Are European Pharmacopoeia Monographs on Extracts a useful basis for the development of Herbal Medicinal Products?

Industrial Viewpoint

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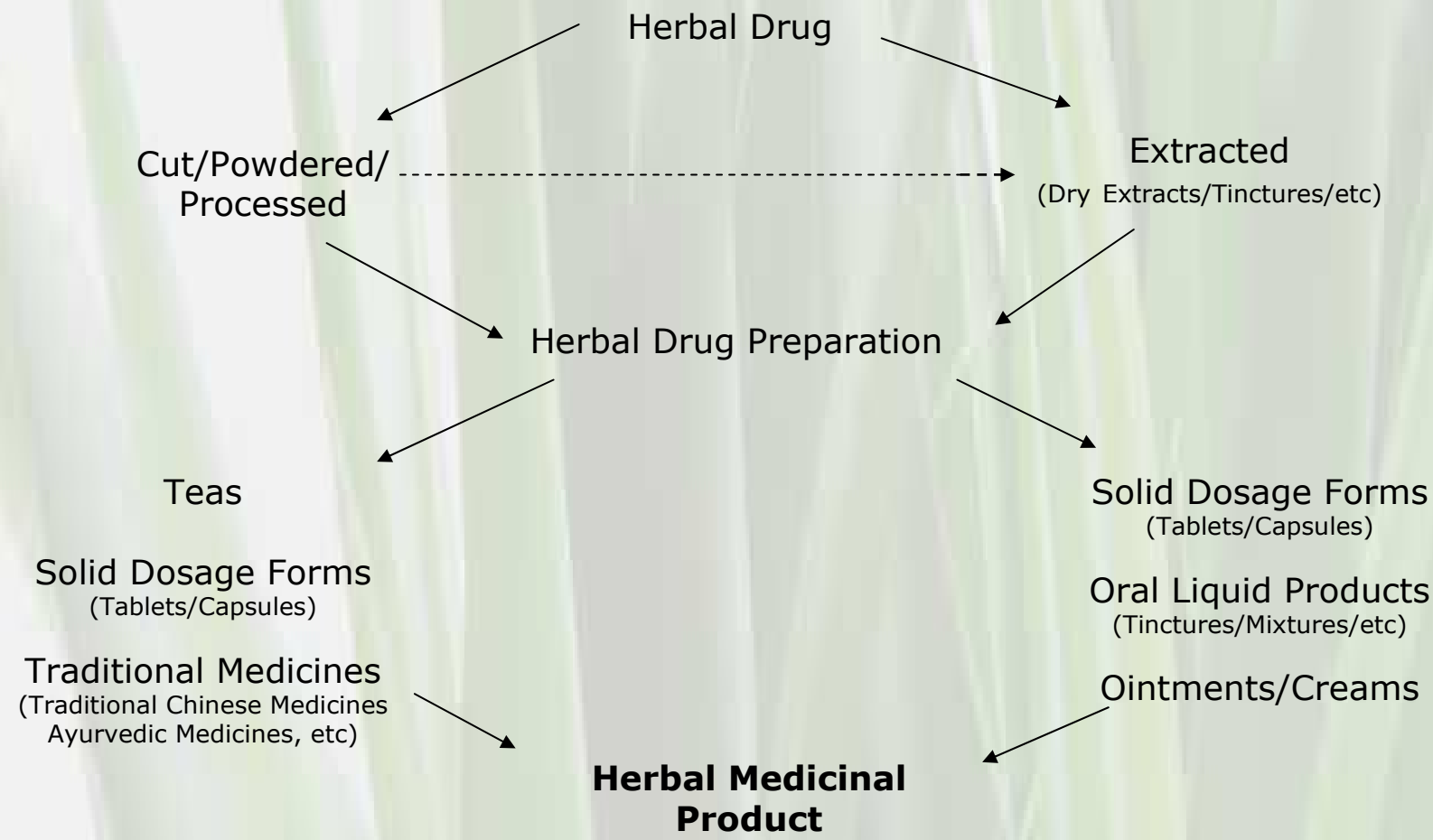
Inter-relationship between Herbal Medicinal Products and their ingredients



'Assay' method for the herbal drugs in the European Pharmacopoeia (up to and including Supplement 6.5)

None	Extractive matter / Swelling Index / Bitterness Value / Colour Intensity	Content of Essential Oil	Titrametric Method	Spectrophotometric Method	Content of Essential oil + spectrophotometry / gc	Gc Method	Lc Method
Limeflower Myrrh Primula root Senega root	Bogbean Centaury Couch Grass rhizome Dandelion herb with root Fenugreek Gentian root Hop strobile Iceland Moss Ispaghula husk Ispaghula seed Linseed Mallow flower Mallow leaf Marshmallow leaf Marshmallow root Mullein flower Psyllium seed Pygeum Africanum bark Red Poppy petal Restharrow root	Angelica root Aniseed Bitter Orange epicarp and mesocarp Caraway fruit Cinnamon Clove Coriander Eucalyptus leaf Ginger Juniper Lavender flower Lovage root Mastic Meadowsweet Peppermint leaf Roman Chamomile flower Sage leaf Three-lobed Sage leaf Wild Thyme Wormwood	Belladonna leaf Benzoin Siam Benzoin Sumatra Fumitory Ipecacuanha root Kelp Peru Balsam Roselle Stramonium leaf Tolu Balsam	Agrimony Alchemilla Aloes Barbados Aloes Cape Ash leaf Bilberry fruit, dried Bilberry fruit, fresh Birch leaf Bistort rhizome Bitter Orange flower Black Horehound Calendula flower Cascara Cinchona bark Digitalis leaf Dog Rose Elderflower Equisteum stem Frangula bark Goldenrod Goldenrod, European Greater Celandine Hamamelis leaf Hawthorn berries Hawthorn leaf & flower Knotgrass Loosestrife Melissa leaf Motherwort Oak bark Passionflower Pelargonium root Rhatany root Rhubarb Ribwort Plantain Rosemary leaf Safflower flower St John's Wort Senna leaf Senna pod, Alexandrian Senna pod, Tinnevelly Sanguisorba root Tormentil Turmeric, Javanese Wild Pansy	Fennel, Bitter Fennel, Sweet Oregano Star Anise Thyme Yarrow	Saw Palmetto fruit	Agnus castus fruit Arnica flower Artichoke leaf Bearberry leaf Boldo leaf Buckwheat herb Butcher's Broom Capsicum Centella Cola Coneflower herb, purple Coneflower root, narrow leaved Coneflower root, pale Coneflower root, purple Devil's Claw root Eleutherococcus Feverfew Frankincense, Indian Ginkgo leaf Ginseng Goldenseal rhizome Ivy leaf Java tea Lemon Verbena leaf Liquorice root Matricaria flower Melilot Milk Thistle fruit Nettle leaf Notoginseng root Olive leaf Opium, Raw Schisandra fruit Valerian root Verbena herb White Horehound Willow Bark

'Assay' method for the Extracts in the European Pharmacopoeia (up to and including Supplement 6.5)

None	Dry Residue/ Bitterness Value / Content of Essential Oil	Titrametric Method	Spectrophotometric Method	Content of Essential oil + spectrophotometry/gc	Gc Method	Lc Method
	Bitter-orange Epicarp and Mesocarp Tincture Matricaria Liquid Extract Myrrh Tincture Sage Tincture	Belladonna Leaf Dry Extract **Standardised** Belladonna Leaf Tincture, **Standardised** Ipecacuanha Liquid Extract **Standardised** Ipecacuanha Tincture **Standardised** Benzoin Tincture Siam Benzoin Tincture Sumatra	Aloes Dry Extract, **Standardised** Cascara Dry Extract, **Standardised** Cinchona Liquid Extract, **Standardised** Senna Leaf Dry Extract, **Standardised** Hawthorn Leaf and Flower Liquid Extract, **Quantified** Hawthorn Leaf and Flower Dry Extract Passion Flower Dry Extract Rhatany Tincture Tormentil Tincture			Bilberry Fruit Dry Extract, Fresh, **Refined** and **Standardised** Capsicum Tincture, **Standardised** Liquorice Ethanolic Liquid Extract, **Standardised** Milk Thistle Dry Extract **Refined** and **Standardised** Opium Dry Extract, **Standardised** Opium Tincture, **Standardised** Capsicum Oleoresin, **Refined** and **Quantified** Ginkgo Dry Extract, **Refined** and **Quantified** St John's Wort Dry Extract, **Quantified** Arnica Tincture Artichoke Leaf Dry Extract Boldo Leaf Dry Extract Devil's Claw Dry Extract Liquorice Dry Extract for Flavouring Purposes Olive Leaf Dry Extract Peppermint Leaf Dry Extract Valerian Dry Aqueous Extract Valerian Dry Hydroalcoholic Extract Valerian Tincture Willow Bark Dry Extract

LIST OF TERMS APPLIED TO EXTRACTS

EU DIRECTIVES

EUROPEAN PHARMACOPOEIA

"QUALITY"

Standardised

Quantified

"Other"

Refined

EMEA HMPC DOCUMENTS

"EFFICACY"

Constituents with known therapeutic activity

Active markers

Analytical Markers

?

Herbal Medicinal Products

Traditional Herbal Medicinal Products

EXTRACT TERMINOLOGY

- Debate has continued unabated since the implementation of these terms into the European Pharmacopoeia in Supplement 4.3 (January 2003).

- Attitudes are changing:

  - Article by Gaedcke, L. *et al* (2008) *Pharmeuropa*, **20**, 51-58

  - Article by Helliwell, K. (2008) *Pharmeuropa*, **20**, 454-455

  - Meeting of HMPC QDG with Chairs and Secretariat of EP Phytochemistry Groups on 7th April 2009 in London.

- Willingness to address various issues.

Extract Terminology: Standardised Extracts

- Traditional Herbal Medicinal products: 30 year rule.
- Standardisation was understood differently prior to 2003.
- Post 2003: Adjustment of "constituents with known therapeutic activity" with excipients to a pre-defined range.
- Pre 2003: Applied to what are now regarded as "active markers" and "analytical markers".
- Change extract and hence traditional herbal medicinal product or accept with *caveats*?

Extract Terminology: Quantified Extracts

- What qualifies as a Quantified Extract and on what basis?

- What qualifies as an "active marker" and on what basis?

Hawthorn Leaf and Flower Liquid Extract, Quantified

(Extraction solvent: 30-70 per cent V/V Ethanol)

[0.8-3.0 per cent flavonoids expressed as hyperoside].

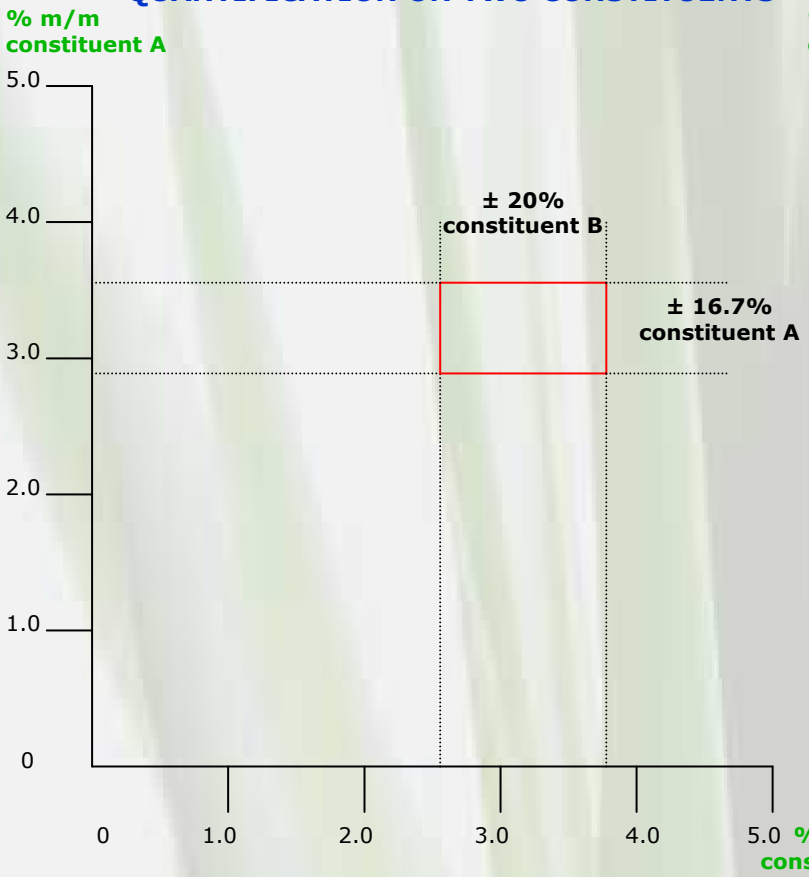
Hawthorn Leaf and Flower Dry Extract

[Aqueous Extract: minimum 2.5 per cent flavonoids expressed as hyperoside.

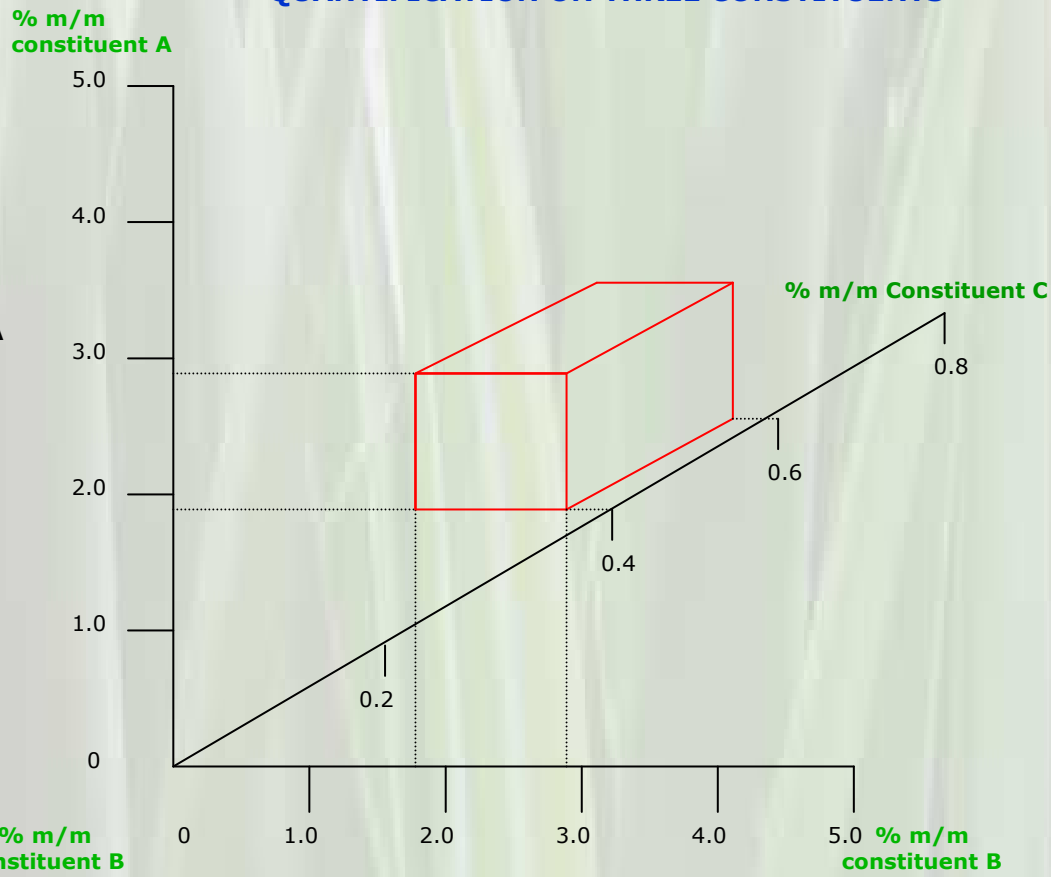
Hydroalcoholic Extract (Extraction Solvent: minimum 45 per cent V/V ethanol): minimum 6.0 per cent flavonoids expressed as hyperoside]

Extract Terminology: Quantified Extracts

QUANTIFICATION ON TWO CONSTITUENTS



QUANTIFICATION ON THREE CONSTITUENTS



For example, Quantified St John's Wort Dry Extract, where the characterised constituents are not solely responsible for the therapeutic and clinical efficacy of the extract. Such extracts do not show a typical dose-related response curve. Such extracts to be assayed for a minimum of two constituents and these constituents to be quantified at typically ± 10-20% (but not more than ± 25%) of the declared value. Adjustments to achieve quantification within stated limits of constituents to be by either blending suitable batches of extract or by blending batches of the starting material prior to extraction.

Extract Terminology: 'Other' Extracts

- Name?

- Is the publication of assays in the European Pharmacopoeia too restrictive for the needs of industry?

- alternative approach is to state for these extracts that: "The chosen analytical markers constitute one method of assaying the extract. This does not preclude the use of appropriate alternative markers for the assay of these extracts."

Extract Terminology: 'Other' Extracts

Valerian root (*Valeriana officinalis* L.) and preparations

Valerian root:

total sesquiterpenic acids: minimum 0.17%m/m determined as:

Valerenic acid + acetoxyvalerenic acid

Valerian root cut:

total sesquiterpenic acids: minimum 0.10%m/m determined as

valerenic acid + acetoxyvalerenic acid.

Valerian Dry Aqueous Extract:

total sesquiterpenic acids: minimum 0.02%m/m determined as:

acetoxyvalerenic acid + hydroxyvalerenic acid

Valerian Dry Hydroalcoholic Extract:

total sesquiterpenic acid: minimum 0.25%m/m determined as:

valerenic acid + acetoxyvalerenic acid [+ hydroxyvalerenic acid]

Valerian Tincture:

Total sesquiterpenic acids: minimum 0.015%m/m determined as:

valerenic acid + acetoxyvalerenic acid [+ ???]

Extract Terminology: Refined Extracts

- Extraction with a given solvent leads to typical proportions of characterised constituents in the extractable matter; during production of standardised and quantified extracts, purification procedures may be applied that increase these proportions with respect to the expected values; such extracts are referred to as 'refined'.

- HMPC Reflection Paper

- Not feasible to base on an arbitrary percentage of measured constituents.

- Should be based on processing methodology

Extract Terminology:

- **Standardised**
- **Quantified**
- **Characterised ("Other")**
- **Refined**

Definitions require clarifying and expanding to overcome interpretational differences. A similar exercise was recently undertaken for the monograph on Herbal Drugs.

Effect of Change of assay method (non-specific → specific) in extract on herbal medicinal product

Considerations:

Non-variable: content of extract in herbal medicinal product

- if z mg prior to change of assay method will be z mg post change of assay method.
- all extracts currently complying with limits for non-specific assay method must be encompassable within limits for specific assay method.

Variable: percentage content of measured constituents in extract.

- if x per cent prior to change of assay method will be y per cent post change of assay method.
- y will probably be significantly lower than x.

Variable/Non-variable: Constituents being assayed.

- prior to change of assay method will tend to be classes of constituents.
- post change of assay method may be a summation of a number of closely related constituents or may be one or more specified constituents.

Effect of Change of assay method (non-specific → specific) in extract on herbal medicinal product

HMPC Guidelines state: '…..the herbal substance or herbal preparation in its entirety is regarded as the active substance….'

Most extracts are **Characterised ('other') extracts** where in HMPC Guidelines the example of the declaration is given as:

Valerianae radix dry extract ethanolic 60% (V/V): 125mg
either ((a-b) : 1) or (equivalent to x-y mg Valerianae radix)

Therefore, if, for example, an assay method for flavonoids in a Characterised extract changed from a non-specific to a specific method (or even to different constituents) there should be no change in declaration of the active substance in the herbal medicinal product and hence no difference in pack declaration for the consumer.

Effect of Change of assay method (non-specific → specific) in extract on herbal medicinal product

HMPC Guidelines state: '…..the herbal substance or herbal preparation in its entirety is regarded as the active substance….'

Standardised Extracts – in the HMPC Guidelines the example of the declaration is given as:

> Sennae folium dry extract ethanolic 60%(V/V): 50-65mg corresponding to 12.5mg of hydroxyanthracene glycosides, calculated as sennoside B.
> either ((a-b) : 1) or (equivalent to x-y mg Sennae folium)

Therefore, a change from a non-specific to a specific assay method would lead to a change in declaration as follows:

> Sennae folium dry extract ethanolic 60%(V/V): 50-65mg corresponding to ? mg of ??, calculated as Sennoside B
>
> where ? mg will probably be <12.5mg and ?? will depend on the chosen assay method.

Is the current EP method used for senna extracts?

Pack declaration changes? Consumer perception of alteration in strength of product?

Loss of consumer confidence?

Effect of Change of assay method (non-specific → specific) in extract on herbal medicinal product

HMPC Guidelines state: '…..the herbal substance or herbal preparation in its entirety is regarded as the active substance….'

Standardised Extracts – a more compliant declaration would be

> Sennae folium dry extract ethanolic 60%(V/V): corresponding to 60 mg Sennae folium dry extract ^{ARC}.

Where ^{ARC} is an ***A***greed ***R***eference ***C***ontent for the percentage content of the constituents measured.

For example, the Definition in the EP for Standardised Senna Leaf Dry Extract states: '……. It contains not less than 5.5 per cent and not more than 8.0 per cent of hydroxyanthracene glycosides calculated as Sennoside B….'

Therefore, Senna Leaf Dry Extract^{ARC} might be set at 7.0 per cent of hydroxyanthracene glycosides, calculated as Sennoside B.

Effect of Change of assay method (non-specific → specific) in extract on herbal medicinal product

HMPC Guidelines state: '.....the herbal substance or herbal preparation in its entirety is regarded as the active substance....'

Advantages of ARC

- HMPC declaration is in compliance with its own guidelines.
- Change in assay method would alter the ARC but would not alter the HMPC declaration.
- ARC is applicable to any type of extract.
- Background activity between regulators and industry with no requirement on industry to alter packaging.
- Consumer is protected from possible confusion with respect to long established products.
- ARC value would be accessible through either EP or HMPC or both.

SUMMARY

Actions required to make EP extract monographs more useful:

EP/HMPC expand/clarify definitions of:

- **Standardised Extracts**
- **Quantified Extracts**
- **Characterised ("Other") Extracts**
- **Refined Extracts**

- **EP: introduce greater freedom of choice of assay method for Characterised ("Other") Extracts.**
- **EP: examine feasibility of more specific methods for those existing Standardised Extracts currently assayed by non-specific methods.**
- **HMPC re-examine/clarify declaration of active substances in herbal medicinal products.**

Thank you for your attention

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