On-going Stability Testing of Herbal Medicinal Products

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Abstract

The principles used for stability testing of herbal medicinal products in the marketing authorisation/registration process apply for on-going stability studies as well. However, also for on-going stability testing the particular characteristics of herbal medicinal products must be taken into account. As some requirements like statistical evaluation and reaction on atypical trends and out-of-specification (OOS) results are difficult to implement for herbal medicinal products, practical approaches are proposed on how to handle critical and uncritical deviations. Critical deviations influence the overall quality, safety or efficacy of the product. They are regarded as confirmed OOS results in the sense of the EU GMP Guideline and should be reported to the competent authority. Minor OOS results may lead to further measures such as e.g. use of alternative markers or broadening of specification ranges, depending on the individual case. The intention of this article is to provide the Marketing Authorisation Holders (MAHs) and the responsible personnel, in particular the Qualified Persons (QPs), with a comprehensive overview on current practical experiences and to give support with regard to the interpretation of results and discussions with the competent authorities.

Zusammenfassung

Fortlaufende Stabilitätsprüfung bei pflanzlichen Arzneimitteln

Die Prinzipien der Stabilitätsprüfung pflanzlicher Arzneimittel für Zulassungs-/Registrierungsverfahren sind auch für die fortlaufenden Stabilitätsstudien anwendbar. Für letztere müssen jedoch auch die Besonderheiten pflanzlicher Arzneimittel berücksichtigt werden. Da einige Anforderungen wie statistische Auswertung und Reaktionen auf atypische Trends und OOS (out-of-specification)-Ergebnisse für pflanzliche Arzneimittel schwierig umsetzbar sind, werden praktische Ansätze vorgeschlagen, wie kritische und unkritische Abweichungen zu behandeln sind. Kritische Abweichungen beeinflussen die Gesamtqualität, Sicherheit oder Wirksamkeit des Produktes. Sie werden als „bestätigte OOS“ („confirmed OOS“)-Ergebnisse im Sinne des EU-GMP-Leitfadens betrachtet und müssen der zuständigen Behörde gemeldet werden. „Geringfügige OOS“ („minor OOS“)-Ergebnisse können in Abhängigkeit vom Einzelfall zu weiteren Maßnahmen wie z. B. der Verwendung alternativer Leitsubstanzen oder der Ausweitung von Spezifikationsgrenzen führen. Mit diesem Beitrag soll den Zulassungsinhabern und den verantwortlichen Mitarbeitern, insbesondere den Sachkundigen Personen (QPs), ein umfassender Überblick über aktuelle praktische Erfahrungen und eine Hilfestellung bei der Interpretation von Ergebnissen und den Diskussionen mit den zuständigen Behörden gegeben werden.

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1. Introduction

Based on the requirements of the European guideline on "Stability Testing of Existing Active Substances and Related Finished Products" [1], a previous contribution [2] has described the regulatory standards for stability testing of herbal medicinal products and presented proposals for appropriate approaches considering practical experiences of manufacturers. Herbal medicinal products have to fulfill the legal requirements with regard to quality including stability testing, but have certain particularities such as a complex nature, an often low concentration of constituents and a natural variability of their raw materials. Thus the mentioned publication triggered discussions on appropriate stability testing of herbal medicinal products on a European level at the same time when the HMPC documents [3,4] were prepared.

The same particularities have to be addressed and discussed in the context of on-going stability testing as well, although it has a different regulatory and legal background. For this reason, similar approaches for on-going stability testing are proposed in the following. However, as already stated in the above-mentioned publication [2], these proposals shall in no way query the basic requirements on the quality of herbal medicinal products, but rather intend to take account of their particular characteristics.

2. Legal basis

The revised version of Chapter 1 of the EU GMP Guideline [5] came into force in 2006. Item 1.4 makes the annual Product Quality Review (PQR) compulsory for all licensed products. This continuous revision of the consistency and validity of the entire manufacturing process also includes a stability monitoring programme as listed under subitem vii. The need to perform on-going stability tests is specified in Chapter 6, in particular Chapter 6.23 ff. of the EU GMP Guideline [6]. It applies to licensed medicinal products which are currently on the market and does not exclude herbal medicinal products. Therefore, the necessity to prepare a PQR and to conduct on-going stability studies applies as well to herbal medicinal products without any restriction.

In accordance with the EU GMP Guideline on the on-going stability programme (chapter 6.23–6.33) [6], the shelf-life of the marketed product should be monitored using an appropriate continuous programme which will permit the detection of any stability issue associated with the formulation in the marketed package (6.23). The purpose of the on-going stability programme is to monitor whether the product remains, and can be expected to remain, within the specification under the labelled storage conditions (6.24).

On-going stability studies are intended to prove that over the period of its labelled shelf-life and under "real life conditions", the product maintains the quality defined in the marketing authorisation/registration documents. They have to be distinguished from follow-up stability studies: if the submission of a new application does not include long-term stability data on three production scale batches, a commitment is needed that follow-up stability studies on the first three production batches through the proposed shelf-life will be performed [1].

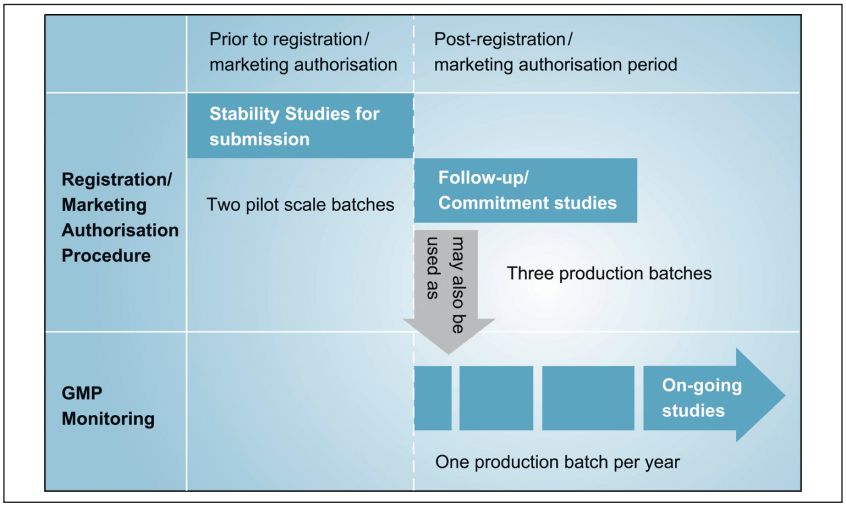
The protocol for the on-going stability programme can be different from that of the initial long-term stability study as submitted in the marketing authorisation dossier if justified and documented in the protocol (e.g. with regard to the frequency of testing) (6.28) [6].

Fig. 1 illustrates the differentiation between stability studies for submission, follow-up and on-going stability studies.

According to the EU GMP Guideline (chapter 6.23–6.33) [6], the requirements for on-going stability testing are as follows:

- All medicinal products/formulations have to be tested.
- All finished products, and in exceptional cases bulk and intermediate products, have to be tested.
- Studies should be performed in principle for each product in each dosage form and pack size or (primary) packaging type/package.

Figure 1



Stability studies in the stages of pharmaceutical development, follow-up and on-going stability studies for a new application of a registration/marketing authorisation in a typical manner for herbal medicinal products (follow-up studies may be omitted if data from three production batches has already been submitted).

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- Studies have to be carried out continuously, usually one batch per year at least over the period of the labelled shelf-life under long-term conditions (e.g. 25 °C / 60 % rh).

A general approach for implementation of on-going stability testing does not exist because the test protocol must be set up for each individual product. Tests following storage under intermediate and accelerated conditions [1] are in general not regarded useful for herbal medicinal products [7] and should be carried out only in special cases when supplementary information is required.

3. Proposals for a pragmatic approach for on-going stability testing

3.1 Reduction of the extent of testing

Item 6.28 of the EU GMP Guidelines [6] specifically states that the protocol for the on-going stability programme may differ from that of the initial long-term stability protocol [1], giving a reduction in the frequency of testing as an example. An overview of pragmatic approaches can be found in literature [8,9,10]. These approaches apply for herbal medicinal products in the same manner.

The principles of Bracketing [11], which have been established for chemically defined medicinal products, are in most cases not applicable for herbal medicinal products, because often only one strength is available. With regard to multi-dose containers only the most sensitive container size would have to be tested on a "worst case scenario" basis. Alternatively, it is proposed to use a rolling scheme in which all pack sizes are tested subsequently, i. e. one of the pack sizes per year [12].

Furthermore, the principle of Matrixing [11] is not applicable due to the rather low number of batches produced of most herbal medicinal products.

Table 1

Protocol with reduced frequency of testing for an on-going study (solid formulation). T = test during on-going study; (t) = optional test; o = omitted test (as compared to studies performed for marketing authorisation/registration).

Test	Start	T3	T6	T9	T12	T18	T24	T36
Organoleptic	T	(t)	(t)	(t)	T	(t)	T	T
Mean weight	T	o	o	o	T	o	T	T
Disintegration time	T	o	o	o	T	o	o	T
TLC fingerprint	T	o	o	o	T	o	T	T
HPLC fingerprint	T	o	o	o	T	o	T	T
Assay (marker)	T	o	o	o	T	o	T	T
Microbiological quality	T	o	o	o	(t)	o	o	T

For this reason, instead of Bracketing and Matrixing a specific modified testing programme including reduced testing frequency is considered an appropriate approach for herbal medicinal products, in particular if it has been shown in former studies that a test parameter is uncritical. Table 1 shows an exemplary schedule for the reduced testing of a herbal medicinal product in a solid dosage form for oral use. It should be noted that at the end of the shelf-life, all test parameters should be checked again in order to prove stability over the entire shelf-life.

"Critical" parameters are those which have a significant impact on the overall quality, safety and efficacy of the product. This may be e. g. the assay in case of standardized extracts or of known toxicologically relevant compounds. Usually also the organoleptic testing is classified as "critical", and it is recommended to check this parameter more frequently. In general, uncritical parameters do not change during stability studies or only in negligible variations without any impact on the overall quality, safety or efficacy of the product. Skip testing is possible, e. g. with regard to the ethanol content in liquid formulations if the density is tested instead. The assessment must be made product-specific and depends on the experiences and the results of the stability studies.

In accordance with item 6.28 of the EU GMP Guideline [6] a justification and documentation is required if the on-going stability programme is modified as compared to the marketing authorisation dossier. For this purpose and also for the evaluation whether a parameter is classified as critical or uncritical, reference is made to results of former stability studies of the identical product as well as to experiences with comparable preparations which may provide additional information.

Due to their natural origin, questions on microbiological quality arise more often for herbal medicinal products than for chemically defined medicinal products. For this reason, particularly in case of new applications, a detailed microbiological investigation programme is often set up for herbal medicinal products. However, for many herbal drugs and extracts prepared thereof, a higher risk of microbiological problems does not exist in practice. E.g. solid preparations or liquid preparations with sufficient ethanol content can be tested less frequently. Therefore it may be acceptable to investigate the microbiological quality only at the beginning and at the end of a stability study.

3.2 Specifications

Specifications are set within the marketing authorisation/registration procedure for batch release and stability testing. They are also binding for on-going stability testing but may lead to problems if the limits have been set too tight at an early stage. Therefore it has been proposed that within authorisation procedures applicants should work towards setting specifications which can be regularly met in practice, i. e. in later on-going studies [13].

Adaptation of specifications may become necessary at a later stage, e. g. in case of new findings from on-going stability studies when broader ranges are required due to confirmed out-of-specification (OOS) results followed by a risk analysis (see [12]). In this case the results of on-going stability studies should be used as an argument when a variation of the marketing authorisation/registration with regard to e. g. broadening of specification ranges is submitted (see also [4] and further explanations below, chapter 3.4, consequences of OOS results).

3.3 Evaluation of results

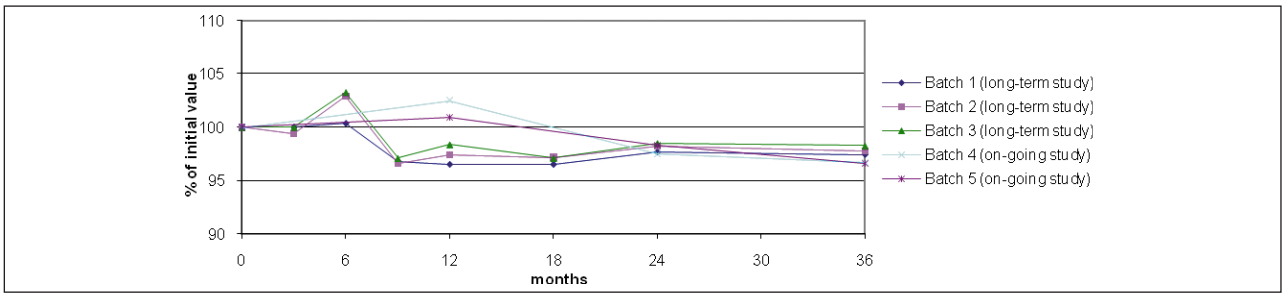
Suitable data analysis procedures have to be established which allow retrospective as well as prospective evaluation. For this purpose, data from previous studies may be used as a basis for evaluation of results from on-going stability studies.

According to chapter 6.32 of the EU GMP Guideline [6], OOS or significant atypical trends should be investigated and any confirmed OOS result or significant negative trend should be reported to the competent authorities. The possible impact on batches on the market should be considered in accordance with chapter 8 of the EU GMP Guideline [14] and in consultation with the competent authorities. Depending on available data, a trend analysis refers to the results obtained at different time points of testing one batch as well as to the results from several batches of the respective product.

In the following, a trend analysis is discussed for the assay as an example. The EU GMP Guideline requires that at the individual time points it must be stated whether it can be assumed that e. g. the active substance (i. e. the extract) content is likely to remain within the specified limits throughout shelf-life. Due to the complexity of the herbal matrix and the analytical determination of very low concentrated analytical markers the variability of results is higher as compared to chemical substances. Furthermore the relationship between the assay of a marker substance and the time cannot be assumed to be linear. Pooling of batches according to the ICH Q1E guideline on the evaluation of stability data [15] is not possible because the regression lines from different batches have often different slopes and intercepts. Therefore a trend analysis is in general not suitable for herbal preparations.

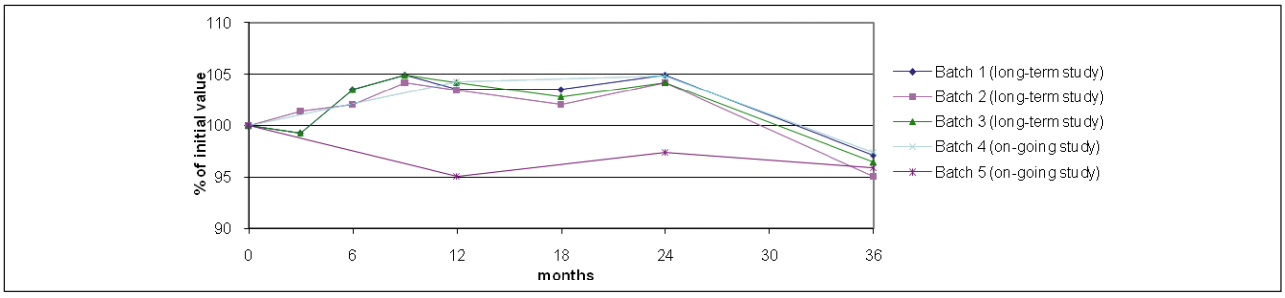
Depending on the analytical method used, variations in the assay can occur, particularly in the case of group determinations or complex (non-baseline) separations (according to the respective Note for Guidance on combination products [16]). Fig. 2 and 3 describe examples of the

Figure 2



Assay of thymol in a combination product of thyme and primrose.

Figure 3



Assay of primula acid 1 in a combination product of thyme and primrose.

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assay variation of thymol and primula acid 1 in a combination product of thyme and primrose. These examples show that a batch which reached the specified limit already after 12 months can nevertheless still be within the specified range after 36 months (specification limit 95–105 %). The degradation or transformation of marker substances, respectively, often does not follow clearly defined kinetics due to the complexity of the material and/or constituents.

■ 3.4 Out-of-specification (OOS) results

According to chapter 6.32 [6] of the EU GMP Guideline, confirmed OOS results lead to important consequences because of the obligation to report them to the competent authorities.

Due to their complex nature and the high variability in their composition which occurs even without any changes of the production processes, OOS results are more probable in case of herbal medicinal products as compared to other medicinal products. Physical changes in the composition may lead e. g. to an increased or decreased water content which may influence the results of an assay and thus produce OOS results when the specified narrow limits are exceeded. Furthermore, in stability studies performed during pharmaceutical development such deviations are normally not detected, because the batches are often produced subsequently without or with only small variations in the composition of the herbal extracts. However, since on-going stability testing is performed over a longer period using production batches, higher variations can be expected due to the natural variability of the raw material (climate etc.). In addition, the precision of the analytical method used for the assay of herbal medicinal products must be taken into account. For this reason it is important to consider the uncertainty of the applied method during evaluation of the results [2].

Consequences of OOS results

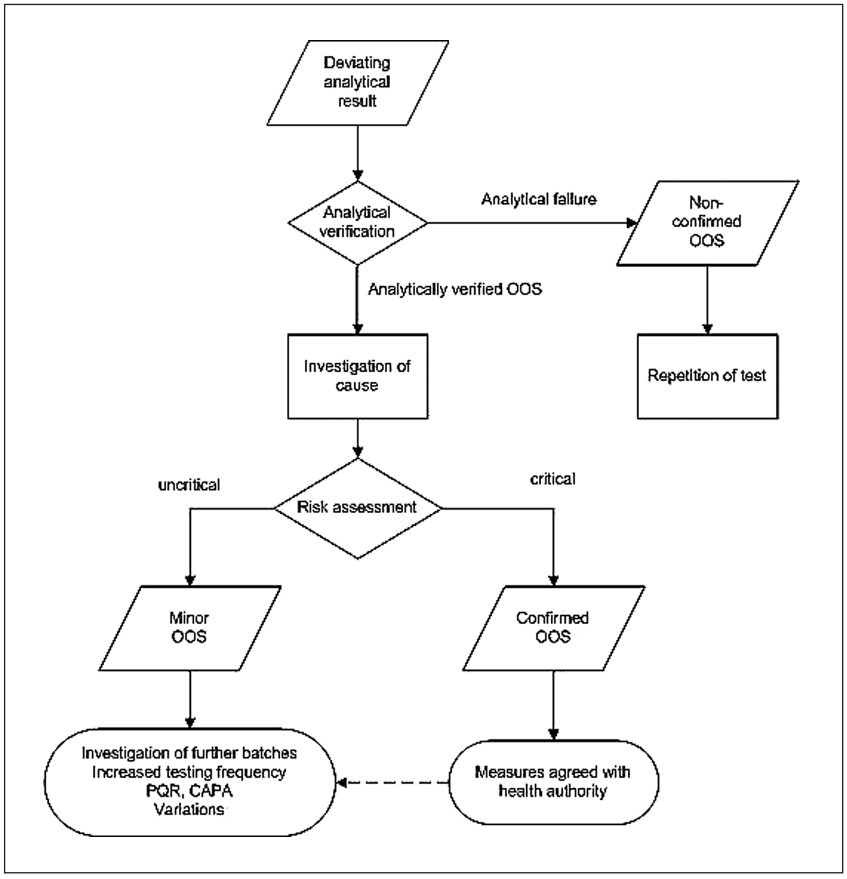
In order to specify which steps should be undertaken in case of OOS results, an appropriate Standard Operating Procedure (SOP) should be installed. Fig. 4 shows a decision tree which explains the different options how to proceed when a deviating analytical result is found. In case of an analytically verified OOS an individual risk assessment should be performed in agreement with the respective Qualified Person(s).

When a deviating result has been analytically verified, an investigation of cause is performed. In order to obtain more information on the product and to assess the relevance of the deviation, this might include a detailed assessment of the manufacturing process as well as testing of retention samples and/or samples obtained from the market. The subsequent risk assessment examines whether an uncritical or a critical deviation exists.

Critical deviations are those which influence the safety, efficacy or overall quality of the product. They are regarded as confirmed OOS results in the sense of chapter 6.32 [6] of the EU GMP Guideline and should be reported to the competent authority. They lead to further investigations in agreement with the authority, such as

- a review of sensitive or relevant areas in the production with the attempt to identify the cause and possible impact on other batches/products,
- a critical review of the labelled stability, and/or if necessary and justified in exceptional cases, a recall of the affected product batch,
- discussion and implementation of measures to avoid errors (corrective and protective actions, CAPA).

■ **Figure 4**



Decision tree with options how to proceed when a deviating analytical result is found.

Uncritical deviations are classified as minor OOS. Anyway, they should be discussed in the respective PQR and the corresponding CAPA processes as defined in the EU GMP Guideline. They may lead to one or more of the following measures, depending on the individual case:

- Investigation of further batches in order to update the stability protocol.
- Increased testing frequency in order to obtain more data and further information on the quality.
- Variations, e. g. if justified, adaptation of specification and/or test procedure(s) or the use of alternative markers or additional fingerprint testing.

This corresponds to the principles described in an EMA Reflection Paper [17] and is accepted by the health authorities, e. g. the German BfArM. In any case the results must be assessed and authorised by the Qualified Person and included in the PQR.

A prospective broadening of the range during pharmaceutical development in order to take into consideration potential higher deviations during on-going stability testing is, however, not permitted.

An example of OOS results can be increasing water content and/or an increasing tablet/capsule mass in solid preparations caused by hygroscopic dry extracts. In this case the finished medicinal product has to be regarded in its entirety and the relevance of this deviation has to be evaluated during a risk assessment. If all other testing parameters are within the specification, particularly the assay of the active substance, disintegration time, microbiological quality and appearance, deviations in tablet mass and water content may be classified as a minor OOS.

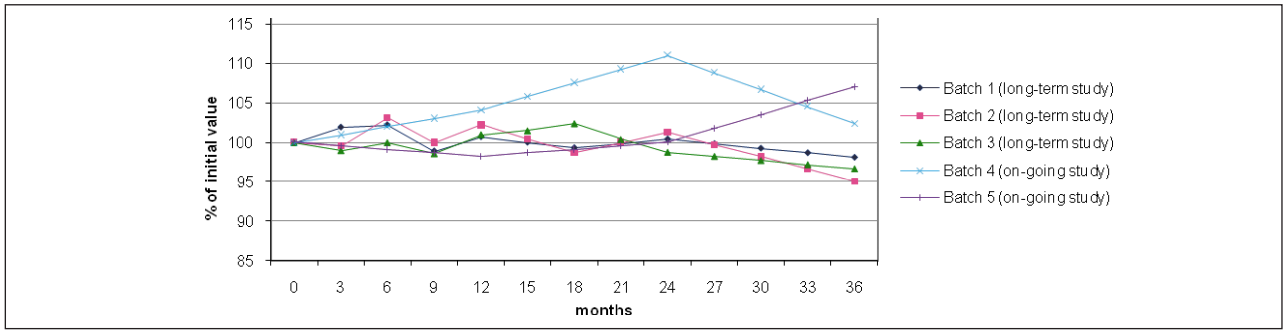
A further example of an OOS result obtained for herbal tea of hawthorn leaf with flower (specification limits 90–110 %) is given in Fig. 5.

Fig. 5 shows a temporary OOS result which occurred during on-going stability testing but not within the long-term stability studies in the dossier. Such temporary deviations may typically occur during stability testing of herbal medicinal products. In this case they were not regarded as relevant for the safety, efficacy or overall quality of the product during the risk assessment and were therefore classified as minor OOS. With a view to the results obtained after 36 months, it is obvious that a balanced interpretation and careful consideration of potential consequences is necessary.

Another example (Fig. 6) shows the assay of hyperoside in film-coated tablets containing hawthorn leaf with flower dry extract.

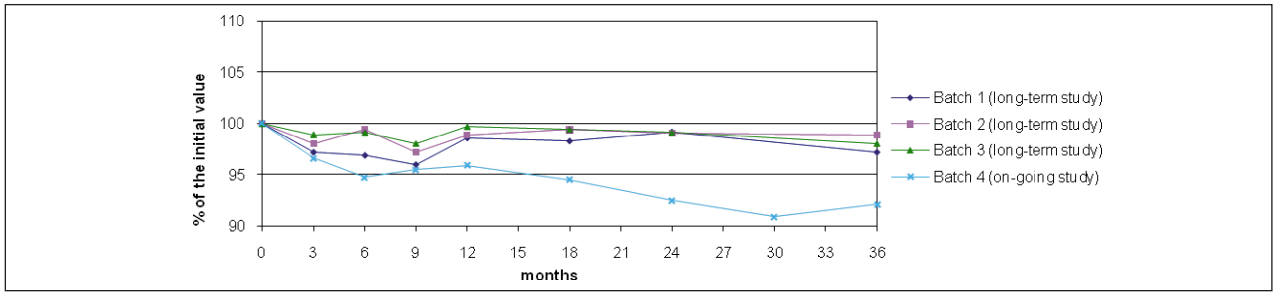
In this case the on-going stability of the first production batch was additionally part of the follow-up studies. For marketing authorisation the shelf-life specification for hyperoside was set at ± 5 % of the initial value.

Figure 5



Assay of hawthorn leaf with flower in a herbal tea (according to the Ph. Eur. monograph "Crataegi folium cum flore") showing the content of hyperoside used as a marker.

Figure 6



Stability of hyperoside in film-coated tablets containing hawthorn leaf with flower dry extract.

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The three pilot batches fulfilled the specification over a period of 36 months, resulting in a shelf-life of 3 years for the marketed product.

With a view to the results of T_{24}, however, the marketing authorisation holder reduced the shelf-life to 24 months and broadened the specification to 90–110 % of the initial value by submitting a variation. In addition, the local health authorities required risk assessment for the batches already marketed with a shelf-life of 36 months. By combination of these three measures a batch recall could be avoided. However, based on the results of T_{30} and T_{36}, the former shelf-life of 36 months was again approved by the authority.

The evaluation of fingerprint analyses can be used additionally for the assessment of OOS results obtained with marker substances. Taking into account that an analytical marker serves as an "analytical tool" only and often very low amounts (traces) of the marker have to be analysed (small changes of the concentration lead to high deviations expressed as percentage of the initial value), fingerprint analyses provide more information on the entirety of the constituents of a herbal medicinal product.

■ 3.5 Herbal teas

Herbal tea formulations usually only contain herbal drugs, packed in flexible packaging materials with limited protection possibilities, even if packaging materials with a barrier coating are used. Therefore especially essential oils would be lost during storage, and the amount lost during storage often exceeds the usually accepted limits of ±5 % for standardised or ±10 %, respectively, for non-standardised herbal preparations.

As explained earlier [2], a loss of markers or constituents like essential oils up to 20 % from the initial value or even higher may occur which is well known for a lot of herbal teas. Hence, as also considered by the authorities for herbal teas in item 19 of the Q & A document [4], the concept of different acceptance criteria for release versus shelf-life specification can be applied to herbal teas.

Although the option of defining wider limits is generally not yet accepted, compliance with the limits defined in the respective monographs of the Pharmacopoeia at the end of the shelf-life should be acceptable as a specification limit.

For this reason, there is no need to restrict the decrease to 5 or 10 % of the initial amount of essential oil, if the amount of this substance is higher than or equal to the limits defined in the Pharmacopoeia. It is proposed to accept this approach also for stability of herbal teas in general, e. g. initial stability studies as well as follow-up and on-going stability.

■ 3.6 Combination products

Combinations of herbal medicinal products consist of more than one single herbal drug or the respective extract. During the development of the combination product its stability has been investigated and the critical components are already known. This should be taken into consideration also during on-going stability testing.

In general there are two options for quantification: a group determination if extracts of different herbal drugs can be quantified by the same marker substance (e. g. rutoside as a representative of flavonoids), or the determination of each individual compound by individual markers.

For herbal combination products the development and validation of assay methods used for batch specific control to determine each active substance via marker substances is always challenging. It is quite evident that OOS results are more probable the more herbal substances and/or herbal preparations are combined.

Table 2 shows an example of a solid combination product for oral use containing three herbal preparations. A slight decrease (below the specification limit of 90 % of the initial value) of the marker content

■ **Table 2**

Results of a combination product during an on-going study (exemplary).

Test parameters	Data T0	Data T6	Data T12	Data T18	Data T24
Organoleptic test	All results comply with the specification.				
Loss on drying					
Average mass					
Disintegration time					
Resistance to crushing					
Identification and purity (via analytical marker)					
TLC fingerprint(s) extract A, B, C					
HPLC fingerprint(s) extract A B, C					
Quantitative analysis of the active substances (via analytical marker)					
Content of extract A relative to initial value in %	100.0	98.0	99.0	98.2	97.6
Content of extract B relative to initial value in %	100.0	100.1	102.0	102.2	98.7
Content of extract C relative to initial value in %	100.0	98.0	99.2	**88.4**	**88.2**
Microbiological quality	Conform				

in one active substance is observed after 18 and 24 months. All other parameters tested still comply with the specification.

Although a comprehensive and careful failure investigation (including manufacturing of extract and finished product) was done on the OOS results, a cause for this deviation could not be found. In order to ensure the quality of the product in the market, a retention sample was tested after 18 months. The result of 97.4 % content of extract C relative to initial value was in compliance with the specification.

However, even a decrease of one (non-standardized) combination partner in a herbal combination product would normally not lead to question the quality and efficacy in its entirety. A pragmatic approach to solve this formal problem is to justify and to accept a wider range for the specification of the marker substance as explained in the Q & A document, item 18 [4].

The principles pointed out in chapter 3.4 of this publication (OOS results) apply for combination products in the same manner. A substantiated risk assessment should be performed to confirm that a deviation has no negative impact on the product and can be classified as minor OOS.

For mixed extracts, a pragmatic approach to perform stability studies was demonstrated in an earlier publication [2]. This principle, in particular the option of group determinations, is applicable for on-going stability testing as well.

4. Conclusions

The conduction of on-going studies which are intended to guarantee uniform stability of products in the market and to detect, explain and avoid potential deviations requires particular attention due to the complex nature and the multi-component character of herbal medicinal products. Natural variability in the composition may lead to particular problems in the determination of stability and the assessment of its importance for the overall quality, safety and efficacy. As some general requirements concerning on-going stability studies and the PQR like statistical evaluation and reaction on atypical trends and OOS results are difficult to apply to herbal medicinal products, different practical approaches should be utilized. In particular, a balanced interpretation of on-going stability studies and of deviating analytical results is absolutely required.

The respective SOP clearly defines the procedure to be followed in case of a deviating analytical result. After its analytical verification, the risk assessment examines whether an uncritical or a critical deviation exists. Only critical deviations i. e. those which influence the overall quality, safety or efficacy of the product are regarded as confirmed OOS results in the sense of the EU GMP Guideline and should be reported to the competent authority. Minor OOS results may lead to further measures such as e. g. use of alternative markers or broadening of specification ranges, depending on the individual case. As on-going stability studies accompany products over their entire life cycle, for each individual case a skilled and pertinent planning of the testing protocol is necessary.

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