Comments on 'European Pharmacopoeia Monographs on Extracts: Reflections Following Recent Discussions'

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This letter is the follow-up to the document: 'European Pharmacopoeia Monographs on Extracts: Reflections following recent discussions', previously published in the Readers' Tribune of Pharmeuropa 22.2.

The reflection paper of Dr. Helliwell tries to summarise most of today aspects and questions that are associated with monographs on herbal extracts.

Despite the fact that there is now a significant number of monographs on extracts in the Ph. Eur. and the typology of 'standardised', 'quantified' and 'other' extracts has found its way into the phytopharmaceutical community a continuous discussion around this topic is going on and the whole concept seems to be not fully understood.

As a matter of fact, monographs on extracts in the Ph. Eur. are useful in order to harmonise quality criteria, to set common specifications, analytical methods and reference substances and thus achieving transparency. Therefore, monographs contribute significantly to the quality and safety of herbal medicinal products enabling an easier international drug registration process.

Still it has to be noted that new monographs on extracts often lead to variations for already existing registration files. As a consequence costly adaption processes (e.g. new stability tests, validation data and variation procedures) have to be conducted by industry. This should be kept in mind when elaborating new monographs or changing existing ones. It is of utmost importance for industry that the HMPC (Committee on Herbal Medicinal Products) and EDQM (European Directorate for the Quality of Medicines & HealthCare) work very closely together (the recent developments are very encouraging).

The 3 types of monographs on extracts have been indeed in the focus of the discussion:

Standardised extracts

This category was defined mainly in order to include a few extracts with constituents of known therapeutic activity. This is not calling into question the basic concept of plant extracts founded on the paradigm that the plant extract in total determines the therapeutic activity. It is clear that this category of standardised extracts will be less important in the future as the prerequisites are very difficult to fulfil. It is evident that Ph. Eur. Groups of Experts cannot be involved in judging the validity of efficacy of *in vitro* or *in vivo* data.

As well, the word 'standardised' has to be distinguished from wordings used in Traditional Herbal Medicinal Products (THMPs). The Ph. Eur. nomenclature should be exclusive for the defined purpose and any confusion by using this word in a different context should be avoided when talking about herbal extracts.

Quantified extracts

An adjustment to a defined range of constituents (especially if those are pharmacologically active markers) reduces the natural variability and certainly increases the quality of an extract. Especially the concept of adjusting more than 1 constituent creates a highly consistent product. As quantified extracts are usually well defined by active markers, it is not necessary to introduce further analytical markers.

Active markers have to be defined under consultation of the regulatory authorities.

Other extracts

Most extracts belong to this type. Neither constituents of known therapeutic activity nor active markers have to be defined or adjusted to. Analytical marker(s) is/are selected to determine the extract in the finished product.

The term 'other' has implied a negative feeling and a kind of disregard in the past although this was not the intention. On the other side a new alternative term like 'characterised' would perhaps devaluate quantified and standardised extracts to be less characterised.

As the term 'other' is not included in the title or the declaration the discussion seems to be idle and as the term 'other' has found its way into other regulations and publications it seems favourable to keep this wording in order to avoid confusion.

It is interesting that within the category 'other extracts' frequent misunderstandings and misinterpretations occur.

The selected analytical markers should be present above a certain concentration limit as a prerequisite for the batch related 100% control of the extract in the pharmaceutical formulation. The real concentrations will be higher in practice; an upper limit must not be stated within the monograph but is part of the validation data (linearity).

This means that analytical markers are not specified within a range (like active markers in quantified extracts) or even as kind of a fixed value (like standardised extracts).

It is mandatory for this type of extract that blending is not allowed in order to achieve a certain amount of the analytical marker.

Sometimes the analytical marker set by the monograph may not be suitable for the analysis of the finished formulation (disturbances by excipients, instability, etc.). If justified the applicant is free to select another suitable marker for the determination of content.

Thus a proposal for a definition for the general monograph on Extracts (0765) would be in this context:

> … *usually a minimum content of one or more analytical marker constituents is defined. In an individual*

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> *monograph for an 'other' extract the chosen analytical marker constitutes one method of assaying the extract. This does not exclude the use of appropriate alternative markers for the assay of these extracts.*

The replacement of an assay established for years by a new one in Ph. Eur. monographs may put industry in a dilemma between modernisation of methods and a chain of subsequent variation processes within an international registration situation.

Especially in cases of standardised and quantified extracts such changes have severe impacts. The stakeholder requirements should be taken into account and a change should only be conducted if it is absolutely necessary.

An expedient is to find a correlation factor between old and new method. Unfortunately such a factor is not very constant between batches in real life and shows fluctuations, as it was demonstrated for example in the cases of milk thistle extract and horse chestnut extract. Thus a mean factor leads only to approximate values. As a factor seems to be the only way out of this dilemma it should be judged with common sense by the relevant authorities. The proposal of the EDQM for an implementation time of a new method in a Ph. Eur. using an established method for assay and gathering data with a new method for a time of 2-3 years is a pragmatic approach and might be helpful in order to achieve a smooth transition.

The alternative approach described by Dr. Helliwell via a new way of declaration with an 'Agreed Reference Content (ARC)' seems to be rather strange.

It may be doubted if a declaration like:

> *"Sennae folium dry extract ethanolic 60% (V/V): corresponding to 60 mg Sennae folium dry extract* ^{ARC}*, where ARC is an Agreed Reference Content for the per cent content of the assayed constituents."*

would be comprehensive for experts or patients.

As well this would completely change the system of declaration, that has been meticulously established over the years. From a more general perspective it seems not feasible to change systems and structures that have been established not too long ago and that work properly and pragmatically in registration and on the market. There is a certain danger for the reputation of herbal products when their basics like extract types, declarations and methodology are subject to many changes. This should be kept in mind and assessed thoroughly before systems that have worked well and pragmatically are changed.