# THE STATUS OF HERBAL DRUG MONOGRAPHS FOR THE PH EUR IN VIEW OF THE EUROPEAN HARMONISATION

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The drafting of quality monographs on Herbal Drugs or Herbal Drug Preparations is a permanent challenge for the responsible experts of the European Pharmacopoeia Commission. They constantly have to consider the latest scientific data and developments in natural product analysis and they must follow the rules that even for the mostly very complex composition of a herbal drug any monograph must be drafted following the structure and the rules for a defined chemical substance.: all tests and assay methods must be validated, mainly if the content of constituents * individual or mixtures of related substances- have to be quantified.
Mostly for Herbal Drug Preparations, i.e. all forms of extracts and tinctures, the situation is even more complex, since in these cases physical parameters such as solvents and solvent concentrations , production technologies etc are highly influencing the outcome and quality of the final product.
Due to the broad spectrum of the different licensed products in the EU member states, any drafting of an individual extract quality monograph is extremely difficult in view of satisfying the Licensing Authorities in the different Member states. Further commercial Herbal Drug Preparations mostly contain varying amounts of excipients besides the so-called native (genuine) extract. These overall problems will be discussed on the basis of some recently published or drafted Monographs for the Ph Eur.

**DEFINITIONS AND PROBLEMS OF THE EUROPEAN PHARMACOPOEIA MONOGRAPHS FOR HERBAL EXTRACTS AND THEIR RELEVANCE FOR MARKETING AUTHORISATION**

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The main focus of the report was the comparison of the requirements set by the German and the European Pharmacopoeia with those set by law and related provisions for marketing authorisation. In order to achieve marketing authorisation the manufacturers of herbal preparations and herbal medicinal products must comply with both. It should be an obligatory prerequisite that the respective requirements and monographs are consistent and not contradictory. However, particularly in terms of definitions, classifications and manufacture of extracts, there are some discrepancies which urgently need clarification. The report is therefore dealing with the definitions and classifications of herbal preparations, and the questions and problems resulting thereof. The German and the European Pharmacopoeia currently distinguish between the following types of extract:

- “Standardised” extracts (Type A extracts)
- “Quantified” extracts (Type B1 extracts)
- “Other” extracts (Type B2 extracts)

These Pharmacopoeia definitions are not fully in accordance with the requirements of the marketing authorisation. Especially the concept of the genuine extract is missing. Furthermore the definitions of following types of monographs of the German and the European Pharmacopoeia are explained

- General monograph “Extracts”.
- Individual monographs
- Family monographs (Frame monographs)

The problems with these definitions are demonstrated and their relevance for marketing authorisation is discussed. With view to these problems, the manufacture of extracts Type A, B1 and B2 is clarified by assessing the pharmacological/therapeutic relevance of a marker in comparison with the native extract.

# STATISTICAL EVALUATION OF STABILITY TESTING OF HERBAL MEDICINAL PRODUCTS

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The evaluation of stability data from Herbal Medicinal Products has to be done according to ICH guideline Q1E [1] like for all other Medicinal Products.
Herbal Medicinal Products however represent a very delicate and special group of pharmaceutics concerning biological matrices and variations between batches. Often intensive sample preparations and poor analytical tools to determine markers that are less than 1 % of the whole preparation lead to variances of analysis that are higher than those recommended in ICH guideline Q2B „Validation of Analytical Procedures“ [2].
Therefore the acceptance criteria each for analytical parameters and for stability specifications have to be set carefully and with relevance to the practice.
The aim of our investigations during stability testing is to define and predict shelf lives that are useful for the marketing department.
The questions we have to concentrate on are:

- Is regression analysis also an appropriate approach analyzing quantitative stability data for retest period or shelf life estimation for Herbal Medicinal Products?
- Is poolability a tool that can be used to make predictions?

Examples illustrate how a systematical approach to evaluate stability data can be done.

[1] ICH Q1E Evaluation of stability data, CPMP/ICH/420/02 Note for guidance on Evaluation of stability data
[2] ICH Q2B Validation of Analytical Procedures

**CONTAMINATION OF HERBAL DRUGS: A SURVEY OF THE REGULATORY ENVIRONMENT AND FINDINGS CONCERNING THE CONTAMINANT BURDEN**

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Herbal Drugs are obtained from cultivated or wild plants. They should be free of impurities such as dirt, fungal, insects and other animal contamination and should be affected with the lowest possible level of micro-organisms and contaminants. In the case of decontamination no harmful residues must remain.The EMEA *Guideline on Specifications* CPMP/QWP/2820/00 Rev 1 provides general principles on setting specifications for herbal substances and preparations. One source for methods and criteria is the Ph. Eur. but also the Guideline itself describes methods and criteria. Since contaminants resulting from environmental factors, improper handling and microbial spoilage occurring during cultivation, harvesting, drying and storage require special attention criteria, methods and maximum levels for the definition of adequate quality.

- **Inorganic impurities and toxic metals**

Potential soil contamination and air pollution must be diligently considered. As Pb, Cd and Hg are not the only elements of interest the recommended analytical methods should be reviewed. Acceptable maximum levels must be defined. The existing regulations are not coherent and require harmonisation.

- **Microbial limits**

Soil, harvesting, drying and storage conditions influence the microbiological quality of herbal drugs. The inclusion of additional possible pathogens should be considered in certain cases. The recommended pharmacopoeial procedures and methods for the determination of microbial counts should be reviewed. The acceptance criteria should be harmonised.

- **Mycotoxins**

Humid conditions promote the growth of moulds potentially forming Mycotoxins on herbal drugs. Especially Mycotoxins formed by Aspergillus, Penicillium and Fusarium species are detrimental to human health because of their serious toxic effects. Since the SCF published opinions on 9 Mycotoxins it is questionable if a test only on Aflatoxins is satisfactory in view to the potential hazard originating from these compounds. Adequate official methods for herbs are not available and feasible limits should be fixed.

- **Pesticides and Fumigation Agents**

Approved plant protection products should be applied at the minimum effective level in accordance with the regulations of the grower and end-user countries. If their use is not limited to the necessary minimum, while cultural measures are applied, their excessive use results in not acceptable residues. The methods and limits of the Ph. Eur. require revision, more pesticides with appropriate limits should be included in the monograph. The above mentioned requirements are referred to retrospective data of analytical tests on many batches of various herbal drugs. The practicability of existing and recommended criteria and maximum limits is discussed. The production of high standard herbal drug preparations requires a permanent and diligent risk evaluation and management of the herbal raw drug.

**SURFACE PLASMON RESONANCE (SPR) FOR PHARMACEUTICAL ANALYSIS**

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The development of biosensors for analytical purposes has attracted a great deal of attention in recent years. A biosensor is defined as an analytical device consisting of a biological component (*e.g*., enzyme, antibody, entire cell, DNA) and a physical transducer (*e.g*., electrode, optical device). Biosensors are mostly designed for routine analysis, like clinical diagnosis, quality control of food, in-process control of fermentations, and in environmental analysis. Many of these sensors are also suitable for screening purposes in order to find new drugs [1,2]. Such systems should yield information either about compounds with known bioactivity or about the bioactivity of samples with known or unknown chemical composition. Besides the widely used enzyme-based sensors, which are mainly combined with an electric or semiconductor device, numerous optical biosensors have been developed. Most of these are based on antibodies specifically binding the analyte of interest. In addition to these more ”classical“ optical approaches like fibre optics, much attention has been paid to a technique known as “surface plasmon resonance” (SPR). SPR is an optical phenomenon that occurs as a result of total internal reflection of monochromatic and polarised light at an interface consisting of a metal-coated prism carrying the biological component and a liquid environment, which is in direct contact with the bio-component. The metal film is either silver or gold and has to be thinner than the wavelength of the monochromatic light. At the point of total reflection, the light waves interact with free oscillating electrons (“electron plasmon”) in the metal film. In the case of resonance of these electrons, light is lost to the metal film resulting in decreased intensity of reflected light. On the basis of SPR, a receptor assay has been developed for substances, which are capable to interact with the dopamine receptor. Also substances interacting with membranes can be easily analysed. Based on sugar-coated gold films, a screening system for lectins has been established. Additionally, rapid detection of bacterial contamination is possible with SPR.

[1] Keusgen M., NaturWissenschaften **2002** *89*, 433-444.
[2] Klein W., Keusgen M., Bioforum **2003** *Okt 10/2003*, 620-622.

**PCR-RELATED METHODS – A FURTHER TOOL FOR AUTHENTIFICATION AND RETRACABILITY OF STARTING MATERIAL IN (TRADITIONAL) HERBAL MEDICINAL PRODUCTS**

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Herbal medicinal products are defined by the manufacturing process including manufacturing of starting material, herbal substance, herbal preparation and the finished herbal medicinal product. Suitable in-process-controls as well as specifications of quality-defining parameters allow to prove adequate pharmaceutical quality as a precondition for safety and efficacy of the finished products.
Routinely, methods from analytical chemistry are used for identification and for assay of content. PCR-related methods will provide a further approach to identify plant material in (traditional) herbal medicinal products. Because of recent implementation of legislation on traditional herbal medicinal products, development of alternative techniques will be of special importance, since pharmaceutical companies could now apply for registration of products from traditional Chinese medicine or ayurvedic medicine, on which phytochemical knowledge may be rather limited.
From a set of known PCR-related techniques [1,2], we chose suitable methods for our own experimental work, following two approaches: i) Development of simplified methods and their validation to target ribosomal sequences by using especially chamomile as a model system. ii) Application of the methods on herbal substances used in traditional Chinese medicine and development of a database with reliable sequences for practical usage.

[1] Shaw J, Lickey EB et al., American J. Botany 2005, 92, 142-166
[2] Techen N, Crockett SL et al., Curr. Med. Chem. 2004, 11, 1391-1401

## MODERN PHYTOANALYTICAL METHODS: REALLY COULDN'T BE BETTER?

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Phytoanalytical methods have been modernised considerably over the past decades. Classical chemical methods have been progressively replaced by high performance instrumental techniques. Methods such as HPLC-MS, GC-MS etc. are considered to be wonder weapons for herbals. In many cases, however, botanicals and herbal medicinal products (HMPs) resist analytical characterisation. This is due to the complex composition of plant extracts and difficulties in finding analytical targets and markers that contribute to the pharmacological and therapeutic effects. There is a need for universal detection methods that allow the simultaneous tracing of a variety of components. The usefulness of UV-short wavelength scanning, RI, ELSD, NMR and MS techniques is discussed. As plant extracts are considered to be active pharmaceutical substances in their total composition, a chemical mass balance would be helpful. However, this has been established in only a few exceptional cases. Some of the constituents of plant extracts look simple, are not very characteristic at first sight and do not attract scientific interest. Sugars and saccharides, proteins and proteids, or tannins/proanthocyanidines are difficult to analyze. Often, so-called group determinations have to be conducted, as chromatographic separation is poor. In these cases, the analytical values may depend very much on the methods and reference substances used. Specification limits for assays have been narrowed for HMPs and, meanwhile, are the same as for chemically-defined products. Nevertheless, even modern phytoanalytical chromatographic methods may show variations which are too large to hold to these specifications. Developing highly sensitive methods suitable for biological matrices is a great challenge for the pharmacokinetic analysis of HMPs. Examples from our own work illustrate all statements.

**THE RELEVANCE OF MARKERS FOR QUALITY AND DEVELOPMENT OF HERBAL MEDICINAL PRODUCTS**

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The term “marker” was originally introduced into the regulatory terminology for Herbal Medicinal Products (HMPs) in the former “Note for Guidance on the Quality of Herbal Medicinal Products” (1). Analytical markers are needed as a surrogate for quality control purposes and may serve as a thread thsat pulls together product quality from cultivation to the finished product. Being the backbone thus for the quality control of HMPs, markers need to be of excellent quality themselves. As current regulations require the specification of ranges for the content of markers, these ranges need to be substantiated on a solid basis of both empiric data and controlled processes including cultivation (or collection). Realization of these requirements affords strong efforts but offers chances at the same time to develop intellectual property.

Pharmacologically active markers constitute the basis of type B1 extracts according to PhEur and will be a focus of this contribution. Whether or not the concept of active markers and quantified extracts will help to solve the question of the satisfactory definition of the active substance, will be important for the future development of phytotherapy.

The contribution will provide a broad view on the issue of markers and draw specific attention to active markers.

[1] Pharm. Eur. 01/2004:0557, „Human anti-D immunoglobulin Immunoglobulinum humanum anti-D“

[2] Pharm. Eur. 4.07/2004, 2.7.13. „Assay of human anti-D immunoglobulin“

[3] Kumpel BM., Immunol Lett. **2002** Jun 3;*82(1-2),* 67-73.

**VARIETY IN THE PRODUCTION OF EXTRACTS – DIRECT PROCESSING AND COMMON EXTRACTION OF PLANTS**

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The European pharmacopoeia defined the commonly used extracts in an own monograph with a classification of four types of extracts: Liquid extracts, tinctures, soft extracts and dry extracts. Today the most finished extracts are solid preparations produced by specialists. For that the genuine liquid extract is dried by a spray-dryer or vacuum belt-dryer, whereby suitable inert materials like maltodextrin or silicon dioxide can be added to improve the technical properties. If the described dry extract preparations are the active ingredients of solid dosage forms, i.e. tablets or coated tablets, the genuine liquid extract can be used also itself. In this case the genuine liquid extract will be given directly to the excipients of the granulate and accepts a function like a granulating fluid. After drying the granulate is ready for tabletting. In the view of regulation the extract has to be declared as native dry extract, although a native dry extract does not exist really. The common extraction of plants considers the experiences of herbal teas, which contain mostly a mixture of herbs. When a patient prepares the tea, he extracts all plants together. This principle can be used also for herbal remedies, which contain more than one plant as active ingredient. The mixed extract as product of a common extraction fulfils all requirements of a standard extract from only one plant. Also the final preparation of a mixed extract can be a liquid extract or a dry extract like standard extracts.

[1] Pharm. Eur. 5.0 **2005**, 798-801
[2] D. Lindemann *et al.*, *Pharm. Ind.* **1998**, *60*, 801-803
[3] M. Tegtmeier *et al.*, *Pharm. Ztg.* **2005**, *150*, 3971-3979

**CURRENT ST. JOHN'S WORT RESEARCH – BIOPHARMACEUTICAL CHARACTERIZATION AND CNS-BIOAVAILABILITY**

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*Hypericum perforatum* (St. John's wort, SJW) is one of the top-selling herbal medicinal products (HMPs) in Germany. More than 30 different products are available in german pharmacies and, in addition, countless SJW products are marketed in supermarkets and the internet. Our investigations showed, that the content of active pharmaceutical ingredients (API) varies significantly from product to product and sometimes also from batch-to-batch, whereas the quantity of APIs in the products from the supermarkets and the internet are lower than in pharmacy restricted products [1]. But even when the batch-to-batch conformity is good, this doesn't necessarily guarantee that the products will be bioequivalent, since absorption from the gastrointestinal tract will depend, at least partly, on the release profile of the APIs from the dosage form. Biorelevant dissolution testing has been developed for chemically defined oral products, but its use for HMPs is in discussion already. Especially for HMPs containing class A (standardized) extracts or class B (quantified) extracts dissolution test make sense [2]. In the case of SJW hyperforin, hypericins and flavonoids are useful dissolution markers. The results of our study clearly indicate that there are glaring differences in the release properties of various products and thus these products could not be considered interchangeable [3]. In the second part of the lecture the pharmacokinetic profiles of the active pharmaceutical ingredients of SJW, particularly with regard to CNS availability of hyperforin, the flavonoids and the naphthodianthrones, are summarized. Plasma concentrations of these compounds have been ascertained by various groups in the 1990s, but these concentrations do not necessarily reflect those at the site of action, e.g. brain tissue. In recent years great efforts have been made to establish the penetration of the APIs across the blood-brain-barrier.

[1] M. Wurglics, K. Westerhoff, A. Kaunzinger, A. Wilke, A. Baumeister, J. Dressman, M. Schubert-Zsilavecz, Pharmacopsychiatry 34 Suppl 1 (2001) S152-156.
[2] F. Lang, K. Keller, M. Ihrig, J. van Oudtshoorn-Eckard, H. Möller, S. Srinivasan, Y. He-ci, Pharmacopeial Forum 29 (2003) 1337-1346.
[3] K. Westerhoff, A. Kaunzinger, M. Wurglics, J. Dressman, M. Schubert-Zsilavecz, J Pharm Pharmacol 54 (2002) 1615-1621.