

Extract monographs- Viewpoint of the European Pharmacopoeia

Dr. Michael Wierer,
Deputy Head, European Pharmacopoeia Department,
EDQM / Council of Europe



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- Divergences with HMPC monographs ?
 - Classification and choice of markers
 - Extraction solvent ranges
 - Introduction of new assay methods
- Cooperation Ph.Eur.- HMPC

Extract classification in Ph.Eur.

- Standardised Extracts
 - ▲ Constituents of known therapeutic activity
- Quantified extracts
 - ▲ Active markers
- Other Extracts
 - ▲ Analytical markers

Standardised Extracts

- Aloes extractum siccum normatum
- Belladonnae folii extractum siccum normatum
- Belladonnae folii tinctura normata
- Cinchonae extractum fluidum normatum
- Frangulae corticis extractum siccum normatum
- Hippocastani seminis extractum siccum normatum
- Ipecacuanhae extractum fluidum normatum
- Liquiritiae extractum fluidum ethanolicum normatum
- Myrtilli fructus recentis extractum siccum raffinatum et normatum
- Opii extractum siccum normatum
- Rhamni purshianae extractum siccum normatum
- Rhei extractum siccum normatum
- Sennae folii extractum siccum normatum
- Silybi mariani extractum siccum raffinatum et normatum

Quantified extracts

- Capsici oleoresina raffinata et quantificata
- Crataegi folii cum flore extractum fluidum quantificatum
- Ginkgonis extractum siccum raffinatum et quantificatum
- Ginseng extractum siccum quantificatum
- Hyperici herbae extractum siccum quantificatum

Other Extracts

- Agni casti fructus extractum siccum
- Boldi folii extractum siccum
- Capsici extractum spissum
- Crataegi folii cum flore extractum siccum
- Cynarae folii extractum siccum
- Harpagophyti extractum siccum
- Liquiritiae extractum siccum ad saporandum
- Matricariae extractum fluidum Melissae folii extractum siccum
- Menthae piperitae folii extractum siccum
- Oleae folii extractum siccum
- Passiflorae herbae extractum siccum
- Salicis corticis extractum siccum
- Saw palmetto extract
- Valerianae extractum aquosum siccum
- Valerianae extractum hydroalcoholicum siccum

Why are sometimes HMPC monographs divergent from Ph.Eur. ?

- HMPC monographs are based on documentary evidence of the therapeutic use
- Ph.Eur. monographs cover **all** qualities legally on the market in Europe and were mostly adopted before HMPC monographs

Resulting problems

- Classification of a particular extract
- Choice of relevant “marker”
- Choice of solvents and solvent range
- Establishing a link between “traditional” and modern analytical assay methods

Discussions HMPC-EDQM

- Mutual participation of observers
- Meeting of Ph.Eur. Chairpersons and with QDG
- Early HMPC input and comments on draft Ph.Eur. Monographs
- Common approach agreed

Action plan proposed

- Distinction between active markers and analytical marker
 - align the Technical Guide for the Elaboration of Monographs on Herbal drugs
 - Ph. Eur. to revise general monograph on extracts
 - HMPC to state in monographs which substances are considered as responsible for therapeutic activity or contributing to this

Action plan proposed (2)

- Limits for quantified extracts
 - Base on approved medicinal products or
 - for new monographs link to well-established use
- “Other Extracts”
 - State in general monograph that for “other extracts” the use of the stated analytical markers is not mandatory and may be replaced by another suitable markers with limits to be justified by the applicant
 - Consider renaming this class e.g. “Characterised extracts”

Action plan for extraction solvents: 3 cases

1. Extracts covered by HMPC and Ph.Eur. ✓
2. Extracts covered by HMPC but not by Ph. Eur.
3. Extract covered by Ph.Eur. but not by HMPC

Case 2: align Ph.Eur range

- Valerian dry hydro alcoholic extract Ph.Eur. 6.0
- HMPC: ethanol 40-70 % V/V
- Ph.Eur: ethanol 45-80 V/V or methanol 40-55 %
- Prop. Rev: ethanol 40-80 V/V or (in PE 21.2) methanol 40-55 %

Case 3: keep Ph.Eur. monograph range

- Even if not covered by HMPC monograph,
- licensed products (in EU) may contain such extracts
- products may be licensed in non-EU member states

Assay methods - problem statement

- HMPC monographs refers to literature and dosages which may have been obtained by methods that are nowadays outdated
- Need to replace assay methods in Ph.Eur. may result in different assay results

Why new assay methods ?

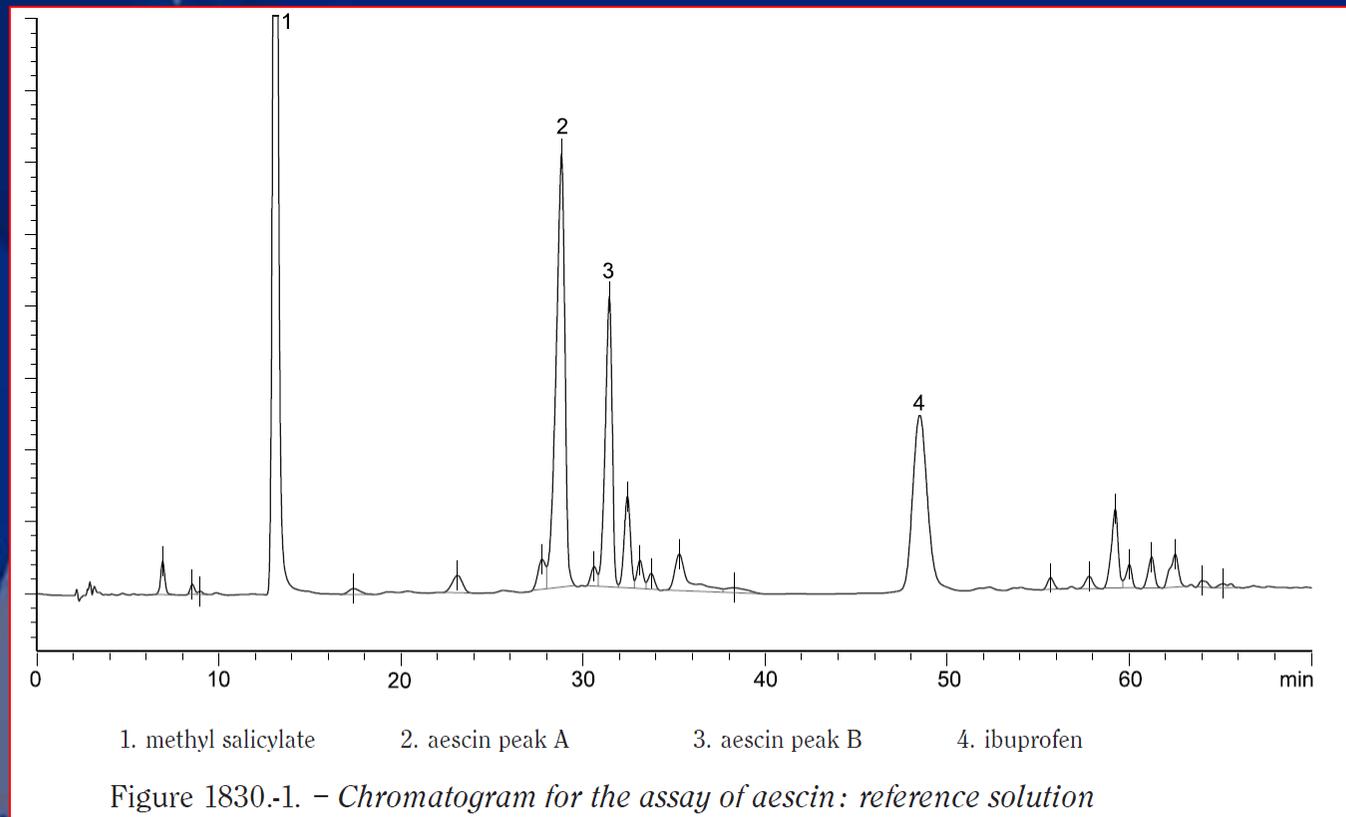
- Modern instrumental methods are more specific
- Provide better reproducibility
- Provide meaningful information in terms of stability
- Example: Colorimetric assays in
 - Aloe dry extract, standardised or
 - Horse-chestnut dry extract, standardised

Horse-chestnut (1)

Current situation

- The colorimetric method as published in the German Pharmacopoeia is widely recognised.
- The applied limits are the following:
 - Horse-chestnut: minimum 3.0 % of triterpene glycosides, expressed as aescin (dried drug);
 - Horse-chestnut dry extract, standardised: 16.0 %-20.0 % of triterpene glycosides, expressed as aescin (dried extract).

Horse-chestnut (2): HPLC method



Horse-chestnut (3)

- A changeover from the colorimetric method to a more specific and precise HPLC method is envisaged.
- Difficulty:
Different content values are obtained with the more specific HPLC method in comparison to the colorimetric method.

Some results ...

Batch	UV %	HPLC %	Ratio
#1	17.6.	10.5	1.7
#2	18.9	12.0	1.6
#3	18.1	11.1	1.6
#4	16.1	9.4	1.7
#5	17.6	11.2	1.6
#6	18.6	12.4	1.5
Average	17.8	11.1	1.6

Assay – transition (1)

- A close collaboration with assessors and industry is necessary:
 - for the determination of the HPLC content values;
 - for the change in labelling of products.
 - Publish new method as non-mandatory method B in addition to the existing method and collect data using both in parallel
 - Review data when adopting new content specification

Assay – transition (2)

- For more details see Pharmeuropa: 20.3
- Apply the same principle to the respective herbal drug as well to keep consistency between herbal drug and herbal drug preparation

Conclusion

- Divergences between HMPC and Ph.Eur. monographs identified
- Close co-operation between HMPC and EDQM working parties
- Common approach agreed
- Action for harmonisation has been triggered



Thank you!

