

Herbal Medicinal Products

Is your product a Herbal Medicine?



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Is the product a Herbal Medicine?

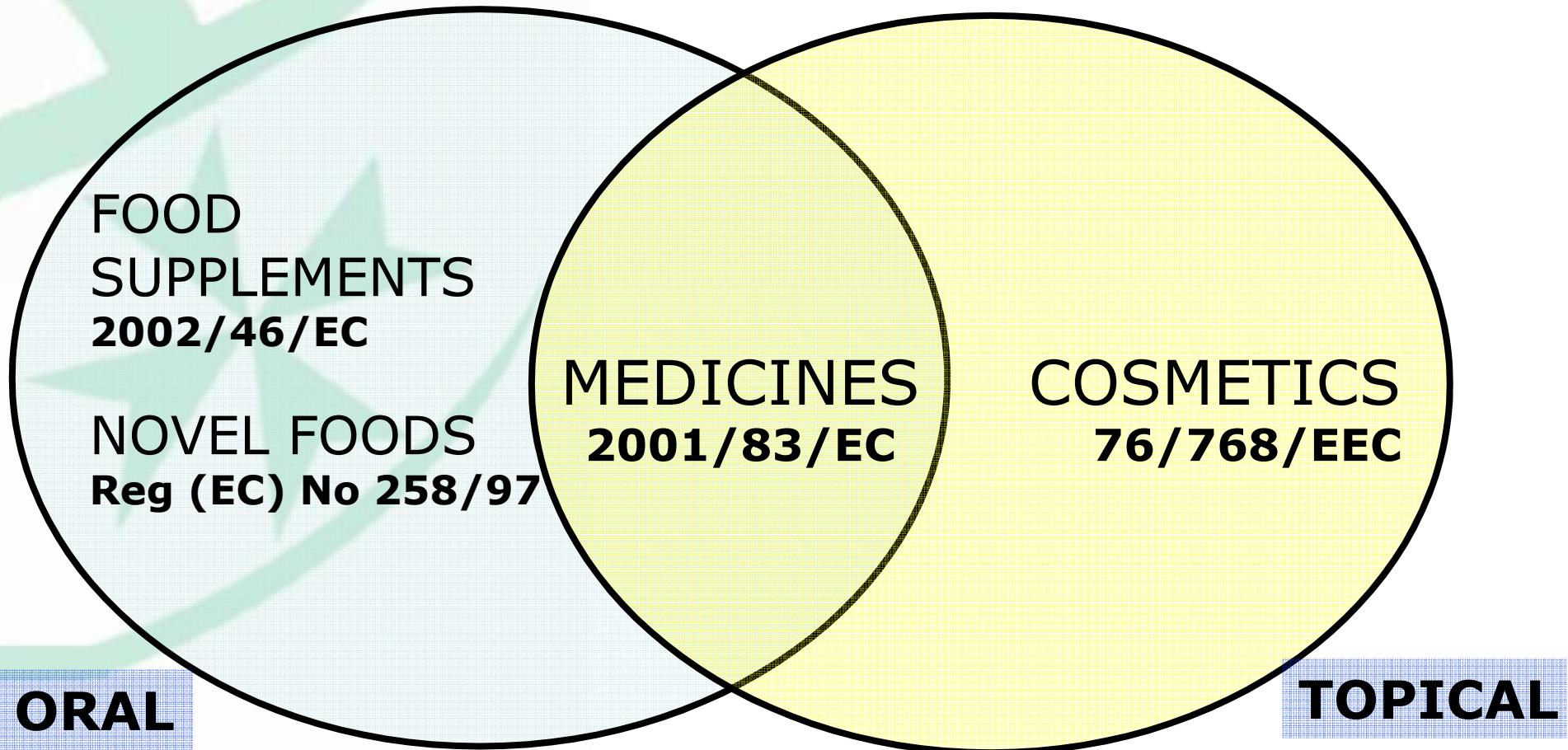


Herbals are products that may be used for human consumption as:

- Food Supplements/Novel Foods
- Medicines
- Cosmetics







European Union Legislation



- Within the European Union (EU) all herbal substances for **oral consumption** come under the control of either food legislation or medicines legislation.
- Herbal substances for **topical application** can fall into either cosmetics legislation or medicines legislation.

Food Supplements - Definition



- 'Food supplements' means foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect...
- 'Nutrients' means the following substances:
 - (i) vitamins,
 - (ii) minerals.

Food Supplements - Definition



These do not include:

- Animal feed; Live animals unless they are prepared for placing on the market for human consumption;
- Plants prior to harvesting;
- Medicinal products, Cosmetics, Tobacco and tobacco products, Narcotic or psychotropic substances, Residues and contaminants

Definition of a Medicine



The legal definition of a medicine is:

1. Any substance or combination of substances presented as having properties for **treating or preventing disease** in human beings.

Definition of a Medicine



The legal definition of a medicine is:

2. Any substance or combination of substances which may be used in or administered to human beings either with a view of **restoring, correcting or modifying physiological, immunological or metabolic action**, or in making a medical diagnosis

Definition of a Cosmetic



- A 'cosmetic product' shall mean any substance or preparation intended to be placed in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view **exclusively or mainly** to cleaning them, perfuming them, changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition.

Food, Cosmetic or Medicine?



- The borderline between food and medicine is complex.
- Many, if not most, botanical extracts and isolates are close to the borderline.

Food, Cosmetic or Medicine?



- **Physiological Effect** - The support and maintenance of normal bodily functions.

Food Supplement/Novel Food/Cosmetic

- **Pharmacological Effect** - The modification of normal bodily functions and/or the prevention, treatment or cure of a disease or condition.

Medicine

Food, Cosmetic or Medicine?



- **Medicine** – A herbal substance or preparation with no food or cosmetic use; e.g. St. John's Wort, Valerian, etc...
- **Food or Cosmetic** – 'Traditional' use as a food or cosmetic. New food/cosmetic uses should be justified. Examples include basil, fennel, garlic, etc...

Borage (*Borago officinalis*)



FOOD SUPPLEMENT

Seeds/
Borage oil



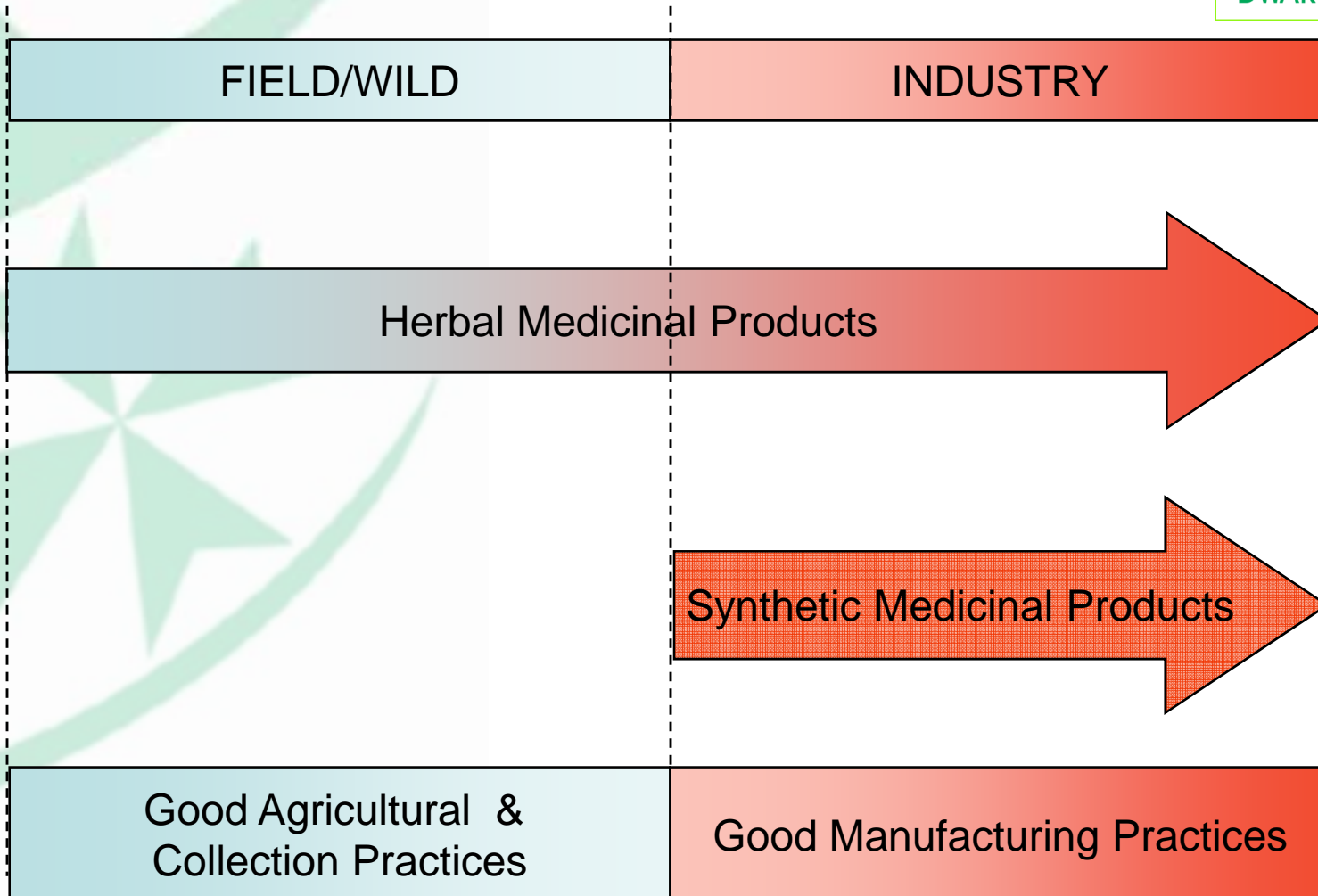
MEDICINE

Other Plant
Parts

Medicines



Synthetics vs Herbal Medicinal



Herbals only List



- Approx. 417 prep.
- Require registration as WEU or THMP

Plants and herbal substances that are exclusively used as herbal medicines i.e. they have no food use and may not be added to food supplements

Latin Name	Synonyms	Common Names	Plant Part
<i>Abies canadensis</i> Michaux.	<i>Pinus canadensis</i> Linné, <i>Picea canadensis</i> Link, <i>Tsuga canadensis</i> Carrière	Hemlock spruce, <i>Tsuga</i> , <i>Pinus</i> bark	bark
<i>Abies spectabilis</i> (D.Don.) Spach.	<i>Abies webbiana</i> Lindl., <i>Pinus spectabilis</i> D.Don.	Himalayan silver fir	leaves
<i>Abrus precatorius</i> L.	<i>Glycine abrus</i> L., <i>Abrus abrus</i> (L.) W. Wight	Indian liquorice	seeds
<i>Acanthopanax senticosus</i> (Rupr. & Maxim.) Harms	<i>Eleutherococcus senticosus</i> (Rupr. & Maxim.) Maxim, <i>Hedera senticosa</i> Rupr. &	Kan jang, devil's root, touch-me-not, Siberian ginseng (it is not a type of ginseng)	
<i>Acokanthera ouabaio</i> Cath.	<i>Acokanthera schimperi</i> (A.DC.) Schweinf	South African arrow poison, Ouabai, Wabai	wood, seeds
<i>Acokanthera schimperi</i> Benth	<i>Acokanthera abyssinica</i> K.Schum., <i>Acokanthera</i>		

[http://medicinesauthority.gov.mt/pub/Plants used as Herbal Medicines.pdf](http://medicinesauthority.gov.mt/pub/Plants%20used%20as%20Herbal%20Medicines.pdf)



What type of medicine is your herbal (medicinal) product (HMP)?



- Herbal Medicines: ~~Green-Natural-Safe~~
- **NOT ALL HERBAL OR NATURAL MEDICINES ARE SAFE**



What type of herbal medicine?

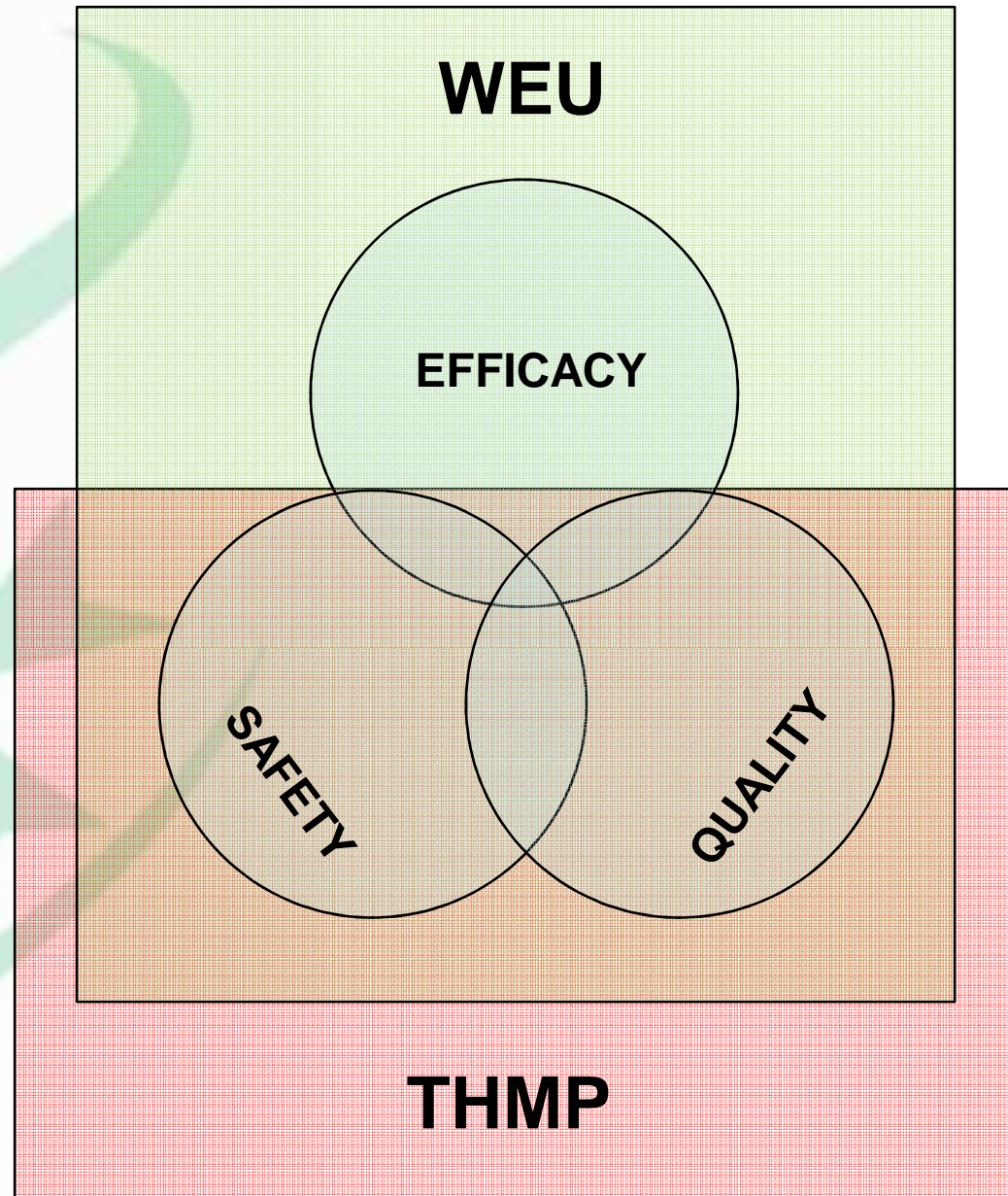


- Herbal medicines with a long-history of medicinal usage particularly within the EC, the so-called **Traditional Herbal Medicinal Products** (THMPs), and
- Herbal medicines which have been tested clinically and showed clinical efficacy, the so-called Herbal Medicines with a **Well-Established medicinal Use** (WEU).

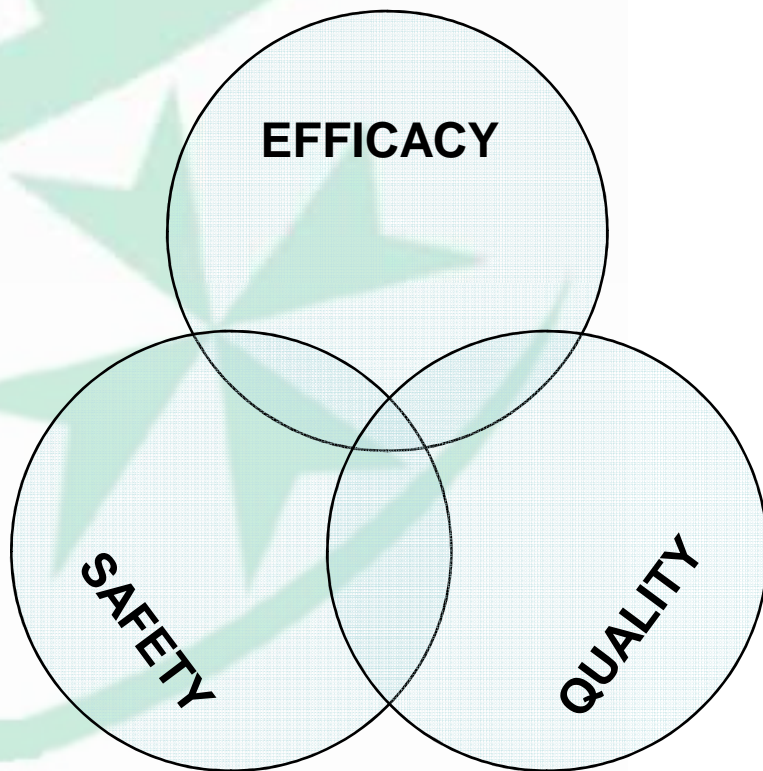
Herbal with TU or WEU?



	THMPs	Herbals with WEU
Discovery of product	Long History of Usage (30 years)	Discovered recently or use proven recently (10 years)
Proof of Efficacy	No proof. Bibliographic traditional information.	Proof of efficacy by bibliographic clinical data
Proof of Safety	<i>In vitro</i> testing for genotoxicity and support by bibliographic data	<i>In vitro</i> and <i>in vivo</i> testing of product
Proof of Quality	Processed under pharmaceutical manufacturing procedures or as stated by an official European or Community Monograph	Processed under pharmaceutical manufacturing procedures. Reference to a Community Monograph can be made
Registration	Simplified Registration (registered HMPs)	WEU Marketing Authorisation (licensed HMPs)
Regulated by Council Directive	2004/24/EC	2001/83/EC



2001/83/EC Obligations



To ensure that the HMP is:

- **Safe** to the consumer
- **Effective** (no fraudulent claims)
- High **quality** with a 'safe and effective' chemical profile

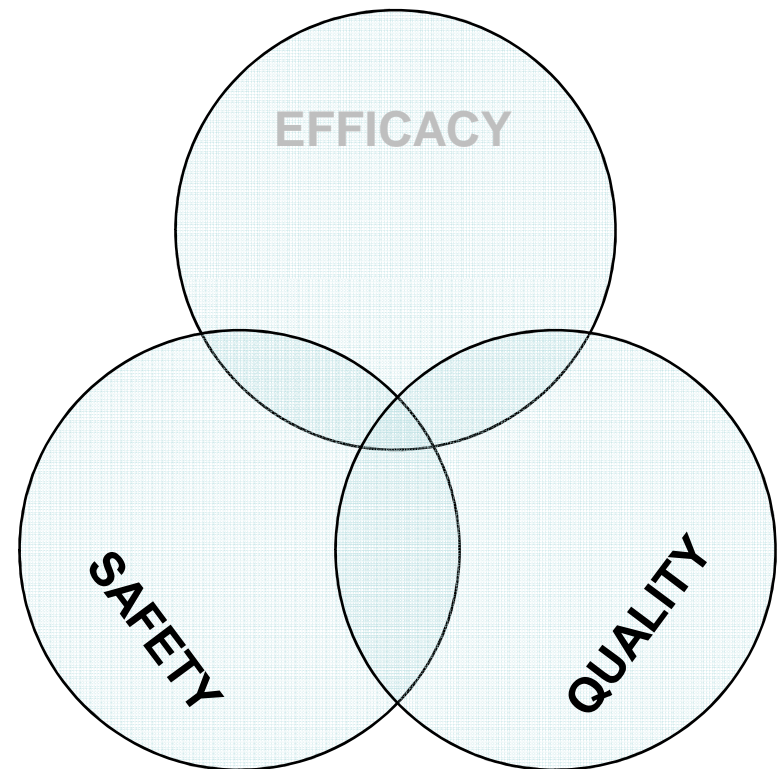
Problem with HMPs



- These three requirements cannot be fulfilled by all herbal medicinal products
- Not all HMPs can be proved to be effective
- However all HMPs should show 'adequate' safety and quality

DIRECTIVE 2004/24/EC

- amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use



Proof of efficacy for HMP?



YES - WEU

- If the product efficacy has been proven scientifically, the HMP is probably a herbal with a WEU.
- Scientific proof should be well founded with appropriate *in vitro* and *in vivo* **clinical trials**, and with the relevant
- **statistical backing.**

Proof of efficacy for HMP?



NO - TMHP

- If no scientific efficacy is proven, the product may be a THMP. However, to qualify under this category the medicinal product should have been used for more than **30 years, with at least 15 years** within the European Union. If this is fulfilled the product may proceed along the THMP line,
- **Bibliographic references** are mandatory

Routes of administration



THMP

- Administered **orally, topically or by inhalation**.
- THMPs are intended to control or treat minor medical conditions that may be presented as **over-the-counter** (OTC) products for **self treatment**
- *E.g. Melilotus officinalis (L.) Lam., herba (melilot)* - relieve symptoms of discomfort and heaviness of legs

Routes of administration



WEU

- Administered through **ANY** route of administration (incl. suppositories, injections, pessaries, etc.)
- Herbals with WEU require **medical supervision** and are usually intended to control or treat (sometimes) more serious medical conditions.
- E.g. *Menthae piperitae aetheroleum* (Cutaneous use) for the symptomatic relief of mild tension type headache.

Doses and dosage regimens



- In spite of their medical intent, herbal medicinal products should contain specific herbal preparations or herbal substances with a **specific dose range** and **frequency of administration**.
- This is mandatory as a guide to the general public and healthcare professionals such as physicians and pharmacists

Doses and Content



- Included within the package leaflet (PL) and HMP packaging
- The extracts are adjusted according to a valuable reference substance. These substances:
 - Active markers
 - Analytical markers.



Extracts

- **Standardised extracts - active markers,** i.e. compounds that exhibit the pharmacological activity stated,
- E.g. Extracts prepared from *Aesculus hippocastani semen* are standardised to contain a defined content between 16% and 28% triterpene glycosides, calculated as aescin.



Extracts

- **Quantified extracts - analytical markers**, i.e. compounds that indicate the strong presence of a class of compounds but do not necessarily contribute to the pharmacological activity.
- E.g. Willow bark, cut (Ph.Eur.).
quantified on 1.5 - 1.7 % of total salicylic derivatives calculated as salicin



Other extracts

- There are other HMPs that cannot be standardised or quantified, and in most cases, such extracts are not granted registration or marketing authorisation.
- Potentially **UNSAFE PRODUCTS**

Additional active constituents



- No additional active constituents - product is likely to be classified either as a THMP or a herbal with a WEU.
- Additional constituents:
 - vitamins and minerals.
 - other constituents.

Additional active constituents



- Vitamins and Minerals
 - If these do not have a pharmacological role, vitamins and minerals may be omitted from the herbal medicinal product.
 - The quantities should be according to or less than the daily maximum requirements*, depending on the frequency of daily administration.

*<http://www.doi.gov.mt/EN/legalnotices/2003/09/LN239.pdf>

Additional active constituents



- Constituents other than vitamins and minerals
 - the product may be either **modified** to eliminate these constituents, particularly if the constituents are toxic, or else
 - considered as **a herbal combination product**. Combination products that are not supported by a traditional use may only be considered as herbals with WEU as long as there is proof of clinical efficacy data.

Combinations



- In the same formulation, you may have the **presence of non-herbal substances**, such as animal products (e.g. glucosamine, cod liver oil, shark cartilage, honey, propolis, etc.), mineral products (which usually fall under vitamins and minerals), and also the presence of synthetic drugs.
- Suppose the Herbal is **Devil's Claw**

Combinations Products



- Devil's Claw (root) may be considered to be a **THMP** for mild joint pain (amongst other uses)
- Devil's Claw with glucosamine - **THMP**, requiring combination safety
- Devil's Claw with aspirin - **WEU**, requiring combination efficacy & safety

HMP Safety



- The primary aim of the European Union, with the registration of medicinal products, is the **protection of the European citizens** from fraudulent and unsafe products.
- Although a THMP has been in circulation for centuries, it is possible that with time, research proves the presence of toxic substances within the product.
- E.g. Phellandrene in fennel seeds/oil



Toxic substances:

- Intrinsic
 - Defence substances - E.g. Phellandrene in fennel seeds/oil
- Extrinsic
 - Unintentional additions – pesticides, heavy metals, mycotoxins
 - Deliberate additions – heavy metals, synthetic drugs

- **In case, where the additional constituent or chemical entity is not declared and/or justified, the product will be **illegal**, i.e. an adulterant with potential health risks.**
- This was the case with several slimming treatments which contained undeclared ephedrine in the capsule/tablet/sachet.

HMP Safety



In some cases, the THMP is either:

- **withdrawn** from the market, if it is already established within the Community, or
- **not allowed** to reach the market, if it is a new product, or
- **modified** to meet the required safety standards, i.e. a 'minus variant'

HMPC monographs (1)



- Committee on Herbal Medicinal Products (HMPC)
- Preparation of herbal monographs to facilitate the registration/licensing of HMPs.
- Focus primarily on efficacy/historical bibliography

HMPC monographs (2)



- Committee on Herbal Medicinal Products (HMPC)
- Distinguish between WEU and THMP
- Monographs may be used as references to understand better the physicochemical and pharmacological properties of the drug.

European Pharmacopoeia



- The European Directorate for the Quality of Medicines & HealthCare (EDQM)
- Preparation of herbal monographs to facilitate the registration/licensing of HMPs.
- Focus primarily on quality of herbals

Summary- Checklist



- Herbal Product: Food, Medicine or Cosmetic
- Herbal Medicine: THMP or herbal with a WEU
- Criteria applying for THMP and WEU
- Different registration requirements according to 2004/24/EC or 2001/83/EC

References on Website



- Decision Tree:

<http://staff.um.edu.mt/eatt1/THMPs/>

- Compiling a dossier:

[http://medicinesauthority.gov.mt/pub/Registering herbal medicinal products Compiling the dossier.rtf](http://medicinesauthority.gov.mt/pub/Registering%20herbal%20medicinal%20products%20Compiling%20the%20dossier.rtf)

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