

Herbal Extracts of the European Pharmacopoeia

Viewpoint of the European Regulators

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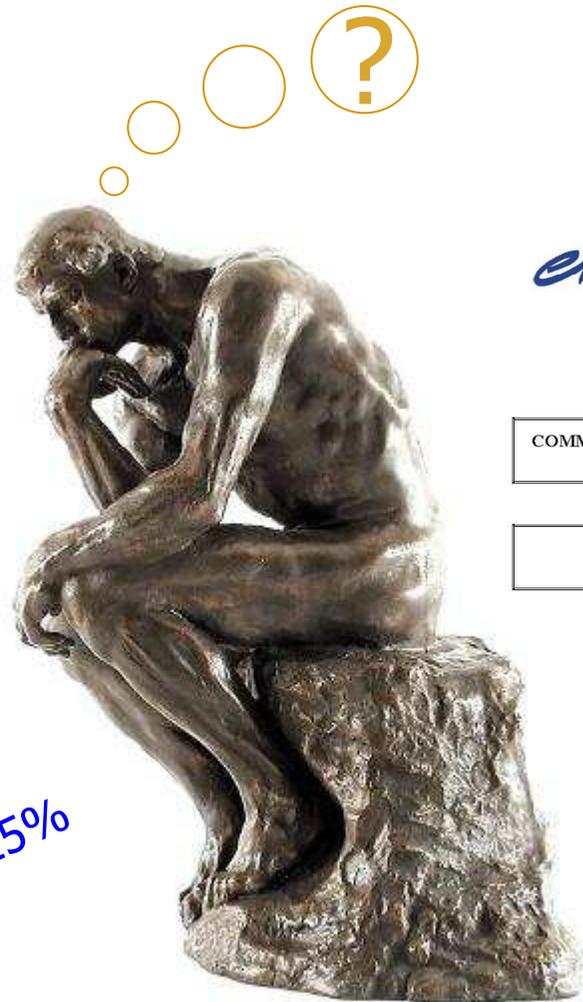
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www.ages.at



30 March 2006
CPMP/QWP/2819/00 Rev 1
EMA/CVMP/814/00 Rev 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP) COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

GUIDELINE ON QUALITY OF HERBAL MEDICINAL PRODUCTS¹/
TRADITIONAL HERBAL MEDICINAL PRODUCTS



Standardised

Quantified

Content: minimum of 0.25%
of sesquiterpenic acids

Monographs: legal basis

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Regulator

Analytical marker

...contribute substantially...

...generally accepted...

Guidelines: recommendations

R. Länger, 16.8.2009

Disclaimer

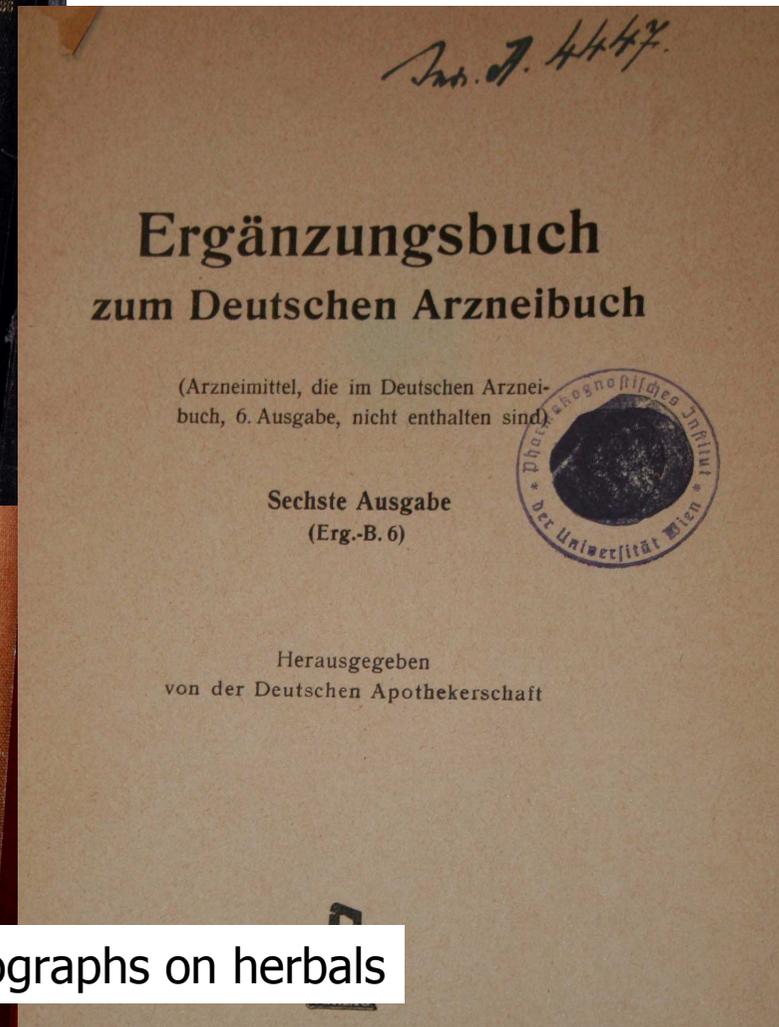
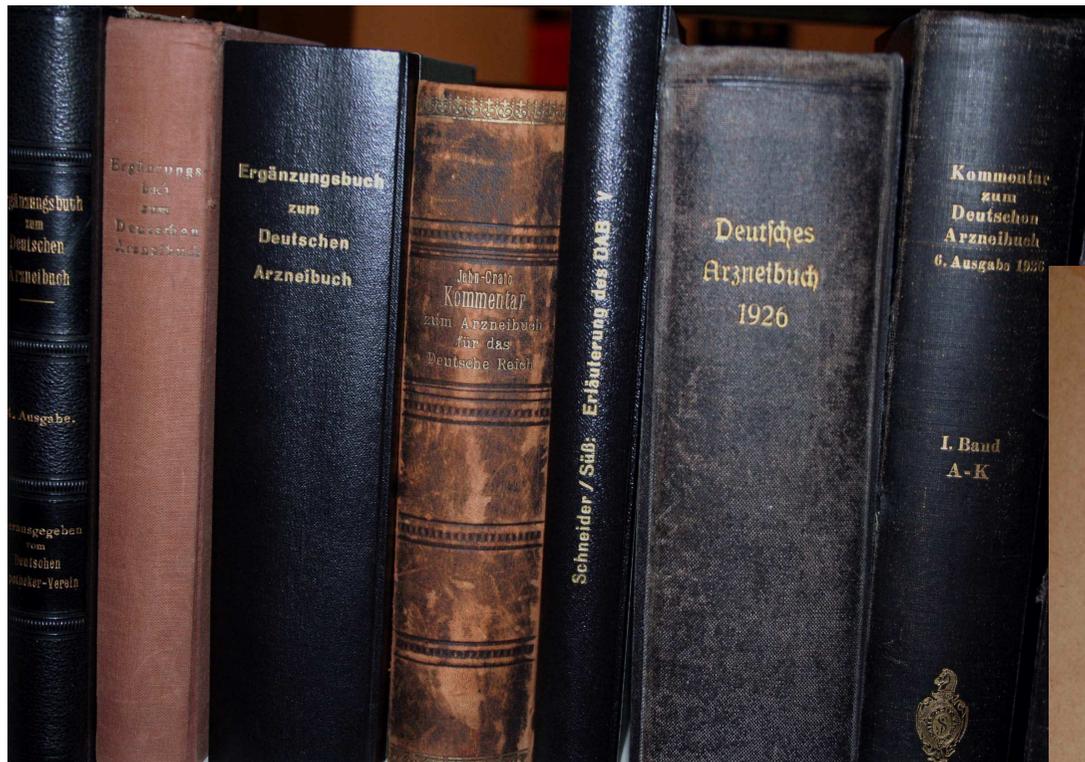


The views I present do not necessarily reflect the official views of the AGES PharmMed in Austria

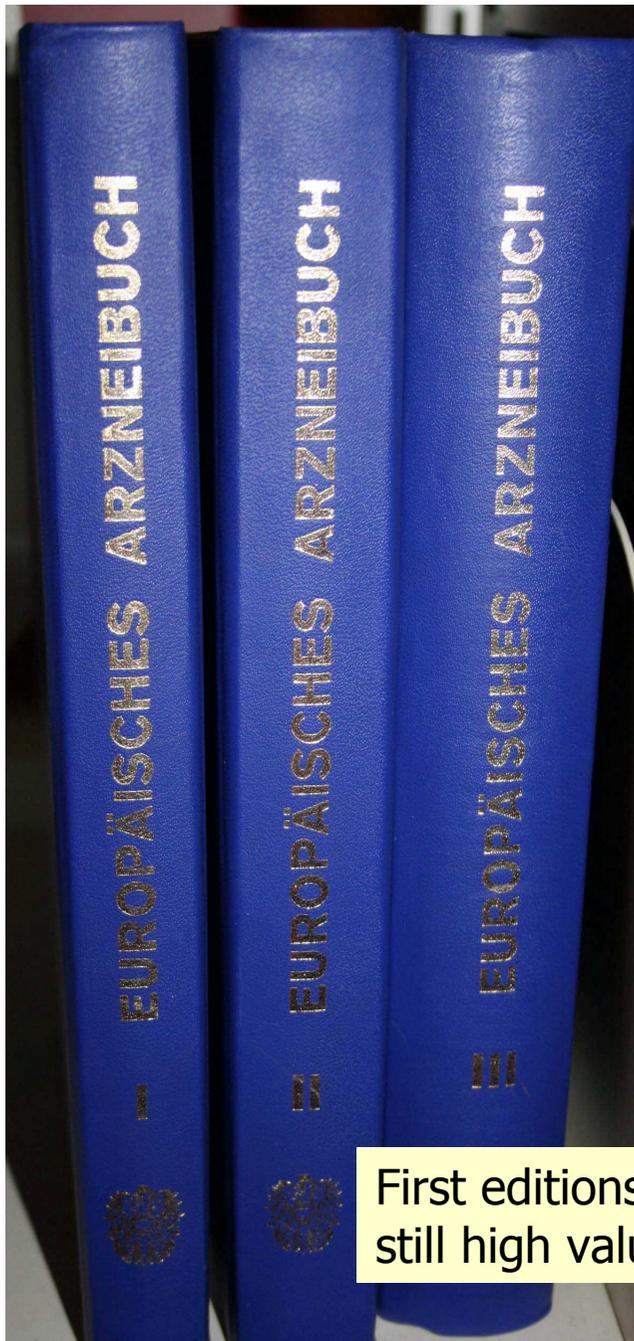
nor

of the committees or working parties of the European Medicines Agency EMEA.

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Old pharmacopoeias contained numerous monographs on herbals



First editions of EP: limited information on herbals,
still high value of national pharmacopoeias

App. 300 monographs for herbal substances or herbal preparations in EP
National pharmacopoeias cover national traditions only

**EUROPEAN
PHARMACOPŌEIA**

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**VERLAG
ÖSTERREICH**

Missions of the European Pharmacopoeia



- Provide authoritative quality standards for the medicinal substances that are IMPORTANT for PUBLIC HEALTH in Europe
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- ENSURING THE SAME QUALITY OF MEDICINES FOR ALL EUROPEAN CITIZENS.
-
- EP monographs and other texts are designated to be appropriate to the needs of regulatory authorities, those engaged in the control of quality, and manufacturers of starting material and medicinal products.
- The official standards published by the European Pharmacopoeia provide a legal and scientific basis for quality control during the development, production and marketing of medicines. Demonstrating compliance with these standards is a necessary part of the marketing authorisation dossier for a medicine. The European Pharmacopoeia is also used by manufacturers and national and European health authorities to check the quality of medicines.

For discussion:

- General definition of extracts
- Categorisation of certain extracts
- Inconsistency within EP
- Analytical methods
- Compatibility with needs of regulatory authorities

Definition of extracts



- Standardised extracts:

- EP: Standardisation = adjustment to a defined content of a constituent with known therapeutic activity
 - Combination of quality standards with interpretation of clinical data
- HMPC: constituents with known therapeutic activity are generally accepted to contribute substantially to the therapeutic activity
- Therapeutic activity of extract = therapeutic activity of isolated constituent with known therapeutic activity
 - Proof: phase II clinical trial
- During discussions at HMPC doubts that categorisation of some extracts actually reflects clinical evidence

Standardised extracts



- Alkaloids

- Belladonna leaf dry extract, tincture
- Cinchona liquid extract
- Opium dry extract, tincture
- Ipecacuanha liquid extract, tincture



- Anthraquinones

- Aloes dry extract
- Cascara dry extract
- Frangula bark dry extract
- Senna leaf dry extract



- Other constituents

- Capsicum tincture ✓
- Fresh bilberry fruit dry extract ?
- Liquorice ethanolic liquid extract ?
- Milk thistle dry extract ✓
- In preparation: Horse chestnut dry extract ?

Standardised extracts?



- Fresh bilberry fruit dry extract
 - o Standardisation to anthocyanidines
 - o Clinical efficacy (venous disorders, night blindness) discussed controversially
 - o 'constituents with known therapeutic activity'?
 - o 'generally accepted to contribute substantially'?
- Liquorice ethanolic liquid extract
 - o 3.0-5.0% glycyrrhizic acid
 - Remaining 95%?
 - o Isoflavones and chalcones also potent constituents
- Horse chestnut dry extract
 - o 16.0 – 20.0% triterpene glycosides
 - o No data that the remaining 80% do not contribute to the activity

Definition of extracts



- Quantified extracts:

- EP: adjustment to a defined range of constituents
 - o Adjustment by blending batches only: not understandable for persons not involved in the development of the monograph
- HMPC: ...range of constituents (active markers)
 - o Active markers are generally accepted to contribute to the therapeutic activity.

-
- Capsicum oleoresin refined (6.5-8.0% capsaicinoids)
 - Hawthorn leaf and flower liquid extract (0.8-3.0% flavonoids)
 - Ginkgo dry extract (22.0-27.0% flavonoids, 2.6-3.2% bilobalide, 2.8-3.4% ginkgolides)
 - St. John`s wort dry extract (0.1-0.3% hypericins)
 - Melissa leaf dry extract (in preparation, 3.0-6.0% rosmarinic acid)

Quantified extracts



- Melissa leaf dry extract
 - 3-6% rosmarinic acid
 - Different indications in clinical trials:
 - Melissa extract: induce sleep, Alzheimer disease, Herpes labialis
 - Clinical trials with rosmarinic acid: atopic dermatitis, allergic rhinoconjunctivitis
 - Rosmarinic acid contributes to activity in all indications?
 - Facts or assumption?

Definition of extracts



- Other extracts:

- EP: essentially defined by their production process and their specification
- HMPC: neither constituents with known therapeutic activity nor active markers are known
- EP: many monographs on 'other extracts' define a lower limit of a constituent
- Per definition this constituent is an analytical marker. What is the meaning of a lower limit of an analytical marker?
 - Discrepancy with EMEA guidelines

Other extracts



- Agni-casti fruit dry extract (in preparation)
- Arnica tincture
- Artichoke leaf dry extract
- Benzoin tinctures
- Bitter orange tincture
- Boldo leaf dry extract
- Cinnamon tincture
- Devil's claw dry extract
- Gentian tincture
- Hawthorn leaf and flower dry extract
- Matricaria liquid extract
- Myrrh tincture
- Olive leaf dry extract
- Passion flower dry extract
- Peppermint leaf dry extract
- Rhatany tincture
- Sage tincture
- Tormentil tincture
- Valerian dry aqueous extract, dry hydroalcoholic extract, tincture
- Willow bark dry extract

Open questions



- Who decides whether a constituent has a known therapeutic activity or contributes to the activity or is just for analytical purposes?
 - Data from pharmacological testing available for nearly all major constituents
 - What kind of data would be expected to shift a constituent from an analytical marker to an active marker?
- Scientific interpretation on markers may change
 - E.g. Hypericum: at the moment flavonoids estimated as more important than hypericins
 - Revision of EP monograph?
- Standardised and quantified extracts
 - Link between extract (active constituent) and indication necessary?

Inconsistency



- **Capsicum oleoresin refined quantified**
 - Where is the principal difference between the standardised tincture and the quantified oleoresin?
 - Are there other constituents than capsaicinoids that contribute to the activity?
- **Hawthorn leaf and flower liquid extract quantified**
 - Dry extract of Crataegus is 'other extract'
- **Boldo leaf dry extract**
 - Boldine contributes to the spasmolytic activity of the extract

Inconsistency



- Gentian tincture
 - Activity strictly assigned to bitter substances
 - Rhatany tincture, Tormentil tincture
 - Tannins are considered solely responsible for activity
 - Willow bark dry extract
 - Salicylates contribute to the activity
 - Willow bark extract in HMPC guidelines an example for a quantified extract
-
- Meaning of 'standardised'
 - Extracts containing constituents with known therapeutic activity
 - 'Standardised dry extract CRS'
 - Defined amount of marker substance
 - = constituent with known therapeutic activity?

Standardised extracts: content



- Fixed content ($\pm 10\%$ tolerance)
 - Belladonna leaf dry extract, tincture
 - Opium dry extract, tincture
 - Ipecacuanha liquid extract, tincture
 - Aloes dry extract
 - Fresh bilberry fruit dry extract
- No defined content, $\pm 10\%$ of the nominal content
 - Cascara dry extract
- Range, content has to be declared, max. $\pm 10\%$ tolerance
 - Frangula bark dry extract
 - Senna leaf dry extract
 - Capsicum tincture
 - Milk thistle dry extract
- Range
 - Cinchona liquid extract (4-5%)
 - Liquorice ethanolic liquid extract (3-5%)
 - In preparation: Horse chestnut dry extract (16-20%)

Analytical methods



- EP has to use analytical methods which are state of the art
- Modernisation of methods for assay:
 - Standardised and quantified extracts:
 - Amount is declared, therefore most correct method necessary
 - Other extracts:
 - Actual amount is of less importance
 - Method should guarantee the batch specific quantity of the herbal preparation in the finished product

Analytical methods



- Modernisation of methods for assay:
 - Importance of herbal substances or herbal preparations may be different in Europe
 - Costs for analyses of slow sellers may be not in balance with the price of the product
 - Balanced ratio between reliability, costs (equipment, human resources) and need for public health

Relevance for regulatory authorities



- Monographs on herbal substances essential
- Need of extract monographs?
 - In many application dossiers deviations to the EP monograph
 - E.g.: use of excipients for the last step from spissum extract to dry extract
 - Validation of analytical methods necessary
 - Only few tests remaining to be included into the specification
 - Some applicants choose different analytical methods
 - Choice of markers
 - In combination products frequently different marker substances
 - Justification by the applicant necessary

Relevance for regulatory authorities



- Bibliographic applications well-established use:
 - o Applicant has to demonstrate that extract is equal to those used in clinical trials
 - o Reference to conformity with EP is not sufficient, definitions too broad
 - o E.g.: for the HMPC monograph on Hypericum not all extracts which comply with EP monograph can be considered similar with respect to their evidence of efficacy
- Traditional Herbal Medicinal Products
 - o Contain frequently extracts which are different to a published extract monograph from the same herbal substance
 - o Need for change of the extract in the dossier?
 - o Change would cause loss of evidence of traditional use

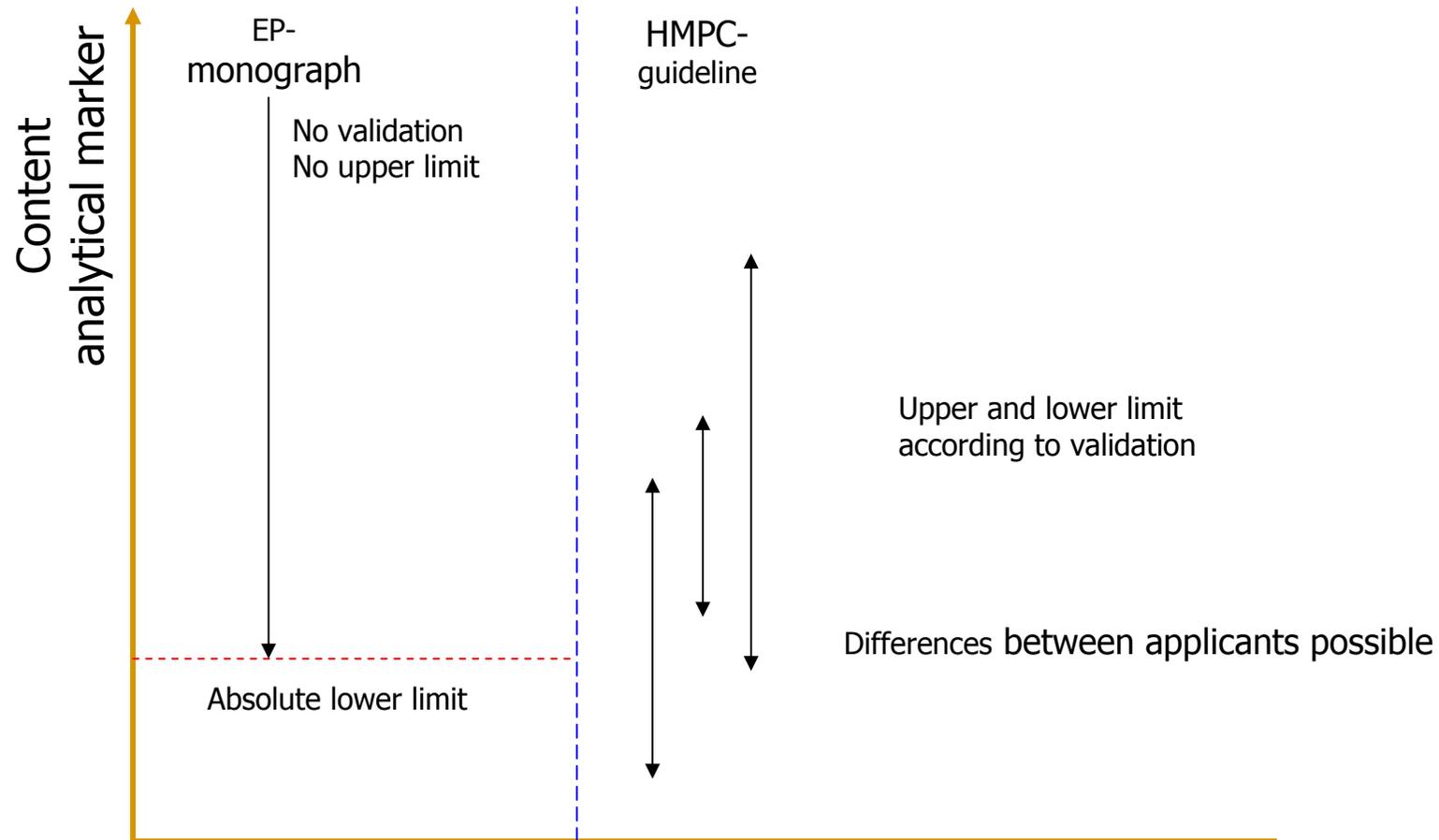
Relevance for regulatory authorities



- Specification - Assay:

- Guideline on quality of (traditional) herbal medicinal products (CPMP/QWP/2819/00 Rev 1)
 - ,In the case of an analytical marker of an extract for which neither constituents with known therapeutic activity, nor active markers are known, the specified minimum and maximum content is related to the validated analytical range as a base for analytical suitability within the frame of batch related control.'
- EP monograph: only lower limit, no information on validated analytical range
- No EP monograph: minimum and maximum value, range based on historical batch data and on validated analytical range

Specification: Assay



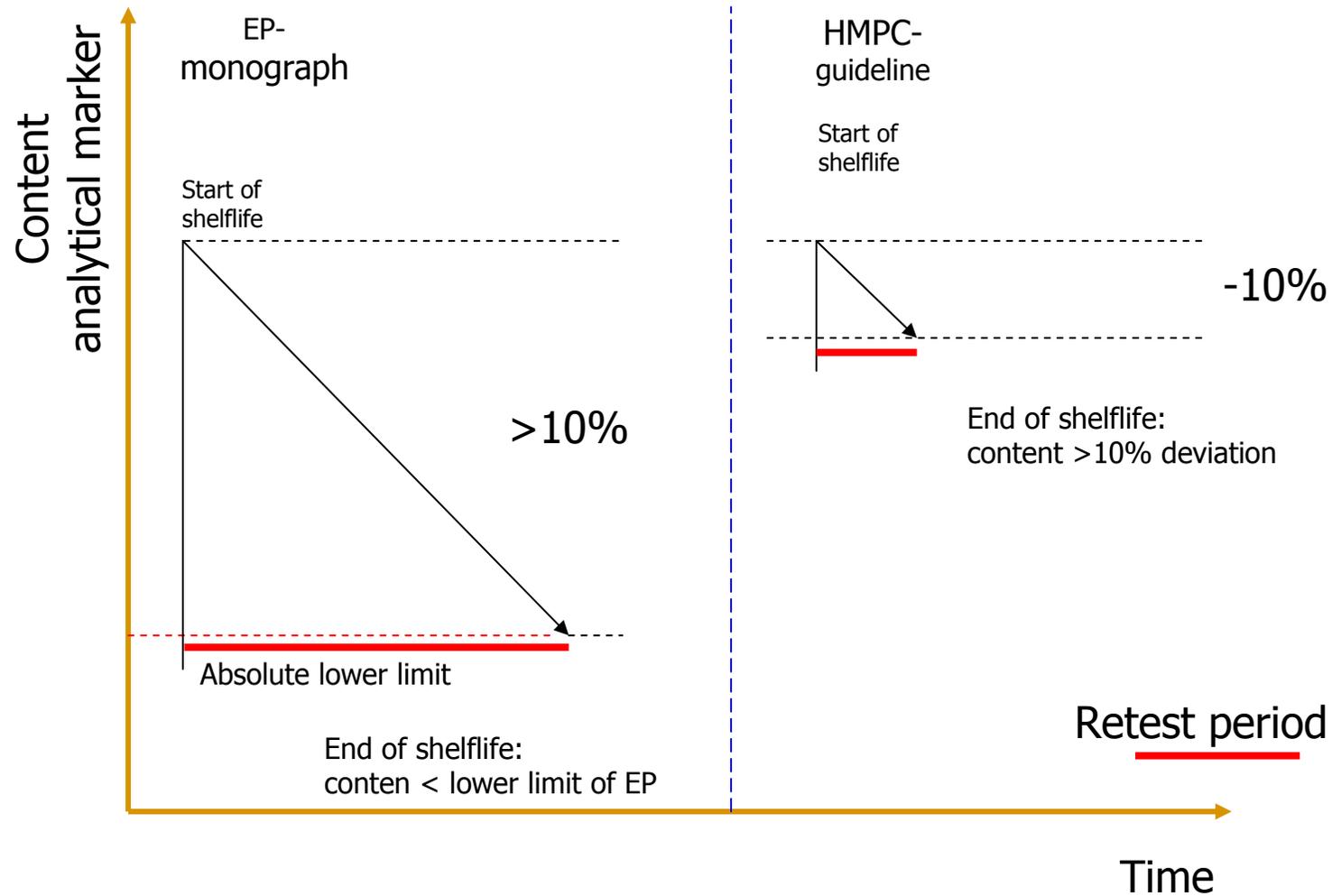
Relevance for regulatory authorities



- Stability testing

- General guidance for tolerable deviations:
 - Standardised extracts:
 - $\pm 5\%$ from the declared value
 - Quantified extracts, other extracts:
 - $\pm 5\%$ to $\pm 10\%$ from the initial value (batch specific)
- No EP monograph:
 - Applicant justifies choice of marker, $\pm 10\%$ deviation tolerable
- EP monograph published:
 - Lower limit of an analytical marker in the definition
 - Extract complies with quality requirements as long as amount of analytical marker is higher?
 - Deviations of more than 10% tolerable?

Stability extracts



(Very personal) Conclusions



- Excellent EP monographs on the starting material
 - Discussion on the content of marker substances
- Need for monographs on extracts in the EP should be questioned
 - Current extract monographs force more questions than provide answers
 - Never ending discussions on the classification of marker substances
- Inconsistencies may be due to workload at EDQM
 - Regulatory authorities need consistent basis for consistent decisions

(Very personal) Conclusions



- Modernisation of analytical methods
 - Inclusion of evaluation of the need for public health into the considerations
- Restriction to quality aspects in EP
- Need for further strengthening of the cooperation between EDQM and HMPC

