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Herbal Extract Monographs (Ph. Eur.)

The Importance of Extract Monographs in the European Pharmacopoeia (Ph. Eur.) for the Quality Review in Switzerland

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... the following presentation is about ...

- **The legal background for the implementation of monographs in Switzerland**
- **A few general points concerning the Pharmacopoeia and the extract monographs**
- **Extract monographs and applications for marketing authorizations**
- **New extract monographs / Revisions of extract monographs and herbal medicinal products already placed on the Swiss market**
- **Short summary and (the attempt of a) conclusion**

Legal background in Switzerland, relevant for medicinal products and medical devices

Federal Law on Medicinal Products and Medicinal Devices (Law on Therapeutic Products – LTP)

Of importance concerning the realization of the specifications given in the Pharmacopoeia is

Article 8
Principle for placing products on the market

- ***Medicinal products and excipients*** placed on the market must meet the requirements of the Pharmacopoeia provided that such requirements exist.

Pharmacopoeia

➢ **Definition**

In Switzerland the Pharmacopoeia consists of the valid versions of the European Pharmacopoeia (Ph. Eur.) and the Swiss Pharmacopoeia (Ph. Helv.) including the respective supplements / addenda.

In the following the term *Pharmacopoeia* will be used as a synonym for the *European Pharmacopoeia*

Extract Monographs in the European Pharmacopoeia

It has to be differentiated between

- **General Monograph Extracts / Extracta (04/2008:0765)**
- **Monographs for selected herbal extracts**

Both have to be kept in mind regarding

- **applications for marketing authorizations as well as for**
- **already licensed herbal medicinal products**

General monograph Extracts / Extracta

… among other aspects

➔ General description of the requirements concerning content and complexity of a monograph for a herbal extract:

It states which aspects have to be considered regarding the relevant Chapters Definition, Production, Identification, Tests, Assay, Labelling

Extract types mentioned:

- **Liquid Extracts / extracta fluida**
- **Tinctures / tincturae**
- **Soft Extracts / extracta spissa**
- **Oleoresins / oleoresina**
- **Dry Extracts / extracta sicca**

… of more importance …

Monographs in the European Pharmacopoeia for selected herbal extracts

Extract monographs became increasingly important in the recent past

- **Permanent addition of new extract monographs to the Ph. Eur.**
- **Revision of already existing extract monographs**

Ph. Eur. 6.5 ⇨ In force July 2009 (CH):

- **21 dry extracts**
- **5 liquid extracts**
- **2 tinctures**

Extract monographs and the consequences for applications for marketing authorizations

***The question is*:**
What has to be considered in case of an application for a marketing authorization for a herbal medicinal product, which contains an

Active substance = Herbal extract, documented in the Ph. Eur. within the framework of an extract monograph?

As mentioned before:

According to Article 8 LTP, the requirements given in the Pharmacopoeia monographs (⇨ extract monographs) have to be met

→ Consequences in the context of an application for a marketing authorization for the herbal medicinal product in question?

Points to consider - illustrated with the help of an example

Passion flower dry extract I Passiflorae herbae extractum siccum (1882)

Definition: Dry extract produced from ***Passion flower (1459)*** .
Content: minimum 2.0 per cent of flavonoids, expressed as vitexin ($C_{21}H_{20}O_{10}$; M_r 432.4) (dried extract).

Production: The extract is produced from the herbal drug and ethanol (40 per cent *V/V* to 90 percent *V/V*), methanol (60 per cent *V/V*) or acetone (40 per cent *V/V*) by an appropriate procedure.

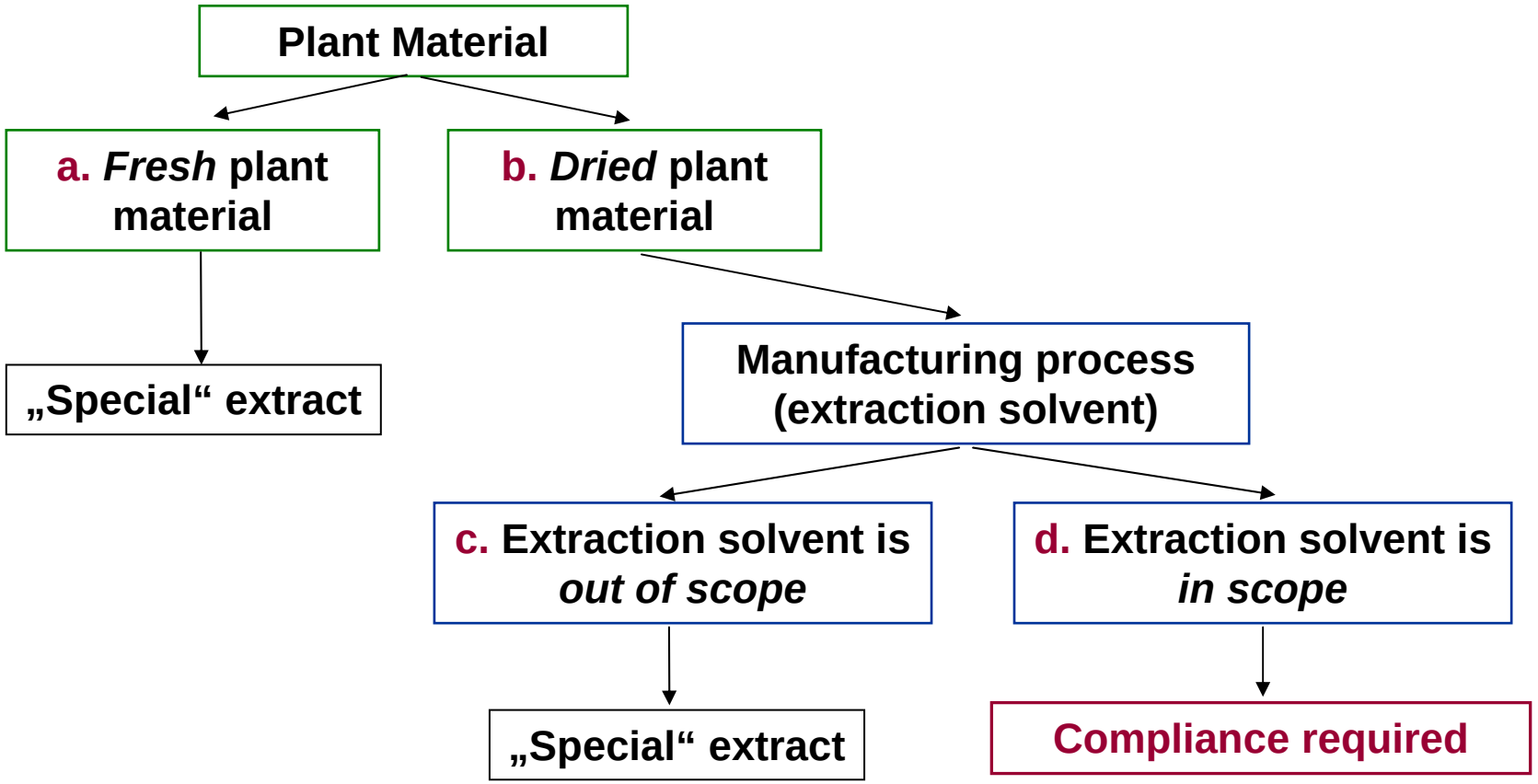
Characters: *Appearance*: greenish-brown amorphous powder.

Identification: Thin-layer chromatography (*2.2.27*).

Tests: Loss on drying (*2.8.17*): maximum 5.0 per cent, determined on 0.500 g.

Assay: Spectrophotometrical determination of flavonoid content

***FAQ*: "Is it true, that <u>every</u> extract called *Passion flower dry extract* has to comply with the Ph. Eur. Monograph 1882?"**
NO ⇨ Follow a *"decision tree"*



Plant material

a) Fresh plant material ↔ b) Dried plant material

a) <u>Fresh plant material</u> → ***Fresh flowering aerial parts of the Passion Flower***

1. **In this case the Ph. Eur. Monograph *Passion flower dry extract* <u>doesn't</u> have to be applied**

⇨ **The plant material that has to be used for the Ph. Eur. Extract is clearly defined:**
*<u>**P**assion flower (1459)</u> → Fragmented or cut, **dried** aerial parts of Passiflora incarnata L. It may also contain flowers and/or fruits.*

2. **"Special extract" requires an own ("in-house") monograph**

⇨ **General monograph Extracts / Extracta should be used for orientation**

a) **Fresh plant material** → ***Fresh flowering aerial parts of the Passion Flower***

3. **Specifications are set, based on data that have been collected during the stages of development of the active substance (= extract)**

⇨ **Most likely: Specifications are not fully compliant with the given Ph. Eur. extract monograph**

4. **Analytical methods → have to be developed, established, validated. Where indicated: Analytical procedures might be performed in orientation to the description in the respective extract monograph**

   However: Validation of methods is required.

And: Do not forget a monograph for the plant material itself.

b) Dried plant material is used for extract production

The plant material used corresponds to the plant material cited in the section *Definition* of the respective extract monograph

⇨ Ph. Eur.: *Passion flower (1459)*

Reminder ...

Article 8 LTP

Concerning the plant material used, compliance with the Ph. Eur. monograph – provided such a monograph exists – is required as well.

In order to make a decision whether in this case → use of dried plant material according to Ph. Eur., compliance with the relevant extract monograph is necessary the second aspect has to be highlighted upon:

⇨ Manufacturing process (→ extraction solvent)

Manufacturing Process

Passion flower dry extract
Production: *The extract is produced from the herbal drug and ethanol (40 per cent V/V to 90 per cent V/V), methanol (60 per cent V/V) or acetone (40 per cent V/V) by an appropriate procedure.*

c) Production is *out of* scope ↔ d) Production is *within* scope

c) Production is *out of* scope

The extraction solvent is different from the solvent (range) described in the above mentioned Ph. Eur. monograph

c) Production is *out of* scope

1. **Extract has to be named a „special extract“ (→ fresh plant material)**

2. **An adjustment to specifications given in the respective Ph. Eur. extract monograph is not required.**
   An own „in-house“ monograph for the extract in question has to be established according to the General monograph *Extracts / Extracta*

3. **Specifications are set, based on data that have been collected during the stages of development of the active substance (= extract)**

⇨ **Most likely: Specifications are not fully compliant with Ph. Eur. extract monograph**

4. **Analytical methods → have to be developed, established, validated.**
   Where indicated: Analytical procedures might be performed in orientation to the description in the respective extract monograph

   However: Validation of Ph. Eur. methods is required.

d) Production is *within* scope

Extraction solvent is in compliance with the range described in the Ph. Eur. extract monograph - in connection with the use of an *appropriate* extraction procedure
Already mentioned: Plant material = *Passion flower, Ph. Eur. (1459)*.

⇨ **Compliance with the Monograph *Passion flower dry extract* is required**

1. **Specifications of the extract monograph (here: *Passion flower dry extract*) have to be kept**

2. **Analytical methods are expected to be adjusted to the respective section of the monograph**

How may the term „Compliance with the specifications of the extract monograph“ be exactly „translated“?

Specifications, given in the monograph *Passion flower dry extract* have to be met

Content: minimum 2.0 per cent of flavonoids, expressed as vitexin ($C_{21}H_{20}O_{10}$; M_r 432.4) (dried extract).

Appearance: greenish-brown amorphous powder.

Loss on drying (*2.8.17*): maximum 5.0 per cent, determined on 0.500 g.

Identification: TLC according to Monograph (appearance, retention factors of chromatogram has to comply with the monograph)

Analytical methods ought to be performed as described in the monograph *Passionflower dry extract*
→ confirmation of the required specifications

***Identification*:** **TLC according to the monograph (described procedure)**

***Assay*:** **Spectrophotometrical determination of the flavonoid content according to the monograph (measuring the absorbance at 401 nm).**

Are there alternatives?

Specification

It is expected that:
Plant material according to Ph. Eur. + Extraction solvent according to Ph. Eur.
⇨ Specifications according to Ph. Eur.

And as the specification defines the quality of the respective extracts, no deviations are allowed

Analytical methods

a) Testing procedures are performed strictly according to the monograph → methods don‘t have to be developed nor do they have to be validated or
b) “Own“, which means „in-house“ testing procedures are used.

⇨ See: *General Notices* in the Ph. Eur.

Analytical methods

a) Testing procedures strictly according to the monograph in question

Reference to *General Notices* Ph. Eur.:
Validation of pharmacopoeial methods. The test methods given in monographs and general chapters have been validated in accordance with accepted scientific practice and current recommendations on analytical validation. Unless otherwise stated in the monograph or general chapter, validation of the test methods by the analyst is not required.

b) Use of in-house testing procedures is - in general – possible, but ….

Reference to *General Notices* Ph. Eur.:
The tests and assays described are the official methods upon which the standards of the Pharmacopoeia are based. With the agreement of the competent authority, alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used.

New extract monographs and the consequences for herbal medicinal products already placed on the Swiss market

The new extract monograph (→ e.g. the *Passion flower dry extract)* - is supposed to describe all extracts, which

- **are already admitted on the market**

<u>and</u> which

- **are produced from the given plant material (dried aerial parts of *Passion Flower, Ph. Eur. monograph 1459)* with the given extraction solvent *ethanol (40 per cent V/V to 90 per cent V/V), methanol (60 per cent V/V) or acetone (40 per cent V/V)***

⇨ Mode of production (extraction solvent) + Defined plant material
= Content + Characters

Compliance with the new extract monograph is obligatory if the herbal extract in question "fits"

Check – according to "Decision tree" ...

- **Nature of plant material used for extract production**

  Fresh plant material ↔ Dried plant material (acc. to Ph. Eur.)

- **Manufacturing process, more precisely: Extraction solvent used for extract production**

  Production in scope ↔ Production out of scope

If the herbal extract in question actually "fits" according to the "decision tree" the following consequences are necessary:

➢ **Specification**

Compliance is required.

➢ **Analytical methods**

a) **The testing procedures are adjusted to the respective section of the monograph**

or

b) **Already approved and applied "own", which means "in-house" testing procedures are still used, but ....**

⇨ **See: *General Notices* in the Ph. Eur.**

Revision of a herbal extract monograph and the consequences for herbal medicinal products already placed on the Swiss market

Usually concerned:

Testing procedures
- **Identification**
- **Assay**

a) **Former Ph. Eur. method was used in the past→ Adjustment is expected (and makes sense, instead of developing a completely new method)**

b) **In-house method was approved and used before**

→ **Adjustment to the monograph or**

→ ***General Notices*** **Ph. Eur. again** … *provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used.*

Short summary of the most important aspects and (the attempt of a) conclusion

- **Legal background for the need to implement the monographs of the Pharmacopoeia: Law on Therapeutic Products (LTP), Article 8 *Principle for placing products on the market***

  → Herbal extract monographs in the Ph. Eur. are legally binding.

- **The number of herbal extract monographs in the Ph. Eur. continues to increase**

  → The monographs - and the consequences connected - become relevant for an increasing number of herbal medicinal products.

- **Affected are herbal medicinal products which are intended for admission on the market as well as already admitted herbal medicinal products.**

- **Whether strict compliance with a herbal extract monograph in the Ph. Eur. is generally required for every extract in question, has to be decided case by case (⇨ "decision tree")**

  →Focus on plant material and manufacturing process (extraction solvent) used.

- **If compliance with a herbal extract monograph is actually required, it has to be differentiated between the specifications (content, character) and the analytical methods (test, assay)**

- **Herbal extract monograph: The use of the given plant material in combination with the documented extraction solvent is supposed to result in the given specification (= extract quality)**

- **Specifications → Compliance is required i.e. the extract in question has to hold the quality described in the respective herbal extract monograph**

- **Analytical methods → Compliance with the underlying monograph is required, but: There are alternative possibilities,**

  a) Use of analytical methods described in the European Pharmacopoeia
  → No Developement, no establishment, no validation is required

  b) Use of *in-house* methods: At any rate → Cross validation with Ph. Eur. Methods

... see *General Notices* Ph. Eur.

- **Manufacturing Process: Validation of the procedure is needed in every case**

A very few final comments …

- ✓ **The aim of a herbal extract monograph is to establish a certain quality standard for a herbal extract.**

- ✓ **The compliance with a given herbal extract monograph leads to a simplification concerning**
  - the setting of specifications and
  - the development, establishment and validation of analytical procedures
  → Simplification of the effort, which is put into documentation
  → Consequences for admission procedure.

- ✓ **Most important and appreciated:**
  Contributions of the marketing authorization holders during the *stages of development* of an extract monograph
  → Drafts are published in Pharmeuropa
  → Comments should be made - whenever thought necessary - via the section Pharmacopoeia at Swissmedic.

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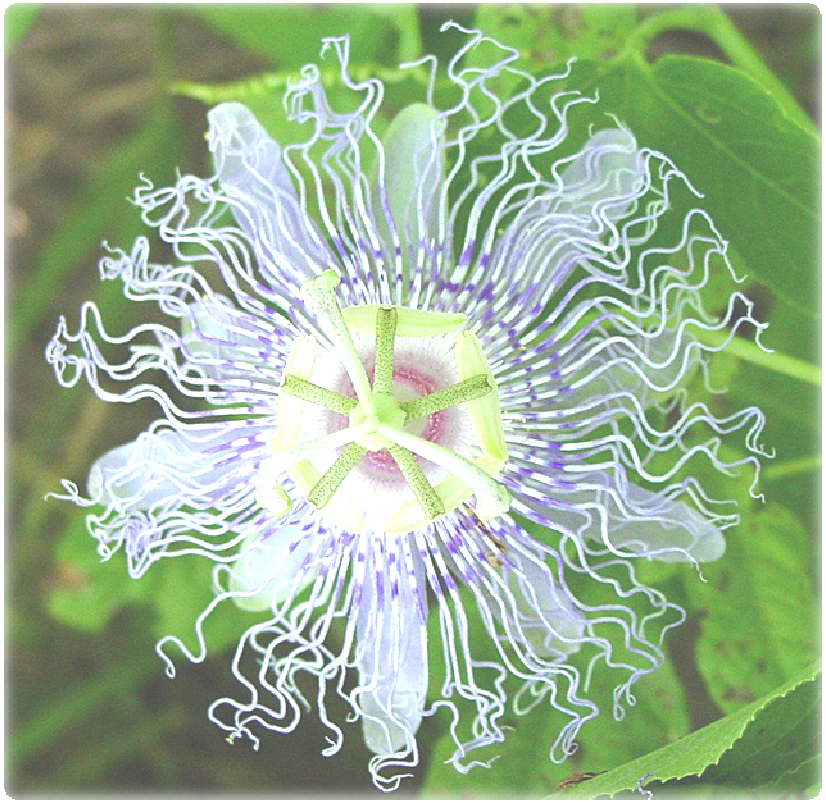
Thank You very much for Your attention!



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