendment (the number and the Notification date of the Amendment should be stated in the Certificate) (89). The certificates are valid for a specific period and may require renewal or re-evaluation to ensure ongoing compliance with the IFRA Standards.

It should be noted that some essential oils have their own IFRA Standard. Although the Certificates of Conformity to the IFRA Standards is not applied for raw material and supplier of the essential oil can only communicate to its clients the conformity of the raw material with the corresponding IFRA Standard the situation is not as trivial as it seems. Usually, the essential oils contain one or more constituents covered by their own IFRA Standards and/or the composition of oil can differ from the composition used for IFRA Standard. In this case the supplier should calculate the maximum permitted use level for essential oil itself and for their individual components. The lowest resulting maximum permitted use level (essential oil or their constituent) will drive its use. For the essential

[*] Depending on functional type, area of use and applications (rinse-off or leave-on) the cosmetic products are categorized into 12 group by IFRA.

oils that are not covered by individual IFRA Standard the constituent approach like for a mixture of fragrance ingredients should be applied.

Another important point for cosmetic ingredient supplier from Cosmetic Regulation is correct labelling of their product. According to the Regulation the ingredients used in cosmetic product should be indicated on the packaging and expressed by using the INCI name set out in the glossary (CosIng) (90). The CosIng register includes the INCI name, short description, CAS number, EC number, identified INGREDIENTS or substances *e.g.* Cosmetics Regulation provisions, functions, SCCS opinions. It is important for cosmetic products to accurately label the essential oils they contain. However, this can be challenging due to the existence of multiple names for the same essential oil, which may vary based on the species or plant part from which it is extracted. For example, the CosIng includer following names for lavender oil:

- Lavandula Intermedia Oil
- Lavandula Angustifolia Oil
- Lavandula officinalis Flower Oil (corresponds to Lavender oil Ph. Eur.)
- Lavandula Latifolia Herb Oil (corresponds Spike Oil Ph. Eur.)
- Lavandula Intermedia Flower/Leaf/Stem Oil
- Lavandula Angustifolia Herb Oil
- Lavandula Angustifolia (Lavender) Flower/Leaf/Stem Oil
- Lavandula Angustifolia Angustifolia Herb Oil
- Lavandula Spica Flower Oil

The essential oil supplier must communicate the cosmetic product manufacturer about correct name of essential product.

2.3.2 Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and Regulation (EC) No 1272/2008 concerning Classification, Labelling and Packaging (CLP)

Although European cosmetic legislation does not require to register cosmetic ingredients, all chemicals manufactured or imported in EU and EEA must be registered under Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (91) until the chemical substance fall under the

exception or the annual volume of imported or manufactured substance is less than 1MT. Unlike cosmetic ingredients the API for medical products and ingredient for feed/food products are out of scope of REACH registration (92).

One of the basic principles of REACH is that manufacturers, importers, and downstream users must ensure that the substances they manufacture, place on the market or use do not adversely affect human health or the environment. For this the natural or legal persons handling chemicals (more than 1T) must submit to European Chemicals Agency (ECHA) a registration dossier containing all available and relevant information concerning potential hazards. The hazardous properties of chemicals include physicochemical hazards (explosivity, oxidising properties and flammability), toxicological hazards related to humans (corrosivity and irritancy to skin, eyes and the respiratory tract, skin and respiratory sensitisation, target organ toxicity, carcinogenicity, mutagenicity, and effects on reproduction), and environmental hazards related to ecosystems (93). The level of data required for registration dossier depends on the tonnage manufactured or imported per year. There are four tonnage thresholds: 1 to 10 tons, 10 to 100 tons, 100 to 1000 tons and above 1000 tons. If the registrant manufactures or imports a substance in quantities of 10 tons or more per year a chemical safety assessment (CSA) (94) must be performed and a chemical safety report as part of registration dossier is required.

It must be stressed that the responsibility for the safe use of chemicals lies on the industry. ECHA and the other regulators targeting their work to spot checks or to especially problematic areas. For more details about registration dossier and registration process under REACH please refer to the REACH regulation text itself, especially to Title II, Annexes VI to XI, and to official ECHA website (95) where the guidelines (96) and manuals can be found.

In contrast to vegetable oils, which are exempted from registration obligation as non-hazardous substances, the essential oils are subject of registration under REACH. Since essential oils are manufactured or imported by more than one company, all the registrants are obliged to be part of the same joint submission (97) to save resources on both side registrants and authority, to reduce costs and to minimize the animal testing. The companies form a consortium (formally known as a Substance Information Exchange Forum, or SIEF) for single essential oil, or group of oils (*e.g.* citrus oils), or all extractives

(such as tinctures, concretes, absolutes, essential oils, oleoresins, terpenes, terpene-free fractions, distillates, residues, etc.) obtained from certain plant (*e.g.* Rosemary, ext.; Peppermint, ext.). The information that needs to be submitted jointly is submitted by one lead registrant on behalf of the other registrants (the so-called 'member registrants'). The lead registrant takes responsibility to prepare the lead dossier, required tests and CSA. After the lead dossier has been accepted for processing the lead registrant gives the member registrants the token to access the joint submission of individual registration dossier to ECHA. In case the new company wants to follow the join registration, this company must contact the consortium and acquires a package of documents for joint submission.

Second key legislation for all chemicals circulated in EEA including natural cosmetic components regardless of tonnage is Classification, Labelling and Packaging Regulation (CLP) EC No. 1272/2008. The purpose of the CLP is to ensure a high level of protection for health and the environment, as well as the free movement of substances, mixtures and articles.(98) It involves the classification of chemicals based on their hazardous properties, the labelling of containers with appropriate warning symbols and information, and the packaging of chemicals in a way that minimizes the risk of accidents or exposure. CLP aims to protect human health and the environment by providing clear and consistent information about the hazards associated with chemicals. The CLP notifications made by EU manufacturers and importers are published on the ECHA classification and labelling inventory (99). Both laws REACH and CLP are closely related to each other and must be considered in combination.

2.4 Safety Data Sheet

All substance, including essential oils, circulated on Community market und regardless of the quantities that are imported or manufactured and application (incl. medical, feed and food) must have their own Safety Data Sheet (SDS) (100, 101). SDS is a key document which provides information about the potential hazards and safe handling procedures for a particular substance and mixtures to recipients in the EU. It includes details such as the chemical composition, physical and chemical properties, potential health effects, first aid

measures, fire-fighting procedures, handling and storage recommendations, and disposal considerations. The purpose of an SDS is to ensure the safe use, storage, and transportation of hazardous materials, and to provide essential information to workers, emergency responders, and other stakeholders. This document includes the requirements of REACH (102), CLP and Globally Harmonized System (GHS) (103). All chemicals require a safety data sheet, whether they are covered by REACH registration or not (< 1 tons or exceptions like vegetable oils). For REACH registered substances, information in the SDS for the substance must be consistent with that provided in the registration dossier. The ECHA has developed many guidelines (104-106) and tools (107, 108) advising on the preparation of safety data sheets.

The SDS must include a 16-section format(100, 101):

1. **Identification of the substance or mixture and of the company or undertaking:**

This section includes the product name (*the name of essential oil and the main components*), manufacturer or supplier information, emergency contact details, and recommended use of the substance or product.

2. **Hazards identification:**

Here, the potential hazards associated with the substance or product are described, including any specific hazards related to health, fire, reactivity, or environmental impact.

3. **Composition and information on ingredients:**

Here, the potential hazards associated with the substance or product are described, including any specific hazards related to health, fire, reactivity, or environmental impact.

4. **First aid measures:**

It outlines the recommended first aid procedures to be followed in case of exposure or accidents involving the substance or product.

5. **Firefighting measures:**

This section provides guidance on appropriate fire-fighting techniques, equipment, and extinguishing agents to be used in case of a fire involving the substance or product.

6. **Accidental release measures:**

It describes the recommended procedures for containing and cleaning up spills or releases of the substance or product, including any necessary personal protective equipment (PPE) and containment measures.

7. **Handling and storage:**

This section provides information on safe handling practices, including recommendations for storage conditions, incompatible materials, and precautions to minimize risks during handling.

8. **Exposure controls and personal protection:**

It outlines the recommended exposure limits, engineering controls, and personal protective equipment (PPE) required to minimize exposure to the substance or product.

9. **Physical and chemical properties:**

Physical and Chemical Properties: This section provides information on the physical and chemical properties of the substance or product, such as appearance, odor, pH, boiling point, melting point, etc.

10. **Stability and reactivity:**

It describes the stability of the substance or product and any potential reactive hazards, including conditions or substances to avoid.

11. **Toxicological information:**

This section provides information on the potential health effects of the substance or product, including acute and chronic toxicity, routes of exposure, and symptoms of exposure.

12. **Ecological information:**

It includes information on the potential environmental impact of the substance or product, such as its persistence, bioaccumulation potential, and toxicity to aquatic or terrestrial organisms.

13. **Disposal considerations:**

This section provides guidance on the proper disposal methods for the substance or product, including any specific regulations or requirements.

14. **Transport information:**

It outlines any special precautions or requirements for the transportation of the substance or product, including proper labelling, packaging, and handling during transit.

15. Regulatory information:

This section includes information on relevant regulations or regulatory agencies governing the substance or product, such as hazard classifications, labelling requirements, and permissible exposure limits.

16. Other information:

This section may include additional information that is not covered in the previous sections, such as date of preparation or last revision of the SDS, abbreviations, and references.

Please find an example of SDS for Cardamom oil at (109).

3. Discussion

Due to their unique properties and various functions, essential oils are widely used in medical, cosmetic, feed and food products. On the one hand, this opens great economic opportunities for essential oils manufacturers and suppliers to sell their products to the customers from diverse industries. On the other hand, essential oils become subject of diverse legislations with strong and complex requirements. Speaking about the widespread use of essential oils, we must keep in mind that often the final products containing oils are niche products (OTC medical products, natural cosmetics, fragrances, feed additives, food supplements *etc.*) with limited sales volume in their sector and hence require limited volume of essential oil in their production. Depending on the essential oil and the final product the annual demand may range from a couple of kilograms to hundreds of tons per year, but the regulatory effort stays the same. This work focuses only on the regulatory requirements in EU for feed additives, medical and cosmetic ingredients. Very important and big segment “essential oils in food products” and the smaller but regulatory more complex segment “essential oils as biocides” were not considered due to resource limitations. Nevertheless, it should be noted that companies manufactured and/or supplied essential oils work with all these industries and hence with the corresponding regulations from EU and worldwide. It is a big challenge for such companies which are often are small and medium-sized enterprises (SME).

Comparing the European legislation for feed additives, ingredients for cosmetics and medicines we can conclude that the most stringent regulation exists for active substance for medical products. The quality and safety of essential oils as active substance/excipient is the essential part of MA dossier of final medical product and the subject of scientific assessment by competent authorities. The European legislation allow to apply special procedures to include the information regarding active substance in the MA dossier (CEP, ASMF, worksharing ASMF). There are clear definition of essential oils and methods of their production, as well as the guidelines on the manufacturing standards (GACP and GMP), quality control, structure, and content of documentations regarding herbal active substance that should be applied to essential oils. At the same time, as noted in the EMA reflection paper “current guidance does not address fully the particular aspects of essential oils and further guidance is needed for manufacturers of essential oils and

applicants on the documentation to be presented to the competent authorities" (37). Thus, some requirements for herbal active substance are difficult to implement in practice or do not have sense in case of essential oil but they are regarded as necessary by competent authorities. It leads to the additional discussions between authorities and applicants and to justification of every deviation from the Guidelines which were developed mostly for extracts. The classic example is the strict requirements for water used for steam distillation. The competent authorities insist that this water should be in line with the Ph. Eur. monograph "Water for Preparation of Extracts" (04/2012:2249) although in case of dry steam distillation the water is used only to generate the steam in a separate boiler and does not have direct contact with the plant material. But even in case of a hydrodistillation the theoretical contaminates could not be over-distilled, *e.g.* bacterial cells will be destroyed under these conditions, the cations could not be over-distilled and in case they were dragged along with the flow, they would stay in the hydrophilic phase after separation. It is necessary that the water used for steam distillation must be appropriate quality and regularly controlled but the quality "Water for Preparation of Extracts" is too high for this type of production.

The conformity to GACP/GMP of all production's steps from seed to the final herbal active substance is the fundamental principles of European regulation and the most challenge for the essential oil manufacturers. Since the usage of essential oils within the pharmaceutical sector, represents only a limited proportion of the commercial market in comparison to the cosmetic and food sectors, it is not easy to motivate the essential oils producers to switch to stricter standards of active substances for pharmaceutical use. This lead in some cases to the gaps in the conformity to GACP/GMP trough the manufacturing chain. It is big challenge for farmers who cultivate or collect the herbal starting material and/or farmers or small companies which manufacture crude essential oils in the traditional way—directly from fresh plant material by steam distillation on the field—fully to comply with GACP. Usually this is the people with limited botanical and scientific education. For example, the Eucalyptus leaves for essential oil are collected in eucalyptus forests or plantations with monoculture of *Eucalyptus globulus* Labill. by ordinary farmers in low season to their primary agricultural activity. The challenge to obtain the GACP conformation from each leaves collectors strives to become the "mission: impossible". On

the other hand, the risk to collect the wrong plant material from the monoculture forests or plantations is not high and it could be enough to train and control of the collectors by a local supervisor with a higher botanical/scientific education instead of GACP conformation of every plant material collector. Thus, the responsibility for GACP conformation could be transferred to the next member of manufacturing chain.

Hubbert, M. et al. developed an elegant risk-based approach using the established model of the Failure Mode and Effective Analysis (FMEA) for essential oils as atypical actives whose production according full GMP requirements cannot be guaranteed (110). The authors suggest this approach as basis for discussion with local health authorities during inspections and import. From our point of view, it could be useful for regulatory purpose as well. The template for risk assessment of essential oils from this publication is included in the Annex 1 of this study.

Another non-trivial task is the demonstration of full traceability of supply chain from plant (starting material) to final herbal active substance. It is crucial to ensure that the herbs used are of proper quality and to identify the potential risks and hazards throughout the supply chain. It means every herbal material supplier and every crude essential oil supplier should be mentioned in the dossier and in case of some change the corresponding variation should be supplied to the competent authority. As mentioned above, many essential oils are produced in the traditional way directly on the field, the batch size (single steam distillation) could be 2–5 kg. It leads to a long list of crude oils suppliers.

When the applicant built a reliable chain of suppliers of plant starting materials, crude oil manufacturers and other manufacturers responsible for further purification or testing, and they are working according to the relevant standards (GACP/GMP), it is the strong basis to successfully fulfil regulatory requirements for active substance. Although the creation of documentation for essential oil as active substance (Part 3.2.S./ASMD/CEP dossier) and the registration process (as part of MA or as CEP procedure) is associated with big effort (expertise, time, costs), the status of active substance opens wide opportunity for essential oil supplier.

Like the active substance for pharmaceutical use the feed additives are strict regulated in European Union. In contrast to active substance, which is used to produce a final medical

product, the essential oil as a feed additive is a “final” product itself. The authorisation of essential oils as feed additives (flavouring compounds 2.b.) is non-holder-specific whereas the authorisation of the active substance is always associated with a specific holder (CEP holder or ASMF holder). Once granted non-holder-specific authorisation is public and can be used by every stakeholder if the specification and the labelling of specific feed additive comply with the authorisation. Usually, the Consortium FFAC takes responsibility to manage the authorisations of essential oils but the single company can decide to submit their own application with unique specification to differentiate themself from competitors. In this case the whole effort required to prepare the necessary authorisation dossiers (expertise, animal testing, costs, etc.) bears the single company. Nevertheless, the authorisation stays non-holder-specific.

Although the traceability of supply chain is critical requirement of European Food/Feed regulation as well (111), it is not a part of authorisation but the subject of inspection of competent authority. The same belongs to the quality management system – the European Feed legislation (112) requires the application of the HACCP (Hazard Analysis and Critical Control Points) principles for feed production but HACCP system is outside the scope of technical dossier for feed additive authorisation.

Unlike the active substances and feed additives the cosmetic ingredients are not detailed regulated in EU. Cosmetics Regulation (EC) No. 1223/2009 is aimed only indirectly to the suppliers or manufacturers of the substances used as a cosmetic ingredient. Nevertheless, the market players obliged to carry out the comprehensive requirements of REACH and CLP for all chemicals manufactured or imported in EU and EEA while the ingredients for medicals and feed are out of scope of these regulations. Thus, REACH and CLP are important pieces of the legislation for European companies that import or manufacture essential oils used in cosmetics. Thanks to the consortiums for essential oils the efforts for testing, preparing the registration dossiers and CSAs can be shared between companies but it still remains quite high especially for SME.

Since the European legislation for cosmetic ingredient is meager, the industry regulates itself. The industry associations (*e.g.* IFRA) and manufacturers of cosmetics themselves develop their own standards and requirements for the suppliers of ingredients including essential oils. Thus, the number of documents and their content that must be provided by

essential oil supplier is not less than for active substance for pharmaceutical use and for feed additives. But in contrast to pharmaceutical and feed industries the documentations are not harmonized. The standard documentations for essential oil as cosmetic ingredient include:

- Safety Data Sheet
- Specification
- Certificate of Analysis
- Allergen declaration
- IFRA certificate
- Certificate of Conformity
- Information on traceability of supply chain
- Compliance of packaging materials (drums) with UN standards
- Quality management system (GACP, HACCP, ISO 9001, EFfCI GMP)
- CITES (Convention on International Trade in Endangered Species) declaration
- Declaration on irradiation; BSE/TSE, gluten, GMO, heavy metals, nanoparticles, microplastic, etc.

The niche sectors of cosmetics require some special documentation such as organic, natural, fair trade, halal, kosher, and vegan certification (113).

To demonstrate the difference between regulatory requirements for quality of an essential oil as active substance and as a feed additive, the specification for “Expressed orange essential oil” authorized as feed additives in animal nutrition (additive category ‘sensory additives’ and to the functional group ‘flavouring compounds’) (114) was compared with specification based on Ph. Eur. 04/2022:1811 for “Sweet orange oil” and general monograph Ph. Eur. 04/2022:2098 for “Essential oils” (Table 6). The chromatographic profiles of both products are almost the same; the limits (except Limonene) in Ph. Eur. are set a little narrower. The specification for “Expressed orange essential oil” are based on ISO standard 3140:2019 (essential oil of sweet orange expressed (C. sinensis (L.)) and include the concentrations of the main volatile components of the essential oil which are responsible for about 97.0–97.8 % of the % GC area (115). In contrast, Ph. Eur. chromatographic profile includes trace components like β-pinene, neral, geranial, valencene as well. In all batches of the expressed orange essential

oil under assessment EFSA detected low concentrations of perillaldehyde, a substance for which EFSA identified a concern for genotoxicity (115), which was confirmed by JECFA (116). From this reason and based on the calculation of permissible concentration the parameter Perillaldehyde: < 0.05 % was added to the specification.

Although such physical characteristics like relative density, refractive index, optical rotation, residue on evaporation and such impurities like heavy metals, aflatoxins, pesticides, and microbial contamination were tested und discussed in EFSA scientific opinion for expressed orange essential oil, these parameters were not included in the final characterisation of feed additive. The European pharmacopeia, on the contrary, requires these tests but where it justified and authorized the parameters impurities and microbial contamination could be neglected.

The specifications for essential oils for cosmetic products are developed usually based on the customer requirements and determined primarily by the application. There is not any official reference source like the Ph. Eur. monographs for active substances or Commission Implementing Regulation for feed additive. The typical specification includes the physical characteristics such as relative density, refractive index, optical rotation, and the gas chromatographic profile. In case the essential oil used for fragrance the odour became critical parameter in the specification, while the Ph. Eur. considers the characters such as colour and odour only as optional part of the oil characterisation and they can be not included in the specification. The limits for the constituents are set depending on the application, *e.g.* the content of cineole can be narrowed for a milder aroma or the content such compounds as estragole, camphor, eucalyptol, and menthol should be reduced due the safety reason and defined by the categories of cosmetic products (rinse-off or leave-on). Including of the impurities like heavy metals, aflatoxins and pesticides in the specification is decided based on risk analysis and economic reasons. Consequently, the requirements for essential oils used in lip stick are higher as for essential oil used for foot bath.

Table 6 Comparison requirements on quality of for "Expressed orange essential oil" authorized as feed additives in animal nutrition (2b143-eo) and "Sweet orange oil" as active substance (Ph. Eur. 04/2022:1811)

Name	**Expressed orange essential oil**	**Sweet orange oil**
Reference	**2b143-eo**	**Ph. Eur. 04/2022:1811**
Definition	Essential oil derived by cold expression from fruit peel of *Citrus sinensis* (L.) Osbeck as defined by the Council of Europe.	Essential oil obtained without heating, by suitable mechanical treatment from the fresh peel of the fruit of *Citrus × sinensis* (L.) Osbeck. A suitable antioxidant may be added.
Appearance	Liquid form	Clear, pale yellow or orange, mobile liquid, which may become cloudy when chilled
Relative density	/	0.842 to 0.850 (Ph. Eur. 2.2.5)
Refractive index	/	1.470 to 1.476 (Ph. Eur. 2.2.6)
Optical rotation	/	+ 9.4 ° to + 9.9 ° (Ph. Eur. 2.2.7)
Peroxide value	/	maximum 20 (Ph. Eur. 2.5.5, Method B)
Bergapten	/	Absence (Ph. Eur. 1811 (TLC))
Fatty oils and resinified essential oils	/	Corresponds (Ph. Eur. 2.8.7)
Residue on evaporation	/	1.0–5.0 % (Ph. Eur. 1811)
Chromatographic profile	Gas chromatography coupled with flame ionisation detection (GC-FID) (based on ISO 3140)	Gas chromatography (Ph. Eur.2.2.28)
	d-Limonene: 93–97 %	Limonene: 92.0–97.0 %
	Myrcene: 1.5–3.5 %	β-Myrcene: 1.522.5 %
	Sabinene: 0.1–1.0 %	Sabinene: 0.2–1.1 %
	α-Pinene: 0.4–0.8 %	α-Pinene: 0.4-–0.6 %
	Linalool: 0.1–0.7 %	Linalool: 0.2–0.7 %
	Decanal: 0.1–0.7 %	Decanal: 0.1–0.4 %
	Octanal: 0.1–0.6 %	Octanal: 0.1–0.4 %
	Perillaldehyde: < 0.05 %	/
	/	β-Pinene: 0.02–0.3 %
	/	Neral: 0.02–0.10 %
	/	Geranial: 0.03–0.20 %
	/	Valencene: 0.02–0.5 %
Microbiology	/	Ph. Eur. 5.1.4 or 5.1.8 *
Heavy Metals	/	Ph. Eur. 2098 *: Pb: max. 5.0 mg/kg (Ph. Eur. 2.4.27) Cd: max. 1.0 mg/kg (Ph. Eur. 2.4.27) Hg: max. 0.1 mg/kg (Ph. Eur. 2.4.27)
Pesticides	/	Ph. Eur. 2.8.13 *
Aflatoxin	/	Ph. Eur. 2.8.18 *

* Where justified and authorized, individual testing of every batch may not be necessary (Ph. Eur. 04/2022:2098)

Not only specifications differ depending on the essential oil application (pharma, feed, cosmetic) but also the regulatory requirements for labelling are not harmonized between industries. The essential oils for pharmaceutical use are labelled according to the Ph. Eur. or other Pharmacopoeia, if applicable, for cosmetic product the INCI Name must be used and for feed additives the labelling should be in compliance with the authorisation.

2b143-eo Expressed orange essential oil

Ph. Eur Sweet orange oil

INCI Name Citrus Sinensis Peel Oil Expressed

Regardless of product type the essential oil suppliers and manufacturers are dealing with diverse European legislations and are obligated to prepare special documentation. This is the most significant challenge for essential oil suppliers, which are usually small and intermediate entrepreneurs, to be familiar with all these regulations. How it was mentioned before, many essential oils are manufactured outside European Union in the third-party countries (China, India, Vietnam, Russia etc.) it causes additional difficulties connected with the language (communication through intermediaries, non-English original documentation), legislation different from European (other standards for water, analytical methods).

The paradox is that the same single essential oil cannot be supplied to different sectors (pharma, cosmetic or feed) because it is subject of the completely different legal standards which are spread on all supply chain. Depend on economic reason and specialisation of manufacturers of first steps (plant material, crude oil) the single supply chain can be qualified only for specific type of product and is not possible to provide the essential oil of cosmetic or feed quality for pharmaceutical use, because the requirements for active substance are much higher. But the essential oils of pharma quality cannot be used for cosmetic and feed products as well because of specificity of documentation.

4. Conclusion

Due to their aromatic smell and specific pharmacological impact, the essential oils are used in the wide range of products: as feed additives, as active substances and excipients in medical products, and as fragrance and active substances in cosmetic products. This opens great economic opportunities for essential oils manufacturers and suppliers to sell their products to the customers from diverse industries. On the other site, essential oils become subject of diverse legislations with strong and complex requirements. In this study the European regulatory requirements for cosmetic ingredients, active substance and excipients for pharmaceutical use and feed additives have been reviewed in detail with the focus on essential oils.

According to the Directive 2001/83/EC the data on the quality of active substance is the integrated part of the marketing authorisation dossier for medical products. The essential oil manufacturers should provide data regarding the characteristics, manufacturing, testing and stability of their product according to the European legislation. Although there are various EMA (HMPC) Guidelines on herbal preparations the requirements, which were developed mostly for extracts, are not fully addressed to essential oils. The complex nature of essential oils, the production features (*e.g.* traditional steam distillation on the field, small batches sizes of crude oil, manufacturing often outside of Europe), many suppliers of plant material and crude oil with limited botanical/scientific education and experience in the manufacturing of active substance lead to the deviation from the Guidelines and intensive discussions between authorities and applicants.

The European Union strictly regulates the feed additives as well. The essential oils used as feed additive must be authorized according to the Regulation (EC) No 1831/2003 before the placing on the European market. In most cases essential oils are authorized under the Category “2” (Sensory Additives) and Functional Group “b” (flavouring compounds). This type belongs to non-holder-specific authorisations and once granted it could be used by every essential oil manufacturer if its product complies with the conditions laid down in corresponding Commission Implementing Regulation.

Compared to the active substances for pharmaceutical use and feed additives the cosmetic ingredients are not so detailed regulated in EU. Cosmetics Regulation (EC) No.

1223/2009 is aimed only indirectly to the suppliers or manufacturers of the substances used as a cosmetic ingredient. From this reason the cosmetic industry developed mechanisms for self-regulations, *e.g.* through standards created by industry associations (IFSA Standards), private certification (ISO 9001, EFfCI GMP etc.) or own requitements of single cosmetic company. Moreover, the market players obliged to carry out the comprehensive requirements of REACH and CLP for essential oils manufactured or imported in EU and EEA while the essential oils as ingredients for medicals and feed are out of scope of these regulations. This results in a significant amount of documentation that must be provided by essential oil suppliers for cosmetic sector, similar to that required for active substances in pharmaceuticals and feed additives. However, unlike pharmaceutical and feed industries, these documentations are not harmonized.

Although the fundamental principles like the high requirements for the quality of essential oils, quality control, manufacturing standards, supply chain traceability are similar for all industries discussed in this work the mechanisms and documentation reflecting these differ depending on the scope of essential oil application. As result, the essential oil suppliers, which are usually small and intermediate entrepreneurs, should be familiar with diverse European regulations and the final product should be consider as a combination from the essential oil itself and the appropriate documentation which play a critical role that the supplier is competitive on the market.

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Anexes 1

Template for a risk assessment of essential oils. The colour in the first column indicates the allocation to GACP (white, Atypical Actives GMP (light blue) or GMP Part II (blue), respectively. Reproduced from Hebbert et al.(110)

Process Step	Potential Risk/ failure	Potential Consequence	Case distinction	Current Activities / control	Probabi-lity of occur-rence	Seve-rity	Detec-tability	Risk Priority Num-ber	If necessary additional action to further reduce the risk
Collection/ Harvest	Wrong herbal substance (100 % wrong species)	Wrong essential oil	A Cultivation						Training of farmers or collectors, quality control of the identity of the oil according to monograph or specification (see quality control of raw material)
			A1 No other types[1] present in the region of collection	Visual control					
			A2 other types present	Visual control					
			B Wild/Semi-wild collection						
			B1 No other types[1] present in the region of collection	Visual control					
			B2 Other types present	Visual control					
	Foreign matter (partly other species or wrong parts of plant)	Impure essential oil	A Cultivation						Training of collectors, quality control of the identity of the oil according to monograph or specification (see quality control of raw material)
			A1 No other types[1] present in the region of collection	Visual control					
			A2 other types present	Visual control					
			B Wild/Semi-wild collection						
			B1 No other types[1] present in the region of collection	Visual control					
			B2 Other types present	Visual control					
	Pesticides	Contaminated	A Cultivation						Quality control of the

Process Step	Potential Risk/ failure	Potential Consequence	Case distinction	Current Activities / control	Probabi-lity of occur-rence	Seve-rity	Detec-tability	Risk Priority Num-ber	If necessary additional action to further reduce the risk
		essential oil	A1 No steam distillation (e.g. pressing)						purity of the oil according to Ph.Eur.[2]
			A2 Steam distillation or checks of the raw material[3]						
			B Wild/Semi-wild collection						
			B1 No steam distillation (e.g. pressing)						
			B2 Steam distillation or checks of the raw material[3]						
	Heavy metals	Contaminated essential oil	A Cultivation						Quality control of the purity of the oil according to Ph.Eur.[4]
			A1 No steam distillation (e.g. pressing)						
			A2 Steam distillation or checks of the raw material[3]						
			B Wild/Semi-wild collection						
			B1 No steam distillation (e.g. pressing)						
			B2 Steam distillation or checks of the raw material3						
	Mycotoxins	Contaminated essential oil	A Cultivation						Quality control of the purity of the oil according to Ph.Eur.[4]
			A1 No steam distillation (e.g. pressing)						
			A2 Steam distillation						

Process Step	Potential Risk/ failure	Potential Consequence	Case distinction	Current Activities / control	Probability of occurrence	Severity	Detectability	Risk Priority Number	If necessary additional action to further reduce the risk
			or checks of the raw material[3]						
			B Wild/Semi-wild collection						
			B1 No steam distillation (e.g. pressing)						
			B2 Steam distillation or checks of the raw material[3]						
	Microorganisms / Moulds & yeasts	Contaminated essential oil	A Steam distillation, Oil has antibacterial properties[3]	No risk					
			B No Steam distillation, Oil has antibacterial properties[5]	No risk					
	Physical Impurities (dirt and dust, metal pieces) in the plant material	Impure essential oil	A Steam distillation, non-volatile compounds	No risk					
			B No Steam distillation (e.g. pressing), sufficient filtration step	No risk					
	Degradation products plant material	Impure essential oil		Immediate further processing reduces risk (visual control)					Quality control of the purity of the oil according to monograph or specification (see quality control of raw material)
Field distillation and/or other distillation in country of origin or other procedures (e.g. pressing)	No suitably cleaned equipment	Impure essential oil (cross contamination, oxidized product)	A Not dedicated	Cleaning instruction, visual control					Quality control according to monograph or specification (see quality control of raw material), second purification step (rectification)
			B Dedicated	Cleaning instruction, visual control					

Process Step	Potential Risk/ failure	Potential Consequence	Case distinction	Current Activities / control	Probability of occurrence	Severity	Detectability	Risk Priority Number	If necessary additional action to further reduce the risk
	Unsuitable material grade of equipment, processing aids (e.g. filter material, lubricants)	Impure essential oil (heavy metals, oxides)							Quality control according to monograph resp. specification (see quality control of raw material)
	Water quality	Contaminated essential oil	Local water quality, steam distillation	Local quality control; no microbial risk					
	Wrong distillation conditions, if applicable	Wrong composition of distillate, burnt oil (degradation)		Local quality control					Quality control of the smell and purity of the oil according to Ph. Eur. [6] (very high or low volatile terpenes missing)
Storage	Cross-contaminated primary storage containers	Impure essential oil	A Not dedicated	Supplier qualification					Suitable cleaning procedure, quality control of the smell and purity of the oil according to Ph. Eur.[6]
			B Dedicated	Supplier qualification					
	Unsuitable inner coating of containers	Impure essential oil	A No qualified material						
			B Qualified material						
	Temperature, Moisture[8]	Loss of compounds, degradation products, crystallisation	A No stability data available						
			B Stability data available	No risk					
Transport and primary transport packaging	Cross-contaminated primary packaging containers	Impure essential oil	A re-used material	Supplier qualification					Suitable cleaning procedure, quality control of the smell and purity of the oil according to Ph. Eur.[6]
			B New material	Supplier qualification					
Transport and transport packaging	Temperature, moisture[8]	Loss of compounds, degradation products, crystallisation	A No stability data available[7]						
			B Stability data available[7]	No risk					
	Unsuitable inner coating of containers	Impure product	A No suitable material						

Process Step	Potential Risk/ failure	Potential Consequence	Case distinction	Current Activities / control	Probability of occurrence	Severity	Detectability	Risk Priority Number	If necessary additional action to further reduce the risk
			B Suitable material	No risk					
	Damage of containers	Essential oil impured by coating material	A Severe damage						
			B No severe damage						
Goods receipt	Contamination during sampling	Contaminated essential oil	A Non GMP area, untrained staff						
			B GMP area, trained staff						
Quality control crude oil	Unsuitable test methods	Wrong positive or negative results	A Non GMP laboratory, unqualified equipment, methods not validated						
			B GMP laboratory, qualified equipment, methods validated or Pharmacopoeia methods	No risk					
Final treatment: Blending	Addition of a essential oil not conform to monograph	Non-conform essential oil	A Non GMP production						
			B GMP production	No risk, documentation					
Final treatment: Batching	Addition of a wrong essential oil	Non-conform essential oil	A Non GMP production						
			B GMP production	No risk, documentation					
Final treatment: Rectification	Wrong process procedures or conditions (temperature, vacuum), Water	Wrong composition of product, burnt oil (degradation), contaminated oil	A Non GMP production						Rectification is a decisive production step

Process Step	Potential Risk/ failure	Potential Consequence	Case distinction	Current Activities / control	Probability of occurrence	Severity	Detectability	Risk Priority Number	If necessary additional action to further reduce the risk
	quality bad		B GMP production	No risk, qualification of process					
	No suitable cleaning equipment	Impure essential oil	A Non GMP production						
			B GMP production	No risk, qualification of process					
	Unsuitable material grade of equipment	Impure essential oil (heavy metals, oxides)	A Non GMP production						
			B GMP production	No risk, qualification of process					
Quality control final product	Unsuitable test methods	Wrong positive or wrong negative results	A Non GMP laboratory, unqualified equipment, methods not validated						
			B GMP laboratory, qualified equipment, methods validated or Pharmacopoeia methods	No risk, qualification of process					
Final Packaging	Cross-contaminated primary packaging containers	Impure essential oil	A Re-used material	Supplier qualification					Suitable cleaning procedure, validated
			B New material	Supplier qualification					
Transport	Temperature, moisture[8]	Loss of compounds, degradation products, crystallisation	A No stability data available						
			B Stability data available	No risk					

Criterion	Classification	Characteristics/Description	Multiplication factor
Probability of occurrence (P)	unlikely	$< 10^{-6}$	1
	remotely imaginable	$< 10^{-5}$ to $\geq 10^{-6}$	2
	occasionally	$< 10^{-4}$ to $\geq 10^{-5}$	3
	likely	$< 10^{-3}$ to $\geq 10^{-4}$	4
	often	$\geq 10^{-3}$	5
Severity (S)	insignificant	Discomfort; intermittent slight disorders	1
	small	Reversible damage or no medical aid/competent medical intervention required or reversible product malfunction	2
	serious	Leads to damage or disability which requires competent medical intervention	3
	critical	Reversible damage or medical aid/competent medical intervention required or permanent particular malfunction	4
	catastrophically	Serious irreversible damage up to death, massive damage of product; serious damage to environment	5
Detectability (D)	often	Share of undetected failure ≤ 1%	1
	likely	Share of undetected failure > 1%	2
	occasionally	Share of undetected failure > 10%	3
	remotely imaginable	Share of undetected failure > 20%	4
	unlikely	Share of undetected failure > 80%	5

The *Risk Priority Number* (RPN) is determined by multiplication of the multiplication factors of P, S and D which are the results of the corresponding risk assessment procedure: RPN = multiplication factor of P x multiplication factor of S x multiplication factor of D. The classification and the related multiplication factors as described is yielding a RPN between 1 and 125.

[1] Other species than mentioned in the monograph.

[2] See Ph. Eur. 2.8.13. If use of pesticides is known, test plan can be reduced.

[3] Steam distillation and checks of the raw material further enhance safety.

[4] See Ph. Eur. “Herbal Drugs”.

[5] Antibacterial properties.

[6] Individual Ph. Eur. Monograph on the essential oil (or other, if not available).

[7] Stability data is generated with the finished API and complies with the respective Note for Guidance (Guideline on Stability Testing: Stability Testing of Existing Active Substances).

[8] Moisture not relevant for essential oils.

Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Hamburg, 07.11.2023

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Unterschrift der Studierenden