

# Stability Testing of Herbal Medicinal Products

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Particular legal requirements for quality control and stability studies of herbal medicinal products (HMPs) focus on those aspects that are absolutely essential.

Up until recently, Herbal Medicinal Products (HMPs) were mostly marketed in the UK as functional food products under section 12.2 of the Medicines Act. In line with the harmonisation of legislation on herbal medicines across the EU, Directive 2004/24 EC on Traditional Herbal Medicinal Products (THMPD) (1) was implemented in the UK on 30 October 2005. After this, companies were not allowed to introduce new (T)HMPs onto the market without complying with this minimum registration. Observers believe that only a very few products are likely to go the whole course of a full marketing authorisation, as the high requirements that a product has to meet to get an HMP-licence for “well established (medicinal) use” (WEU) make this an extremely difficult venture. Existing products can still be sold until the end of the transitional period, April 2011. Those companies that want to keep their products on the market will need a new registration before that date.

While there has been some leniency compared with the WEU full application concerning proof of efficacy, the requirements for proof of pharmaceutical quality have not been eased. This includes state-of-the-art methods for quality control (QC) and stability data according to the current guidelines (2, 3). Since creation of the required documents and data for submission takes almost one year to prepare, it is high time for companies to start the analytical procedures.

It is appreciated that the Medicines and Healthcare product Regulatory Agency (MHRA) in the UK has been open-minded for goal-oriented discussions right from the start. In Germany, there is already a long tradition of manufacturing, quality control and use of HMPs on a licence (WEU) or registration (traditional) basis. A group of members of the German Medicines Manufacturers' Association (4) founded a working group to discuss special items about quality control and especially stability studies of (T)HMPs (5). Some aspects of the paper prepared by this working group are presented in this article; the aim is to introduce pragmatic solutions to meet the legal requirements, while

at the same time limiting efforts to those that are absolutely essential. The cost of analytical testing represents a major part of the investment for a registration – not only initially on a one-off basis, but for continuing quality control (QC) as well. This has special implications due to the fact that most herbal companies in the UK are Small and Medium-sized Enterprises (SMEs), or the products are of minor importance within the portfolios of ‘Big Pharma’ companies. On the other hand, the THMPD registration presents a number of advantages compared with a licensed WEU herbal medicinal product; these include saving on the costs of expensive clinical trials, facilitating the placing on the market of combination products (for example, combinations of herbal substances with vitamins and minerals), a comparatively faster access to the market (for new products in particular) and interesting claims for herbal OTC products.

## SPECIFIC CHARACTERISTICS OF HERBAL MEDICINAL PRODUCTS

Herbal drugs and preparations are classified in their entirety like the Active Pharmaceutical Ingredient (API) in the HMP. From the chemical and analytical point of view, herbal drugs, herbal preparations and HMPs are complex in nature due to the high number of constituents belonging to different chemical classes and having different analytical behaviours (for example, flavonoids versus essential oils). In many cases, these constituents have only very low concentrations, especially in the finished product.

With regard to the constituents that are responsible for the pharmacological activity of a herbal preparation, the European Pharmacopoeia (6) and the “Quality Guideline” (2) subdivide them into:

- ◆ Standardised extracts
- ◆ Quantified extracts
- ◆ “Other” extracts



Standardised extracts have a declared content of constituents with known therapeutic activity – for example, silymarines in *Silybum marianum*. Therefore, standardised extracts are generally treated in the same way as chemically defined APIs, including for example dissolution testing for solid oral forms.

Quantified extracts are limited to a defined range of constituents that are known to contribute to therapeutic activity – for example, hypericines in *Hypericum perforatum*.

Other extracts without known effective constituents are essentially defined by their production process and their specifications – that is, the ratio of herbal substance to genuine herbal preparation ('drug-extract-ratio', DER, genuine).

### CHOICE OF MARKERS

As described earlier, herbal drugs/preparations are complex mixtures and, to calculate the quantity of a herbal substance or preparation in an HMP (2), single chemically-defined constituents or groups of constituents are used as 'markers'; these are also called 'active markers' for quantified extracts and 'analytical markers' for other extracts. The choice of marker(s) should be justified by its ability to identify and assay in a selective and robust manner (7). It is generally recommended to take account of the following:

- ◆ Literature research about known constituents
- ◆ EP Monograph or other pharmacopoeias and monograph drafts (Pharmeuropa)
- ◆ Analytical feasibility of the marker in the drug substance and drug product
- ◆ The marker's suitability for stability studies
- ◆ Reference standards: availability, quality and costs

Monographs may be a helpful tool to define a marker and can give helpful information about a suitable method. But it should be taken into consideration that these monograph methods can only be used for the purpose mentioned in the pharmacopoeia. Often, these methods are not applicable for a finished product containing this drug substance/preparation because the resulting concentration is too low, or matrix effects lead to a lack of selectivity. Methods and markers mentioned

in pharmacopoeias are intended for batch release purposes only – not for stability studies – and they are, therefore, not often considered for this kind of use. For this reason, the authorities should not bind the applicant to the markers mentioned in the monographs, and should allow alternative approaches in the sense of 'where applicable' and 'if justified'.

### CHOICE OF METHODS

Again, due to the complex composition of herbal preparations, an analysis for QS is mostly done by running high performance liquid chromatography (HPLC) or gas chromatography (GC) and thin layer chromatography (TLC) methods, quantitative determinations by UV-visible spectroscopy or combinations of these. HPLC and GC methods have the benefit that a specific fingerprint chromatogram for identification and purity testing, as well as the detection of single compounds for assay, is possible during one analysis. These specific methods are nowadays generally expected by the authorities. But especially in the case of a combined product with two, three or even more active ingredients, a specific determination and quantification of each drug preparation is often impossible. The use of highly sophisticated and expensive methods – for example, LC and GC mass coupling (LC-MS/GC-MS and so on) that have become part of the methods listed in EP 2.2 (8) – should be limited to a rational level and not become a choice for routine QC. An option to run the determination jointly, for example by UV-visible spectroscopy, is expressly mentioned in the Guideline on Quality of Combination Herbals Medicinal Products/Traditional Herbal Medicinal Products (9). Although the group determination is a useful tool for an assay, the identity of all individual active substances should be proven by appropriate fingerprint chromatograms, or the proof of an individual specific constituent, for example by TLC. If applicable, the identification can be carried out at an earlier production stage, for example, in the primary bulk extract before

**Table 1:** Types of extract and marker (Guideline on Quality of HMPs/THMPs)

Extract	Specification	Marker
Standardised	Content, tolerance	Efficacious constituents (such as silymarines in <i>Silybum marianum</i> )
Quantified	Defined range	Active marker (contributing to the therapeutic activity, for example hypericines in <i>Hypericum perforatum</i> )
Other	Related to the validated analytical range	Analytical marker (for analytical purposes, such as valerenic acids in <i>Valeriana officinalis</i> )

blending and mixing. The necessity and appropriateness of the method combination has to be demonstrated by the applicant.

These general considerations particularly apply to so-called 'mixed extracts'. They originate from the preparation of tea from a mixture of different herbal drugs in the same way that herbal drugs are blended before a joint extraction using mostly organic solvents. The resulting product can be regarded as one extract – that is, one single substance.

THMPs are sometimes combinations of herbal preparations with vitamins and/or minerals. The (pharmacological) action of the vitamins and minerals should only be ancillary and linked to the indication(s) of the herbal preparation. If the vitamins and minerals are categorised as an API of the product, they should be analysed with regard to the effective requirements (chemical defined substances, vitamins, and so on).

#### SHELF-LIFE SPECIFICATIONS

There are generally no differences between specifications set up for HMPs and chemically-defined APIs, but again the special nature of the herbal product should be taken into consideration. Shelf-life specifications are geared to release-specifications. Some tests – like uniformity of mass, identification of colouring agents in tablet coating and so on – can be omitted. On the other hand, it may be necessary to add some tests during stability testing, for example, fingerprint chromatograms, if applicable, or water content.

The specifications for assay deserve a closer look. The common limits for assay of  $\pm 5$  per cent of the declared value (10) should be applied to the standardised extracts. For the batch release of quantified and other extracts, the limits should also be  $\pm 5$  per cent, unless it is justified to

widen the range up to  $\pm 10$  per cent or even higher. This may be justified by low concentrations of the marker in the finished product, which will have a negative influence on the method's precision.

Additionally, due to the influences of climate, harvesting and biological variance, the natural variation of the marker content needs to be taken into account. For example, the linearity of the method may be tested over a range of 40-160 per cent of the marker's expected content in the extract and/or product. During stability testing, a setting up of the limits to  $\pm 10$  per cent is accepted for the finished product, by the justification of matrix effects (placebo), the lack of precision and selectivity (combination products) and the low analyte concentrations. Considering that the marker content cannot be defined to a specified level, the relative changes from the starting value are specified (95-105 per cent or 90-110 per cent 'from the initial value').

#### ASPECTS SPECIFIC TO HMPs

The complex nature of HMPs is not only influenced by the factors mentioned above, but also by the production process. During production – from cultivation of the plant to the finished product – a lot of changes take place in the chemical structure of the constituents and these must not stop at the end of the production cycle. These changes are more often to be found in liquid preparations than in solid forms. Nevertheless, they should not necessarily be seen as 'degradation' as would be the case for chemical APIs. As an example, the hydrolysis of acetoxyvaleric acid to hydroxyvaleric acid, and even down to valeric acid by dehydroxylation in valerian roots products, does not represent degradation in the sense of a loss of activity. In this case, determination and specification of the "sum of valeric acids" is reasonable and recommended.

The guideline on stability testing of existing drug substances and related finished products was established for chemically-defined substances, and does not take account of the particular case of HMPs, although some specific exemptions are included. For herbal drugs and herbal drug preparations, a testing under accelerated or intermediate conditions may be omitted. This should apply to finished products as well, because it is known that most products fail at 30°C/65 per cent relative humidity (RH) and at 40°C/75 per cent RH in particular. It would be highly appreciated if case studies in the literature would be accepted for justification by the authorities; however, the requirements for adequate labelling still endure. If intermediate conditions are

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tested, the three-month time-point is omitted (that is, 0, 6, 9 and 12 months). In some cases of combination products, it is hardly possible to provide the required two batches of each extract at the same time due to different harvesting times. This should be taken into consideration when planning the schedule for stability studies. Moreover, due to a possible lack of availability of different batches of the drug substance(s), it may also prove difficult to provide the required two or three batches of the finished product.

Multi-dose preparations are very common among HMPs, particularly in the case of liquid extract preparations and finished products thereof. For this reason, in-use stability data are obligatory for these preparations (11). The following items, amongst others, should be taken into consideration:

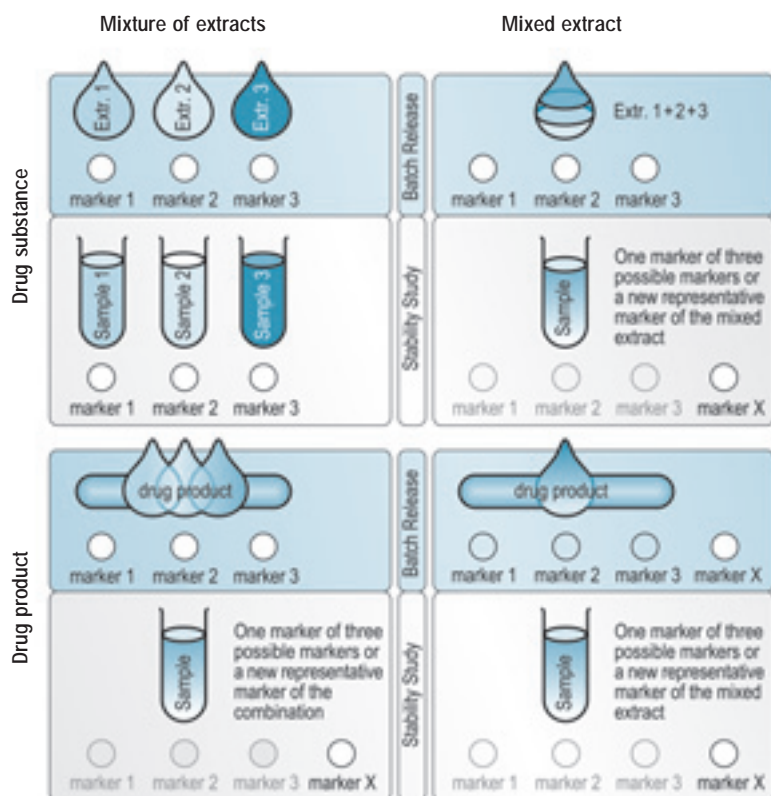
- ◆ At least two batches of the finished product, one to be tested at the end of shelf-life
- ◆ Worst-case or bracketing (12) rationale for skip-testing for different packaging sizes
- ◆ Simulation of sampling under 'real-life' conditions
- ◆ Storage under labelled conditions
- ◆ Choice of testing parameters, for example, clarity of the solution

### ONGOING STABILITY

After the revision of Chapters 1 and 6 of the EU GMP Guidelines (13) in 2006, an annual Product Quality Review (PQR) became mandatory for all licensed products on the market. This continuous revision of the consistency and validity of the entire manufacturing process also includes a stability monitoring programme. It should be kept in mind that ongoing stability testing differs from other stability tests with regard to its regulatory and legal background.

HMPs are not specifically excluded and so the requirements concerning PQR and the integrated ongoing stability studies apply for Herbals as well, in a non-restrictive manner. The categorical requirements of the GMP Guidelines for ongoing stability testing state the following:

- ◆ All medicinal products/formulations have to be tested



- ◆ All finished products and, where appropriate, bulk products also have to be tested (for example, when stored or shipped for longer periods)
- ◆ Requirements apply in principle to every product in every dosage and pack size or (primary) packaging type/package
- ◆ Tests have to be carried out continuously – usually one batch a year
- ◆ Studies are to be carried out under long-term conditions (for example, 25°C / 60 per cent RH) continuously over the period of the labelled shelf-life

In principle, all decisions that affect the test protocol, the frequency of testing and the choice of test samples should be product-based, targeted and based on a risk analysis. In this context, the requirements for herbal products should be paid particular attention. An overview of pragmatic approaches that apply equally to HMPs has been discussed in the literature (14).

### CONCLUSION

The stability testing of HMPs, in view of the complex and natural composition of their constituents, should take account of the particular requirements and

**Figure 1:** Use of markers for testing in combination products, mixtures of extracts and 'mixed extracts'

conditions. Although studies are generally comparable with those for products containing chemically-defined substances, the specific features for herbals are as follows:

- ◆ Two batches of the drug substance and three batches of drug product
- ◆ Herbal drug substance at only 25°C/60 per cent RH, with no requirement for intermediate/accelerated testing
- ◆ No three-month testing-point at 30°C/65 per cent RH for the drug product
- ◆ Assay of marker substances for 'quantified' and 'other' extracts
- ◆ Choice of methods, combination of methods and fingerprints
- ◆ Assay  $\pm 5$  per cent or  $\pm 10$  per cent from the initial value for quantified and other extracts (rather than for the declared value, as for standardised extracts and chemical APIs)
- ◆ A requirement for ongoing stability-studies

To summarise, the new legal requirements will lead to increased efforts in the analytical quality control of HMPs and, as a consequence, will lead to rising costs for the registration, production and maintenance of a product. But, from a positive aspect, there will be a clearly defined level of quality established for (T)HMPs

on the market, enabling marketing statements to be made re a product's excellence and indications officially approved by the MHRA. Furthermore, UK products will be adjusted to the EU level of quality and acceptance, opening up new markets across Europe. Last but not least, from a safety aspect, consumers will benefit from the new THMPD regulations.

#### Acknowledgement

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