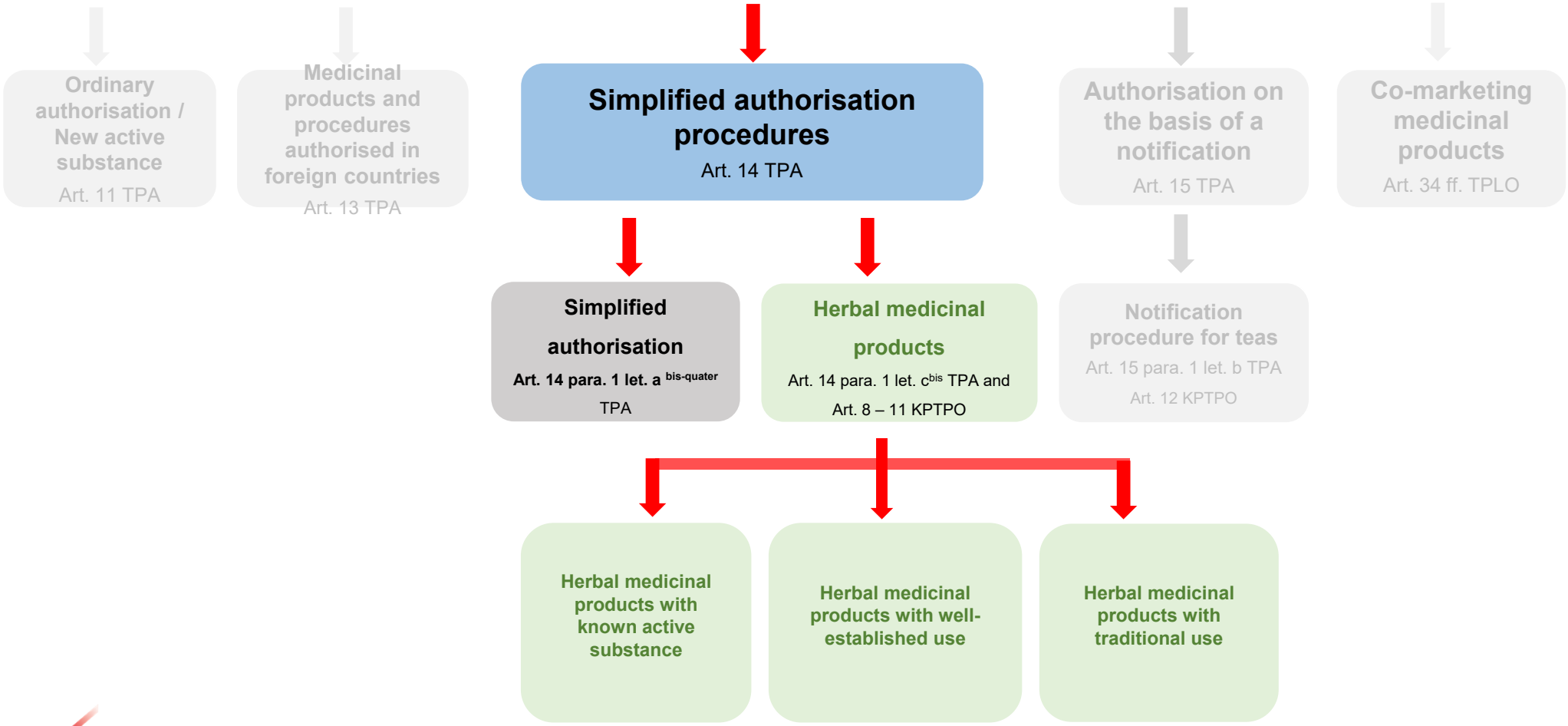
swissmedic

Proof of pharmaceutical equivalence and tolerability for herbal medicinal products with "traditional use" and "well-established use"

(Revision of Guidance document *Authorisation of herbal medicinal products)*

Tobias Schlechtinger, Regulatory Manager
Complementary and Herbal Medicines

The simplified authorisation procedures for herbal medicinal products (human medicinal products)



swissmedic

Today
we give you a behind-the-scenes look at the ongoing revision of

Guidance document *Authorisation of herbal medicinal products*

NB: Wording quoted from the Guidance document is not final/translated

Source: iStock

Revision of Guidance document *Authorisation of herbal medicinal products*

The Guidance document gives a more accurate definition of herbal medicinal products with "well-established use" (WEU):

***The herbal active substance** of the proposed herbal medicinal product has been in use in the proposed indication and use in at least one EU or EFTA country for at least 10 years ... demonstrated by adequate bibliographical documentation.*

-> Emphasis for WEU is on the **herbal active substance** (new aspects/dosages can be requested with corresponding additional clinical / preclinical documentation).

Art. 4 para. 2 let. c KPTPO:
At least 10 years' medical use of a herbal medicinal product as a medicinal product in the proposed indication and use in at least one EU or EFTA country with adequate bibliographical documentation of efficacy and safety.

The Guidance document gives a more accurate definition of herbal medicinal products with "traditional use":

*The **proposed herbal medicinal product – or a comparable medicinal product –** has been used medically for at least 30 years, and for at least 15 years in an EU/EFTA country.*

-> Emphasis for proof of traditional use on specifically cited **30 years auth. / registered herbal medicinal products**
-> The aim is to safeguard traditional "medicines heritage".

Art. 4 para. 2 let. d KPTPO
at least 30 years' medical use for a herbal medicinal product, of which at least 15 must have been in an EU or EFTA country (Art. 4 para. 2 let. d KPTPO).

swissmedic

Revision of Guidance document *Authorisation of herbal medicinal products*

Herbal medicinal products with "well-established use"

The herbal active substance *of the proposed herbal medicinal product has been in use in the proposed indication and in at least one EU or EFTA country for at least 10 years ... demonstrated by adequate bibliographical documentation.*

Can be further refined:

Known literature for the active substance

+

Own clinical/preclinical documentation for new aspects/new dosages can also be submitted ("**mixed application**").

Herbal medicinal products with "traditional use":

The ***proposed herbal medicinal product – or a comparable medicinal product –*** *has been used medically for at least 30 years, and for at least 15 years in an EU/EFTA country.*

Fixed comparator medicinal product:

Indication, dosage, etc. must match the cited herbal medicinal product that has been authorised/registered for 30 years.

swissmedic

Proof of tolerability in simplified authorisation procedures in accordance with the revised Guidance document *Auth. herbal medicinal products*

New stand-alone section 7.2.5 "Proof of tolerability" for the pharmaceutical form

Proof of tolerability must be provided in all cases (Art. 7 and Annex 1 no. 4.3 KPTPO).
Tolerability can be based on the use data (e.g. PSUR data) for pharmaceutically equivalent medicinal products with comparable excipient composition.

If the pharmaceutical form and/or excipient composition of the medicinal product submitted for authorisation deviates from the comparator medicinal product investigated in the studies or from the reference product – especially as regards bibliographical proof – *or if ... there is insufficient literature data, tolerability must be demonstrated or discussed by means of appropriate investigations (discussion in Module 2.5).* *(More detail provided)*
Proof of tolerability can ... be provided by means of the applicant's own investigations ***(at least observational studies)****, by bridging studies or – if available – bibliographical evidence.* *(New)*

-> Explanations of proof of tolerability now provided in greater detail for all pharmaceutical forms in stand-alone section.

swissmedic

Example: Proof of tolerability with literature documentation

A): New medicinal product submitted for authorisation = **gelatine capsule with no further excipients.**
Active substances = pharmaceutically equivalent to literature documentation.

Pharmaceutical form "gelatine capsule" with no further excipients **=** literature

For comparator medicinal product = capsule without excipients, tolerability data exist in the literature (or PSUR data).

Proof of tolerability (discussion in Mod. 2.5):
possible **without** applicant's own studies if the tolerability data for the comparator medicinal product are accessible from the literature and are presented.

B): New medicinal product submitted for authorisation = **tablets containing lactose.**
Active substances = pharmaceutically equivalent to literature documentation.

Pharmaceutical form tablets with lactose **≠** literature/PSUR

No reference to literature tolerability data for new tablets = capsules possible (literature only exists for excipient-free capsules).

Proof of tolerability (discussion in Mod. 2.5):
Several investigations of tolerability are required (e.g. observational studies) or a bridging study.
Study comparing the tolerability of the literature preparation (capsules) with the medicinal product submitted for authorisation (new lactose tablet)

More detailed definition of the "type" of clinical study for WEU

New addition to Guidance document *Authorisation of herbal medicinal products*:

*For herbal medicinal products with **well-established use (WEU)**, reference should, as a rule, be made to at least one **randomised controlled clinical trial** (RCT) of statistically sufficient size conducted either by the applicant or published in the literature.*

-> "Observational studies" are not sufficient in **WEU**

-> The RCT must have been conducted with a pharmaceutically equivalent medicinal product

-> Proof / discussion of pharmaceutical equivalence between product submitted for authorisation and literature studies in Module 2.5

Note:
Conversely, the efficacy of herbal medicinal products **with traditional use** is assessed for plausibility via 30-year use and not primarily via RCTs

swissmedic

Herbal medicinal products with (30 years') traditional use I

"Proof of 30 years' traditional use" referencing the HMPC's EU herbal monograph

t0

New Guidance document *Authorisation of herbal medicinal products*:

*To **assess the plausibility** of 30-year use, reference can also be made to recognised monographs containing specific details of traditional use (e.g. **assessment report** from an HMPC EU herbal monograph) if that monograph includes a corresponding **reference to medicinal products** that provides proof of 30 years' medical use.*

-> NB: This is **not** the case with every HMPC assessment report.

Dietary supplements may **not** be used as evidence of 30 years' medical use.

-> Key point: No medical use, no ADR reporting system.

t0 Bitte prüfen!: “Neue WL” [sic]
translator; 2024-11-13T10:39:46.946

Herbal medicinal products with (30 years') traditional use II

More detailed definition of documentation to be submitted in Module 4/5 if making reference to HMPC monograph

Addition to Guidance document *Authorisation of herbal medicinal products* regarding Module 4/5:

*If an HMPC EU herbal monograph exists for traditional use or well-established use and includes an **assessment report** that can be used as reference (pharmaceutical equivalence), there is generally no need to submit the literature references cited in the assessment report in Module 4/5.*

*However, should the monograph omit **genotoxicity tests** for the herbal active substance, corresponding investigations must be added (and discussed in Module 2.4).*

*Literature documentation for the HMPC assessment report must be reviewed to ensure it is **up to date and complete**, and updated documentation should be added if necessary.*

-> In short:

No need for literature references to documents that have already been officially reviewed in Europe

Herbal medicinal products with (30 years') traditional use III

Addition to "period" for proof of traditional use

t0

New Guidance document *Authorisation of herbal medicinal products*:

*If the documentation on 30-year medical use refers to a **period in the past** because there is no authorised/registered comparator medicinal product at present, the authoritativeness of the evidence of plausible effectiveness from this past use diminishes accordingly.*

-> At the time of submission, the cited comparator medicinal product(s)
should cover a period of at least 30 years of medical use
of which at least 15 should be in the EU / EFTA

-> Additional evidence of plausible effectiveness (OS) or extensive traditional use

t0 Bitte prüfen!: “Neue WL” [sic
translator; 2024-11-13T10:40:48.742

Herbal medicinal products with (30 years') traditional use IV

More accurate definition for dispensing category D and E for "trad. use"

New wording in Guidance document *Authorisation of herbal medicinal products*:

*The indication must be derived from the traditional use, **match the comparator medicinal product** and be intended solely for simplified self-medication (**dispensing category D and E**). For this reason. the indication must be comprehensible to a lay audience and diagnosable by the patients themselves. It must not delay or conceal diagnosis or causal treatment or be associated with other risks.*

-> Herbal medicinal products with traditional use are restricted to dispensing category **D** and **E**.

Specific example:
Downgrading the authorised indication for the comparator medicinal product – *e.g.* ***"rheumatoid arthritis" (disp. cat. B)*** – to a non-prescription "traditional indication" e.g. ***"traditional treatment for joint pain" (disp. cat. D)*** on the grounds of dispensing category requirements **will result in rejection** of the "traditional application" because the indication no longer matches that of the comparator medicinal product.

Part II

Pharmaceutical equivalence in WEU/traditional use

New Guidance document *Herbal medicinal products*: **Section 7.2.4 "Evidence of comparability"**

The pharmaceutical equivalence (PE) between 2 herbal medicinal products is acknowledged if conditions ***a-i*** (*now in greater detail) are* ***cumulatively*** satisfied:

a. Same herbal substance of comparable quality;
b. Comparable variation in the **native** drug extract ratio;
c. Comparable extraction solvent;
d. Comparable manufacturing process;
e. For standardised extracts: identical content of constituents with known therapeutic efficacy;
f. For quantified extracts: identical content range for the key active substances;
g. Comparable dosage;
h. Same indication, same method of administration and
i. Comparable pharmaceutical formulations.

-> Discussion of pharmaceutical equivalence (PE) – with literature studies – in Module 2.4/2.5

Pharmaceutical equivalence in WEU/traditional use

3 examples to illustrate PE: *

1. **Ginkgo biloba dry extract in WEU ("quantified special extract"):**
   PE in WEU for special extract with narrow interpretation for DER / extraction solvent / manufacturing

2. **Literature documentation for a devil's claw dry extract ("other extract"):**
   Proposed dosage diverges from literature documentation on efficacy

3. **Pharmaceutical / therapeutic equivalence of an ivy hot drink:**
   PE before and after preparation of the medicinal product with hot water

* All examples are hypothetical or engineered

Pharmaceutical equivalence in WEU: Ginkgo biloba

Planned new application ("fictitious"):

"*Ginkgo biloba, tablets*"

Tablets: **120 mg quantified** ginkgo leaf dry extract (**DER 40-60:1**)

Extraction solvent **acetone 30% m/m**

Indication: "To improve mental performance".

Comparator medicinal products in the literature:

PhEur extract

Film-coated tablets: **120 mg quantified, refined** ginkgo dry extract **(DER 35-67:1)**

Extraction solvent: **acetone 60% m/m**, corresponding to **26.4–32.4 mg flavonoids**, and **6.48–7.92 mg terpene lactones**.

Indication: "To improve mental performance".

Pharmaceutical equivalence in WEU: Ginkgo biloba

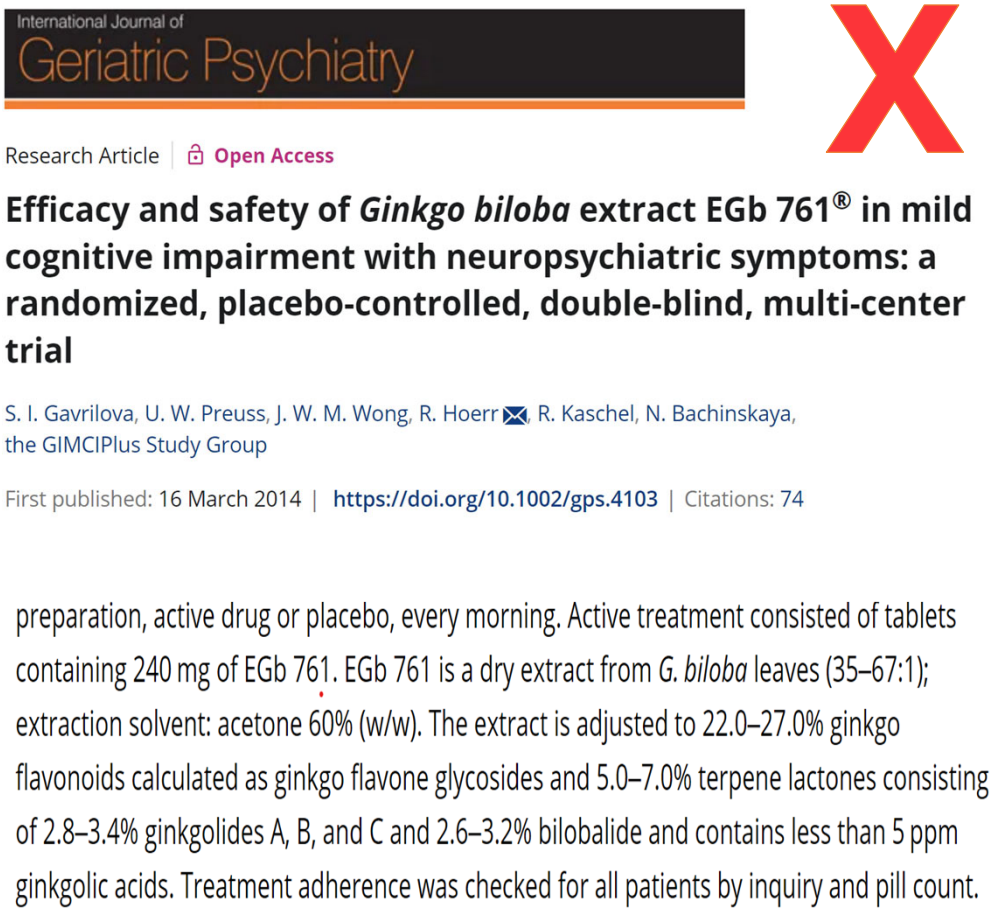
Conditions for PE	Comments
a) **Same herbal substance** (plant/plant part) **of comparable quality**	☑
b) Comparable variation in the **native drug extract ratio**	? Different range, different manufacturing?
c) Comparable **extraction solvent** (type and concentration)	X Acetone 30% instead of 60% m/m
d) Comparable **manufacturing process** (particularly for special extracts in WEU)	?
e) For **standardised extracts**: identical content of constituents with known therapeutic efficacy; f) For **quantified extracts**: identical content range for the key active substances;	? Flavonoids / terpene lactones versus "Other extract", manufacturing?
g) Comparable **dosage**	☑ 120 mg extract/day
h) Comparable **indication**, same **method of administration**	☑
i) Comparable **pharmaceutical formulations**.	☑

Pharmaceutical equivalence in WEU: Ginkgo biloba

Discussion of pharm. equivalence in Module 2.4/2.5

-> In short:

- The literature data with the **PhEur extract** are **not** comparable with the medicinal product or herbal active substance submitted for authorisation (not pharmaceutically equivalent)
- The literatures studies involving the PhEur special extract can only provide support
- An "**ordinary authorisation procedure**" in accordance with Art. 11 TPA is required or the applicant's **own clinical / non-clinical studies** to demonstrate the efficacy + safety of the submitted "*Ginkgo biloba, tablets*" in WEU.



International Journal of Geriatric Psychiatry

Research Article | Open Access

Efficacy and safety of *Ginkgo biloba* extract EGb 761® in mild cognitive impairment with neuropsychiatric symptoms: a randomized, placebo-controlled, double-blind, multi-center trial

S. I. Gavrilova, U. W. Preuss, J. W. M. Wong, R. Hoerr, R. Kaschel, N. Bachinskaya, the GIMCIPlus Study Group

First published: 16 March 2014 | https://doi.org/10.1002/gps.4103 | Citations: 74

preparation, active drug or placebo, every morning. Active treatment consisted of tablets containing 240 mg of EGb 761. EGb 761 is a dry extract from *G. biloba* leaves (35–67:1); extraction solvent: acetone 60% (w/w). The extract is adjusted to 22.0–27.0% ginkgo flavonoids calculated as ginkgo flavone glycosides and 5.0–7.0% terpene lactones consisting of 2.8–3.4% ginkgolides A, B, and C and 2.6–3.2% bilobalide and contains less than 5 ppm ginkgolic acids. Treatment adherence was checked for all patients by inquiry and pill count.

Pharmaceutical equivalence: Literature on devil's claw

New medicinal product A submitted for authorisation: Film-coated tablets 400 mg devil's claw root dry extract (DER: 1.5–2.5:1); extraction solvent: water.

Dosage: 1 film-coated tablet 3 times a day
= 1200 mg extract
(corresp. to 2400 mg drug).

Indication: symptomatic treatment of pain in mild degenerative joint diseases.

EMA/HMPC/627058/2015 «Assessment report on *Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne.,radix

In an open prospective study Müller *et al.* (2000) assessed the clinical effectiveness of capsule containing 400 mg dry *Harpagophythum* extract (DER 2:1[2]; extraction solvent: water), 3 capsules daily, on a period of 4 weeks. Five hundred fifty three patients with non-acute diseases of the musculoskeletal system were enrolled. An average improvement of symptoms was reported to be 45% but only minor anti-oedematous and anti-inflammatory effects were found. The ratio of adverse events was reported to be 0.9% and 5 patients suffered from severe adverse effects (abdominal symptoms). This open study with no control group is insufficient to prove the efficacy of *Harpagophytum* extract.

Daily dosage **literature source 1** (Müller et al.): 3x capsules containing 400 mg aqueous extract (DER 2:1) corresp. to **1200 mg extract / day.**

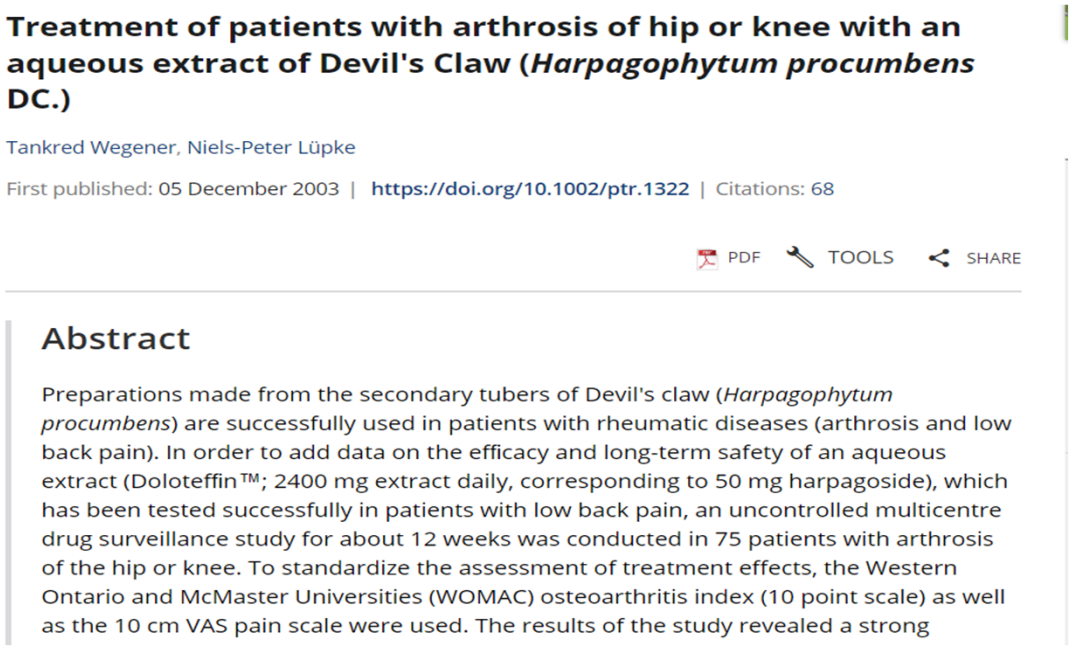
swissmedic

Pharmaceutical equivalence: Literature on devil's claw

New medicinal product A submitted for authorisation: Film-coated tablets 400 mg devil's claw root dry extract (DER: 1.5–2.5:1); extraction solvent: water.

Dosage: 1 film-coated tablet 3 times a day
= 1200 mg extract
(corresp. to 2400 mg drug or approx. 25 mg harpagoside acc. to PhEur).

Indication: symptomatic treatment of pain in mild degenerative joint diseases.



Treatment of patients with arthrosis of hip or knee with an aqueous extract of Devil's Claw (*Harpagophytum procumbens* DC.)

Tankred Wegener, Niels-Peter Lüpke

First published: 05 December 2003 | https://doi.org/10.1002/ptr.1322 | Citations: 68

PDF TOOLS SHARE

Abstract

Preparations made from the secondary tubers of Devil's claw (*Harpagophytum procumbens*) are successfully used in patients with rheumatic diseases (arthrosis and low back pain). In order to add data on the efficacy and long-term safety of an aqueous extract (Doloteffin™; 2400 mg extract daily, corresponding to 50 mg harpagoside), which has been tested successfully in patients with low back pain, an uncontrolled multicentre drug surveillance study for about 12 weeks was conducted in 75 patients with arthrosis of the hip or knee. To standardize the assessment of treatment effects, the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index (10 point scale) as well as the 10 cm VAS pain scale were used. The results of the study revealed a strong

Daily dosage **literature source 2** (T. Wegener et al.):
2400 mg aqueous dry extract
(corresp. to 4800 mg drug
or approx. 50 mg harpagoside acc. to PhEur)

swissmedic

Pharmaceutical equivalence: Literature on devil's claw

Conditions for PE	Comments
a) **Same herbal substance** (plant/plant part) **of comparable quality**	☑
b) Comparable variation in the **native drug extract ratio**	☑ = DER: 1.5–2.5:1
c) Comparable **extraction solvent** (type and concentration)	☑ = water
d) Comparable **manufacturing process** (particularly for special extracts in WEU)	☑
e) For **standardised extracts**: identical content of constituents with known therapeutic efficacy; f) For **quantified extracts**: identical content range for the key active substances;	-- --
g) Comparable **dosage**	☑ 1.) Literature: 1200 mg extract/day X 2.) Literature: 2400 mg extract/day
h) Comparable **indication**, same **method of administration**	☑
i) Comparable **pharmaceutical formulations**.	☑

swissmedic

Pharmaceutical equivalence: Example: ivy hot drink

New medicinal product submitted for authorisation:

Granulate for oral solution for a **hot drink** containing

Dry extract of ivy leaves (DER 5-7:1); extraction solvent: ethanol 30% (m/m).

Dosage information: Drink 3x 7g granulate / day (corresp. to **800 mg drug equivalent**) after preparing in **hot water** (90°C).

Both pharmaceutical forms comparable:

Oral, liquid with identical active substance release

Comparator medicinal products in the literature:

Syrup (with identical herbal active substance)

Dry extract of ivy leaves (DER 5-7:1); extraction solvent: ethanol 30% (m/m).

Dosage information: Take 3x 7 ml syrup / day (corresp. to **800 mg drug equivalent**)

swissmedic

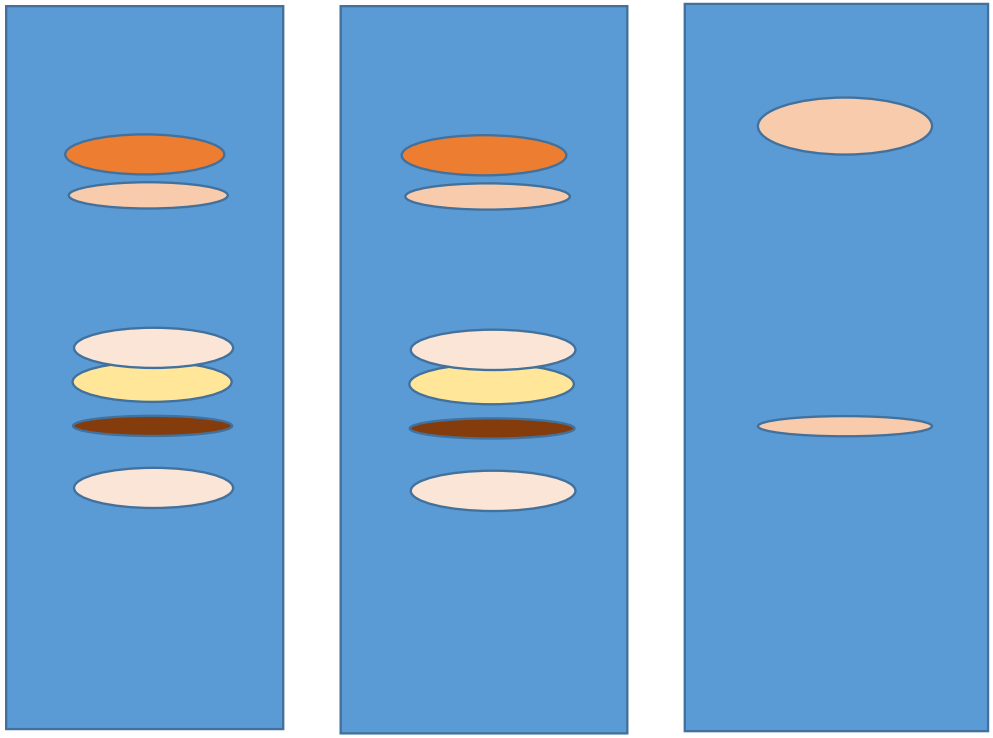
Pharmaceutical equivalence: Example: ivy hot drink

Conditions for PE with ivy syrup	Comments **BEFORE hot water**
a) **Same herbal substance** (plant/plant part) **of comparable quality**	☑
b) Comparable variation in the **native drug extract ratio**	☑ DER 5-7:1
c) Comparable **extraction solvent** (type and concentration)	☑ Ethanol 30% (m/m)
d) Comparable **manufacturing process** (particularly for special extracts in WEU)	☑ **Before** preparation
e) For **standardised extracts**: identical content of constituents with known therapeutic efficacy; f) For **quantified extracts**: identical content range for the key active substances;	-- --
g) Comparable **dosage**	☑ **Before** preparation
h) Comparable **indication**, same **method of administration**	☑
i) Comparable **pharmaceutical formulations**.	☑ Oral, liquid, ident. release

Pharmaceutical equivalence: Example: ivy hot drink

Ivy preparation corresponds to "other extract"; no distinct efficacy-(co)determining constituents known.

- Therefore TLC chromatograms to usefully characterise the herbal active substance in its entirety
- Note:
  Where there are known efficacy-(co)determining constituents, it would be useful to demonstrate pharmaceutical equivalence by determining the content of these constituents before and after preparation in boiling water



Syrup | Cold dissolved granulate | Hot drink 90°C

swissmedic

Pharmaceutical equivalence: Example: ivy hot drink

Conditions for PE with ivy syrup	Comments AFTER hot water
a) **Same herbal substance** (plant/plant part) **of comparable quality**	☑
b) Comparable variation in the **native drug extract ratio**	☑ DER 5-7:1
c) Comparable **extraction solvent** (type and concentration)	☑ Ethanol 30% (m/m)
d) Comparable **manufacturing process** (particularly for special extracts in WEU)	X **After** preparation with 90°C water
e) For **standardised extracts**: identical content of constituents with known therapeutic efficacy; f) For **quantified extracts**: identical content range for the key active substances;	-- --
g) Comparable **dosage**	X Constituents differ **after** preparation in 90°C water
h) Comparable **indication**, same **method of administration**	☑
i) Comparable **pharmaceutical formulations**.	☑ Oral, liquid, ident. release

Source: iStock

The end

Encore:
Pharmaceutical equivalence ⟺ Therapeutic equivalence

Message: **"Herbal medicinal products can never be completely identical"**

- Full extract is effective: Bioequivalence tests – to demonstrate comparability – do not make sense for herbal medicinal products.
- Pharmaceutical equivalence is a **compromise** on proving the comparability of 2 herbal medicinal products that takes account of the special characteristics of the school of therapy
- Proof/discussion of pharmaceutical equivalence between the herbal medicinal product submitted for authorisation and the literature studies is thus a **minimum requirement** that must be demanded for all relevant literature studies.
- Proof/discussion of pharmaceutical equivalence (PE) to the literature studies in **Module 2.4/2.5**

-> If it is not possible to demonstrate pharmaceutical equivalence, the applicant's own clinical studies will be required.

-> PE is the basis for any simplified authorisation of herbal medicinal products.