Change Management of Herbal Medicinal Products

A pragmatic and risk-based approach to meet regulatory requirements

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Life cycle management in general plays an important and increasing role for medicinal products. Adaption to technical progress and simplification of processes require procedural changes that may lead to modification of documentation and variations within the marketing authorisation dossier. For such modifications pragmatic solutions are necessary which take legal requirements as well as feasibility in daily practice and economic aspects into account. Due to their particularities the risk assessment and change management of herbal medicinal products often differ from chemically defined drug products. For this reason proposals for solution are developed which may help to implement the rules for variations within the marketing authorisation dossier for herbal medicinal products in an adequate and reasonable manner. The overall goal is to produce state-of-the art herbal medicinal products and to enable further technical progress in a very strictly regulated area.

1. Introduction

Life cycle management in general plays an important and increasing role for medicinal products. Adaption to technical progress, simplification of processes, optimisation of quality and elimination of faults/deficiencies require procedural changes that may lead to modification of documentation and variations within the marketing authorisation dossier. These changes take place in an extensively regulated environment. The marketing authorisation, granted by the competent health authority, is the model in which the production processes, specifications and quality control methods are fixed. The management of the required changes during each product´s life cycle plays an important role within all pharmaceutical companies including companies manufacturing herbal medicinal products (HMPs). Due to the particularities of HMPs, risk assessment and change management in these cases, however, often differ from the situation of chemically defined drug products. Within this publication, the authors would like to reflect the existing and relevant differences and develop solution proposals of how to follow the rules of the variation guideline for HMPs in an adequate and reasonable manner.

2. Particularities of Herbal Medicinal Products

HMPs have to fulfil the same legal requirements with regard to quality including stability testing as chemically defined pharmaceutical products [1]. However, they have certain particularities due to the complex nature of their raw materials as well as often low concentrations and a natural variability in the composition of their constituents. Therefore, herbal preparations, e. g. extracts, are complex mixtures which contain a large variety of constituents in different concentrations representing different chemical classes. According to the relevant guidelines, the entire herbal preparation is regarded as the active substance of the medicinal product [2].

A naturally occurring variability of the composition of constituents is typical and product-immanent, especially with regard to different origins, sites or years of harvest. However, such variabilities are not necessarily linked to pharmacological and therapeutic effects. Thus, an assessment of changes and their consequences needs particular consideration.

The variability of the composition of herbal substances and preparations is taken into account by the specifications of the Pharmacopoeias and of the manufacturers. This is why the corresponding pharmacopoeia monographs on herbal drugs require only minimum levels for defined constituents.

Due to their natural origin, herbal preparations and HMPs show many analytical challenges, e. g. an exhaustive analytical characterisation of plant extracts is generally not feasible. Furthermore, in many cases individual constituents used as markers have a low concentration. As a consequence, the complex ma-

trix requires a complex sample preparation and sophisticated analytical techniques for the determination of such individual components.

Individual European Pharmacopoeia monographs define quality requirements for herbal drugs – independent from cultivation sites or geographical origin. The same applies to HMPC monographs which define assessment criteria for efficacy and safety. A change, e.g. of cultivation sites or geographic origins, which does not affect the pharmacopoeial requirements, should therefore be acceptable without variation application or at least without prior approval of a variation application. This is of particular relevance because changes in sourcing are often a consequence of conditions during growing of plants or harvesting which cannot always be influenced by the manufacturer of the HMP. All options to interpret guidance documents in a pragmatic manner should be applied by manufacturers and authorities in order to avoid over-regulation.

In order to produce state-of-the-art herbal medicinal products and to enable further technical progress in a very strictly regulated area, intelligent solutions are required taking into account economic aspects as well. This, however, does not only include regulatory requirements, but also in-house processes and communication as well as cooperation with suppliers and external units as regards the implementation of changes.

3. Changes Based on GMP Requirements

Besides regulatory changes and technical progress, requirements for change often result from the need to comply with Good Manufacturing Practice (GMP) rules. In the context of annual Product Quality Reviews (PQRs) recurring deviations in the manufacturing process or Out of Specification (OOS) results of in process controls, control of starting material/finished product parameters or within the stability monitoring may be detected. These observations are assessed and may lead to the obligation to define Corrective and Preventive Action (CAPA) measures. These CAPAs in turn may trigger changes within the dossier through a variation of the marketing authorisation.

However, deviations and OOS results should be evaluated carefully on a case-by-case basis. One of the first steps of the change control procedure should clarify whether the results are one-time events and/or do not have significant impact on the quality of the medicinal product. The decision to submit a variation to the dossier of the marketing authorisation or not and which kind of variation is appropriate should be based on a risk assessment.

Moreover, in the everyday practice of a pharmaceutical manufacturer situations can arise where short-term variances in sourcing, production and quality control are unavoidable to guarantee the availability of the product. Often this has to be decided before the required variation has been approved, e. g. within only a few days. These variances cannot be ruled out due to the limited time. In these cases a GMP-compliant approach is possible by performing the process of a planned deviation covered by a corresponding risk assessment. In this context, appropriate specifications in the dossier as well as GACP/GMP requirements provide a sufficient framework to ensure the quality and safety of the product. In line with internal change control procedure and the responsibility of the manufacturer, an immediate update of the marketing authorisation dossier via variation application prior to implementation is not necessary.

4. Approach to Implement Changes

The intention of this publication is to propose pragmatic solutions when modifications and variations within the dossier are made which may be caused by adaption to technical progress, simplification of processes, optimisation and advancement of quality as well as elimination of faults/deficiencies. Such proposed solutions take legal requirements and recommendations of the respective guidelines but also economic aspects as well as issues of environment and sustainability into account. The overall goal is to produce state-of-the-art herbal medicinal products and to enable further technical progress in a very strictly regulated area.

The EMA reflection paper on "minor deviations" [3] recommends *"to minimize future occurrence of deviations that are caused by unnecessary detail. It should be noted that details that fall within the scope of GMP are inappropriate for inclusion in submissions. Updates to detail in the dossier, including removal of unnecessary detail, may be provided as variations."* Therefore, process parameters such as stirring time, pump speed, pressure differential, torque force, tightness of bottles, conformity check of packaging and yield are considered to constitute basic GMP-relevant process parameters. As such they are routinely defined, controlled and documented in the manufacturing record of each batch but represent inappropriate details in marketing authorisation applications and may be deleted by type IA variation, e.g. Type IA-B.II.b.5.c (deletion of a non-significant in-process test) or B.II.b.3.a (minor change in the manufacturing process).

The conformity and repeatability of the process is demonstrated during validation and presented in the module 3 section 3.2.P.3.5.

The following considerations intend to demonstrate along the steps of the process chain in which cases and to which extent submission of a variation application is deemed necessary.

■ 4.1. Raw Material

Regarding variations in the plant raw material, characteristic batch-to-

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■ **Table 1**

Changes in Origin and Production of Plant Raw Material (made by Anja Hoppenheit, Schaper & Brümmer GmbH & Co. KG).

Description of change	Classification according to Guideline	Proposed variation application	Justification
Addition of a new supplier – supplier uses the same plant production, e.g. only wild growing resp. only cultivated plants	Type IB according to **B.I.a.1 z)**	Type IA Batch analysis data (in a comparative tabular format) for one batch (minimum pilot scale) of the active substance from the current and proposed manufacturers/sites.	The quality of the herbal substance is proven by conformity with the release specification. Natural variabilities, e.g. climatic conditions, are even usual at batches delivered from the same supplier. Therefore, the comparison between old and new suppliers or batches gained in different years is meaningless. The submission of only one certificate of analysis increases the flexibility at crop failures and small harvesting periods (often only one harvest period is possible per year).
– supplier uses a different plant production (e.g. cultivation instead of wild growing)	Type II according to **B.I.a.2 d)**	Type IB	The quality of the herbal substance is proven by the GACP confirmation and compliance with the specification.
Change of origin of the herbal substance – supplier uses the same plant production, e.g. only wild growing resp. only cultivated plant	Type II according to **B.I.a.2 d)**	Type IA Batch analysis data (in comparative tabular format) of one batch (minimum pilot scale) of the active substance manufactured according to the currently approved and proposed process.	The quality of the herbal substance is proven by the GACP confirmation of the new supplier and compliance with the specification.
– supplier uses a different plant production, e.g. cultivation instead of wild growing	Type II according to **B.I.a.2 d)**	Type IB	The quality of the herbal substance is proven by the GACP confirmation of the new supplier and compliance with the specification.
Change of technical parameters during harvesting (e.g. drying temperature)	Type IA according to **B.I.a.2 a)**	No variation should be necessary if the quality of the herbal substance complies with the release specification.	The quality of the herbal substance is proven by conformity with the release specification (comparability between fingerprints HPLC and/or TLC is given).
Change in immediate packaging of the active substance Qualitative and/or quantitative composition	Type IA according to **B.I.c.1 a)**	No variation should be necessary if food-grade quality is given.	If the requirements of Regulation EC 1935/2004 are met (confirmation), a safe transport and storage in the new packaging material is ensured.

batch variabilities basing on seasonal conditions, e.g. drought, flooding or pest infestation, should be considered. Based on this aspect and on the examples for changes in origin and production of plant raw material listed in table 1, the necessity and extent of each variation should be checked thoroughly.

■ 4.2. Manufacturing Process

The EU guideline on the details of the various categories of variations [4] classifies substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product as a Type II variation. However, minor changes in the manufacturing process of the active substance can also be classified as Type IA variation. This depends on the assessment on how "significant" the impact of the change on the final product will be. For this reason, the examples given in table 2 shall demonstrate in which cases of possible changes during the manufacturing process of herbal preparations submission of a variation application Type II, IB or IA is considered necessary or in which cases even no variation is justified.

■ 4.3. Quality Control

During recent years further development of analytical methods and techniques is evident, e. g. the Ultra High Performance Liquid Chromatography (UHPLC) has become "state-of-the-art equipment" in many laboratories. Potential advantages of UHPLC in contrast to conventional LC are especially shorter run times and reduced solvent consumption, but also a better resolution and higher sensitivity. But often this improvement will not be implemented because of bureaucratic effort and time-consuming steps with respect to the variation guideline. In a worst case scenario

Table 2

Examples for possible changes during manufacturing of herbal extracts (dry, soft, liquid and tincture) (made by Dr. Andreas Andersen, Queisser Pharma GmbH & Co. KG).

Description of change	Classification according to Guideline	Proposed variation application	Justification
Change of extraction solvent	Type II according to **B.I.a.2 d)**	Type II	A change of solvent type or concentration may influence the spectrum of components obtained from the herbal substance.
Ratio of raw material: extraction solvent without change of the drug extract ratio (DER)	Type II according to **B.I.a.2 d)**	– Type IA according to **B.I.a.2 a)** if an exhaustive extraction is reached – Type II for maceration	The amount of solvent does not influence the spectrum of components obtained from the herbal substance in case of an exhaustive extraction.
Change of temperature during extraction	Type II according to **B.I.a.2 d)**	Type II	A change of temperature of extraction may influence the spectrum of components obtained from the herbal substance.
Change in duration of extraction process	Type II according to **B.I.a.2 d)**	→ No variation should be necessary for both steady-state and exhaustive extraction	A shortened or prolonged time of extraction does not affect the spectrum of components obtained from the herbal substance if shown by comparison of yield (DER)
Change of pressure during evaporation or heat treatment, duration of blending process (liquid extracts) or of sedimentation process (liquid extracts and tinctures)	Type II according to **B.I.a.2 d)**	Type IA according to **B.I.a.2 a)**	Minor change in the manufacturing process not affecting the spectrum of components obtained from the herbal substance
Change of process details that fall within the scope of GMP, e.g. inlet pressure or filter pore size during filtration (liquid extracts and tinctures)	Type II according to **B.I.a.2 d)**	Type IA according to **B.I.a.4 c)** when parameters are deleted	Unnecessary details inappropriate for inclusion in submissions according EMA reflection paper on "minor deviations"

this would lead to remain with obsolete methods. The aim, therefore, should be to simplify changes within analytical methods and to find a pragmatic approach to get more flexibility. The basis for this could be defined already in the dossier, e. g. by replacing comprehensively described methods by means of an "analytical framework", specifying the methodology (like LC-DAD or GC-MS) and some core data like column material class, reference substance, short description of procedure, etc. Adjusting parameters (like particle size, column length, etc.) allows e. g. switching from LC to UHPLC. Also replacement of reagents (due to REACH) could be a reason for a revised method. Of course adaptations have to be controlled and documented within an internal formal change control procedure according to GMP conditions and on the responsibility of the applicant/the qualified person. This could be done e. g. as part of a risk analysis, which includes the documentation of an analytical comparison of the methods and the revalidation. These internal change control procedures could be verified during GMP inspections.

Some examples for changes in analytical methods and an assessment of their impact on necessary variation are given in table 3.

Choice of Methods Different from the European Pharmacopoeia

In order to follow technical progress, the pharmaceutical industry is obliged to implement new analytical strategies and revised methods. The European Pharmacopoeia (Ph. Eur.) [5] in chapter 1 "General notices" permits the use of alternative methods: *"With the agreement of the competent authority, alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used."* In contrast, section 29 of the German Medicines Law [6] requires that *"changes to the specification of an active substance or other substances used in the manufacture of medicinal products in order to comply with a monograph of the pharmacopoeia if the change is made exclusively to comply with the pharmacopoeia and the specifications for product specific properties remain unchanged"* have to be reported to the competent authority within twelve months since their introduction. This, however, should only be applicable in cases when a new Ph. Eur. monograph is published and the company-own specification has to be adapted. In accordance with the CMD(h) Q&A document on variations [7], this does not apply to changes within an existing Ph. Eur. monograph with a reference to the current edition in the dossier.

Furthermore, according to the Ph. Eur. the alternatively used method

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■ **Table 3**

Examples for possible changes in analytical methods (made by Cornelia Höhne, PhytoLab GmbH & Co. KG).

Description of change	Classification according to Guideline	Proposed variation application	Justification
Change of analytical marker (other extracts)	Not clearly classified	Type IB according to **B.I.b.1 h)** or **B.II.d.1 g)**, respectively	Grouping of changes in marker and method for active substance, finished products and stability possible
Change of limit for analytical marker, e.g. new batches of herbal substance or finished product show higher or lower amount of analytical marker exceeding or falling below specified limits	Type II according to **B.1.b.1 f)** (active substance) or **B.II.d.1 e)** (finished product)	Type **Condition**: test procedure remains the same **Documentation:** If applicable, details of validation data, e.g. range of analytical method and justification of the new specification limits	In the case of an analytical marker of an extract for which neither constituents of 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.
Widening of specification limits during stability testing	Type II according to **B.1.b.1 f)** (active substance) or **B.II.d.1 e)** (finished product)	Type II according to **B.1.b.1 f)** (active substance) or **B.II.d.1 e)** (finished product) Type IB according to **B.II.d.1 z)** (finished product) for "other extracts" (e.g. enlargement of the specification to +/-10 %)	Due to the particularities of herbal medicinal products, adaptation of specification of the analytical marker may be required.
Slight adaptation of method parameters analogous to Ph. Eur. chapter 2.2.46, e.g. particle size of LC column, exchange of reagents (e.g. due to REACH) or change from TLC to HPTLC	Type IA	No variation, but documentation within a formal change control procedure according to GMP requirements.	Acceptable as far as no full revalidation of a method is necessary or comparability can be demonstrated.
Change to comply with an update of the relevant monograph of the Ph. Eur., e.g. from photometry to HPLC or from TLC to HPTLC	Type IA according to **B.III. 2 b)** or no variation, respectively, in case of reference to the current edition	No variation is required.	In case reference is made to the current edition and there is no impact on the declaration of the finished product.
Other changes to a test procedure, e.g. from photometry to HPLC	Type IB according to **B.II. d. 2 d)**	Type IB according to **B.II. d. 2 d)**	Acceptable.

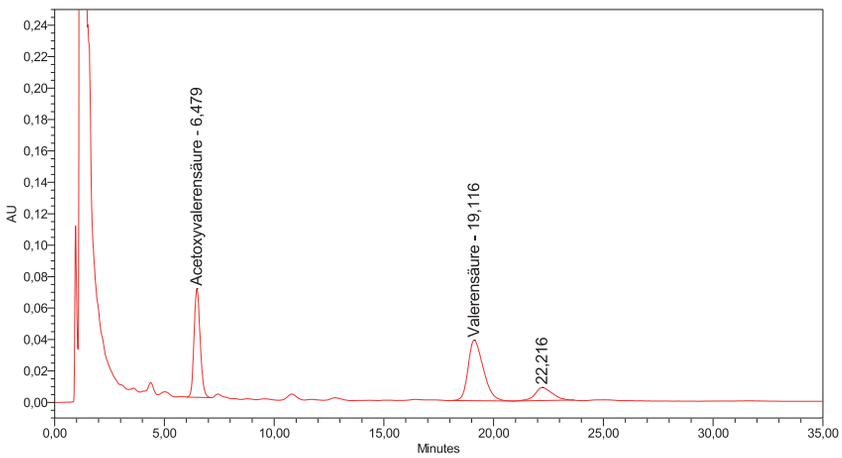
should "*enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used.*" This means that the alternative methods should lead to equivalent results and have to be validated. Due to the equivalent results, stability data obtained with the former method can be regarded as still valid. The variation is classified as Type IA. The following examples may represent a pragmatic approach in case of changes in analytical methods.

Ph. Eur. Chapter 2.2.27 [8] describes the different applications of thin layer chromatography. The implementation of horizontal development leads to a reduction of the solvent up to 90 % in comparison to the common vertical development. This sustainable technique can be used after appropriate validation and with regard to the requirements of Chapter 2.2.46 "Chromatographic separation techniques" [9] without notification. In the case of liquid chromatography (Chapter 2.2.29) [10], the change to modern techniques like UHPLC is more difficult or not possible because the requirements of Chapter 2.2.46 especially for the gradient elution are difficult to fulfil. If the analytical validation has been successfully adapted to the changes and the criteria for assessing the system suitability are fulfilled, the minor adjustments have not to be notified to the authority.

The example of Valerian (fig. 1 and 2) demonstrates that the use of modern HPLC columns leads to a pronounced decrease of time as well as of used amount and waste of solvent. It can be shown that after validation, both methods lead to comparable results.

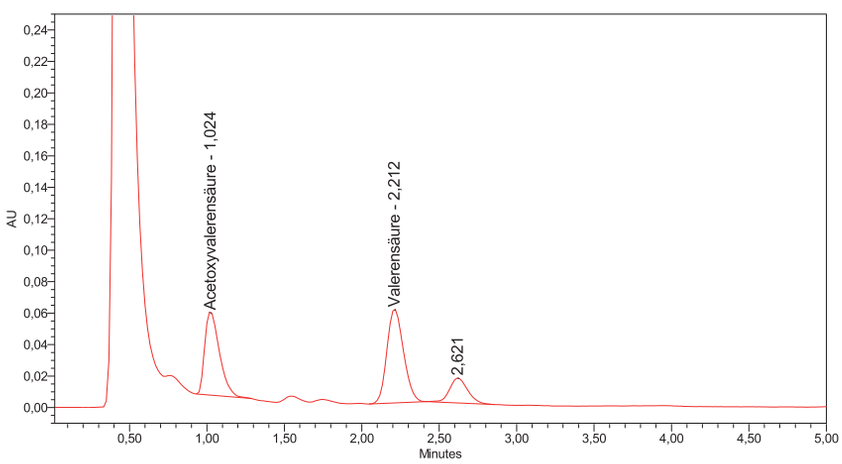
The following thin layer chromatograms of a combination product (fig. 3) demonstrate that a change of the stationary phase from an aluminium TLC plate to an HPTLC plate leads to comparable results. All characteristic zones of the finished product are detectable with both stationary phases and, therefore, a notification of the change of the analytical procedure is not considered necessary.

Figure 1



Isocratic HPLC Separation Valerian root powder, column RP18, 4 µm, 125 * 4 mm (all figures are made by Kneipp GmbH).

Figure 2



Isocratic HPLC Separation Valerian root powder, column C18, 2.6 µm, 50 * 3 mm.

The Option of a „Method Master File“

Unlike product-specific testing like identity and assay of defined constituents, different suitable methods for analysis of contaminants like pesticides, aflatoxins and heavy metals do exist. Specialised and experienced laboratories offer their services and are responsible to ensure that all relevant requirements concerning validation, GMP, etc. are taken into account. Apart from these aspects other quality assurance measures are also implemented continuously to keep all standards and requirements up to date. Knowledge acquired in the course of validations, ongoing validations and proficiency tests sometimes leads to slight adaptations of the method. This fact would lead to frequent variations within the dossier. Furthermore, it must be taken into account that these variations would affect a lot of registration/marketing authorisation dossiers and many companies. Therefore, these documents cannot be included and kept up to date in the dossiers. A formal reference to the method or a brief description of the method (with reference to the “current edition”) should be accepted in the dossier without the need to submit all internal documents including validation data. In order to cover the requirements of the authorities with regard to approval of all methods and validation data, an expedient and practical approach would be to lodge a “method master file” with the authority. Thus, in case of adaptations only one central submission of a variation by the holder of the method validation file would be sufficient. This would reduce the bureaucratic burden for companies and health authorities related to the submission of documents or their assessment, respectively. A detailed verification of validity of methods and GMP compliance could be performed during GMP inspections of concerned laboratories.

Change in Immediate Packaging Materials

Some examples given in table 4 shall demonstrate in which cases of possible changes of immediate packaging materials submission of a variation application is required or in which cases no variation is justified.

In the following, a proposal for a future approach is made which may simplify assessment of documentation regarding container closure system(s) presented in chapter 3.2.S.6 and 3.2.P.7:

Most medicinal products, particularly HMPs, are based on national marketing authorisations. Thus, regulatory activities, such as variations, have to be done in several Member States in parallel for the same activity, normally with the same set of documents, but with a wide range of additional requirements from different National Competent Authorities (NCAs). This can be observed especially for container closure systems, where other regulatory fields than pharmaceutical regulation may primarily be applicable. In many cases material of usual container closure systems used as immediate packaging of several medicinal products are not covered in full by respective monographs in the Ph. Eur. Furthermore, scientific guidelines such as the “Guideline on Plastic Immediate Packaging Materials” [11] are not accepted by several NCAs.

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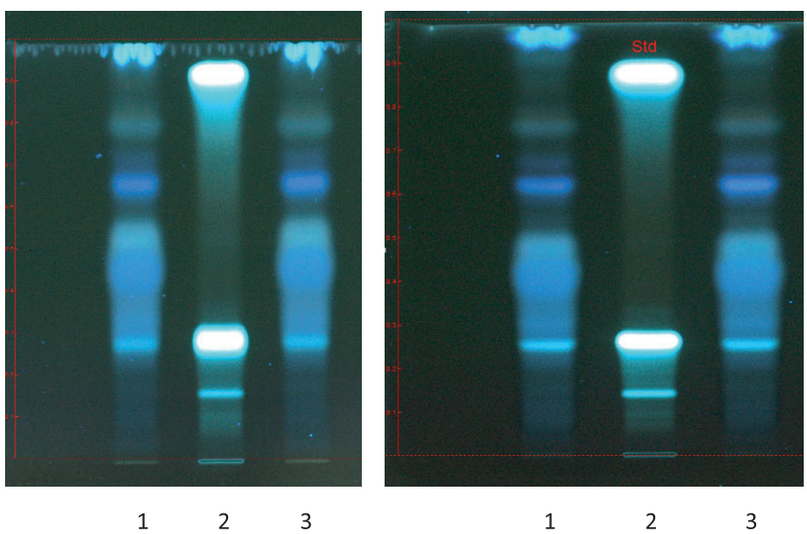
Moreover, the variety of usual container closure systems for medicinal products is quite limited concerning material characteristics (quality of glass, blister foil materials incl. heat-seal coating and stove lacquer) and suppliers, as they are used in the same manner by most of the medicinal product manufacturers. In consequence, the same set of documents is enclosed in the dossiers of a large number of products and each application which needs to be assessed by NCAs. In order to reduce workload for agencies as well as for applicants, and apart from the possibility of work-sharing, a kind of master file concept, similar to that with CEPs, could help to streamline approval procedures, especially in national procedures. Conceivably, those master files could be requested by the manufacturers of container closure systems at a certain place to be defined.

5. Conclusions and Recommendations

Changes during the life cycle of (herbal) medicinal products require appropriate variations in the marketing authorisation dossier. With regard to the different steps of the supply and production chain (starting material, manufacturing process and quality control), it should be considered after thorough assessment and risk evaluation in which cases variations have to be submitted.

The discussed approaches follow the legal requirements and recommendations of the respective guidelines and monographs. They show how these requirements can be interpreted in a more practicable manner for HMPs. Taking into account the large variability in their characteristics, it should be challenged whether

Figure 3



Thin layer chromatography of a combination product, stationary phase: aluminium TLC plate (left) and HPTLC plate (right).

Table 4

Examples for possible changes in packaging materials for solid and liquid herbal preparations (made by Dr. Frank Kreutz, PASCOE pharm. Präparate GmbH).

Description of change	Classification according to Guideline	Proposed variation application	Justification
Change of size of container closure system for liquid herbal preparations	Type IB according to **B.I.c.1 c)** for liquid herbal preparations	→ No variation necessary as long as the material is identical with the packaging material described in 3.2.S. 6 and 3.2.S. 7.	Stability studies cannot be performed using the original container closure size. Small size containers represent a worst case scenario with regard to the relation of surface to content
Change of material of container closure system for solid herbal preparations	Type IA according to **B.I.c.1 a)**	→ No variation should be necessary as long as the material is comparable to the packaging material described in 3.2.S. 6 and 3.2.S. 7.	Stability data in 3.2.S. 7 usually have not been collected using the original container closure system, but packaging material comparable to the packaging material described in 3.2.S. 6.
Change of material of container closure system for liquid herbal preparations	Type IB according to **B.I.c.1 c)**	Type IA according to **B.I.c.1 a)** as long as the material is at least equivalent to the packaging material described in 3.2.S. 6 and 3.2.S. 7.	Stability data in 3.2.S. 7 usually have not been collected using the original container closure system, but packaging material equivalent to the packaging material described in 3.2.S. 6.

changes e. g. within details of production and quality control are really relevant for the overall quality, efficacy and safety of the product. As a conclusion, the type of variation procedure (Type IA, Type IB or Type II) chosen for the change process for an HMP should take the respective particularities of the product into account. In case of Type II variations, the competent authority could consider attaching a condition to the approval of the variation which should then be fulfilled by the applicant. Moreover, verification and control of detailed modifications could be performed during GMP inspections. This would move responsibility to industry to a larger extent than already defined in the extensively regulated environment for medicinal products. Thus, the bureaucratic burden for companies and health authorities related to the submission of documents or their assessment, respectively, can be reduced.

A dialogue with health authorities would, therefore, be appreciated. The authors would like to support this process by discussing examples from the daily business within this publication and further discussions.

6. Acknowledgements

We thank the following members of the Working Group for their contributions to the discussion and to the manuscript:

Dr. Andreas Andersen, Queisser Pharma GmbH & Co. KG, Dipl.-Biol. Cornelia Höhne, PhytoLab GmbH & Co. KG, Anja Hoppenheit, Schaper & Brümmer GmbH & Co. KG, Dr. Sven Oliver Kruse, Diapharm GmbH & Co. KG, Dr. Frank Kreutz, PASCOE pharm. Präparate GmbH, Dr. Friedrich Lang, Dr. Willmar Schwabe GmbH & Co. KG, Dr. Andrea Lutz-Röder, Kneipp GmbH, Dr. Frank Poetsch, Bad Heilbrunner Naturheilmittel GmbH & Co., Dr. Alexander Schenk, Max Zeller Söhne AG, Dr. Katharina Schroeder, Rodisma-Med Pharma GmbH, Dr. Barbara Steinhoff, Bundesverband der Arzneimittel-Hersteller e. V. (BAH), Dr. Maria Wiedemann, A. Nattermann & Cie. GmbH.

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Chefredaktion: Claudius Arndt. Sekretariat: Gudrun Below. Verlag: ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, Baendelstockweg 20, 88326 Aulendorf (Germany). Tel.: +49 (0) 75 25 94 00, Fax: +49 (0) 75 25 94 01 80. e-mail: redaktion@ecv.de. http://www.ecv.de. Herstellung: Reemers Publishing Services GmbH / Holzmann Druck GmbH & Co. KG.