

# HERBAL DRUGS & HERBAL DRUG PREPARATIONS

International Symposium  
organised by the  
European Directorate for the Quality of Medicines  
& HealthCare (EDQM), Council of Europe

**25 September 2009**  
**Vienna, Austria**

**PROCEEDINGS**



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### Opening Remarks

Dr Susanne Keitel, Director, European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe

Prof. Dr Brigitte Kopp, the Society for Medicinal Plant and Natural Product Research (GA)

#### **Dr Susanne Keitel**

Ladies and gentlemen, Dear colleagues,

It is my pleasure to welcome you to our Conference on Herbal Drugs and Herbal Drug Preparations. We are very happy to see so many of you today. Indeed we have more than 80 participants from almost 20 countries from university, industry and regulatory authorities. Our programme today is dedicated to the scientific update of the European Pharmacopoeia in the field of herbal drugs and herbal drug preparations. As you know, the interest in this field and accordingly the number of monographs in the European Pharmacopoeia, have increased considerably over time. The 7<sup>th</sup> Edition of the European Pharmacopoeia, to be published next year, will contain around 240 texts concerning herbals, and incidentally, we have decided that to make the European Pharmacopoeia more user friendly, for the first time these texts will be presented in one common place in the European Pharmacopoeia, namely in the first volume. During the work on the monographs our groups of experts, their chairs and we, as the secretariat, have touched more than once the overall topic of the day – the necessary update of monographs according to the state of the art, which needs to be well balanced to the needs and possibilities of the users as well as the regulatory authorities. Therefore my colleagues have prepared four sessions to address the following subjects: The first session will focus on progress in analytical techniques and we have identified two very well known and experienced speakers addressing the scientific perspective. The second session will specifically be dedicated to new assay or quantitative test methods and analyse the regulatory implications of such a change – very important. We are aware of the consequences of revisions in this area and would really appreciate feedback from our stakeholders on this topic.

In the field of microbiological examination of herbal medicinal products and in the reference standard area we have already adopted some changes. You will hear updates as well as updates on the work programmes of the European Pharmacopoeia and our HMPC colleagues with whom we closely collaborate.

Last but not least, the round table discussion will give an opportunity to review the proceedings and discussions of the day and have an open forum for dialogue between the different parties. We are very pleased to have many colleagues from regulatory authorities participating today and we should make good use of this opportunity to get their input and understand their point of view. From our side, the EDQM, we hope very much that this will give us important feedback on the necessary modernisation of methods and facilitate their implementation hopefully supported by users and regulators. A common understanding of the problems to me seems to be the key for a successful way forward.

In this spirit, I would like to wish all of us a very interesting day full of useful and constructive interaction.

**Prof. Dr Brigitte Kopp**

Dear Participants in this workshop, Dear colleagues, Ladies and gentlemen,

It is a pleasure for me to welcome you to this workshop. As a professor of pharmacognosy at the University of Vienna I am delighted that we could host this event at the Department of Pharmacy at our university. As president of the GA, the Society for Medicinal Plant and Natural Product Research, and on behalf of the GA, I would like to express my thanks that our society was invited to co-operate in this field.

Our society, the GA, is an international, neutral, independent association of scientists, research institutions of universities and companies, as well as other interested people engaged in the advancement of research and science in the field of medicinal plants, particularly identification and authentication of plant material, chemistry of plant constituents and natural compounds, development of improved and new analytical methods and at least search for new biologically active natural compounds. The interest in herbal medicinal products is continually growing and the public popularity of these products is very high, but in the last years conflicting reports exist, not only in Europe, with respect to the quality. The consequence is that such products need to be monitored and regulated at the same time. This means there is a demand for quality control of all these products including not only analytical studies and quality assessment of natural material but also molecular biological characterisation. The implementation of new analytical techniques as well as new assay methods and other methods in the Pharmacopoeia monographs will be discussed today furthermore the problem of regulatory implications of the introduction of the new assay methods or the pragmatic approach of reference standards etc. All these aspects have or will result in a range of concerns especially from the herbal industry and I estimate that this point will be one of our main subjects in our discussion.

Experts in all these fields are gathered here, the comprehensive programme covers many important and current aspects of pharmaceutical sciences and pharmaceutical industry, letting scientists from universities, industry and regulatory authorities participate in this meeting. I expect from today not only interesting lectures, but also fruitful discussions between the parties and I am sure that this meeting will be a success with very interesting and relevant topics and various highlights. I wish you an informative, interesting and successful workshop.

Thank you.

## FIRST SESSION :

### **Progress in analytical techniques applied to quality control of herbal drugs or herbal preparations: concrete case examples**

Prof. Dr Markus Veit, International Drug Regulatory Affairs Services (D)

Prof. Dr Markus Veit's slides are available on the following link:

<http://www.edqm.eu/en/Proceedings-of-International-Conferences-83.html>

Recent Conference Proceedings - Herbal drugs and herbal drug preparations, 25 September 2009 - Session 1: Progress in analytical techniques applied to herbal drugs or herbal drug preparations: concrete case examples.

The establishment of sophisticated methods in routine quality control of herbal drugs or herbal preparations is driven in the first instance by commercial advantages such as saving time and expenses for materials. In the second instance increased sensitivity and selectivity might be a driving force for establishment. Thus the inventory of methods used does not necessarily represent the state of the art of science and technology. However, some more sophisticated methods, despite being expensive, are used in a generic context as they offer excellent selectivity and sensitivity. This applies to High Performance Liquid Chromatography (HPLC) or Ultra High Performance Liquid Chromatography-Mass Spectrometry (UHPLC-MS) and quantitative <sup>1</sup>H Nuclear Magnetic Resonance (HNMR) spectroscopy. As a case study the application of UHPLC-MS is presented in order to overcome problems with Gas Chromatography – Mass Spectrometry (GC-MS) methods used frequently for analysis of toxic pyrrolizidine alkaloids in herbal drugs and herbal preparations. UHPLC permits direct determination of N-oxides apart from the non-oxidised alkaloids and thus reduction and/or derivatisation steps are no longer needed. The method has an increased sensitivity, selectivity, precision and accuracy.

As a second case study the quantitative nuclear magnetic resonance spectroscopy (qNMR spectrometry) as primary and highly selective method is increasingly used for the establishment and content assignment of reference standards of markers, active markers and plant constituents with known pharmacological activity. Its employment essentially simplifies and increases the reliability of the establishment of reference substances and their certification. The purity determination can be performed for the structurally identified principal component alone. It is important to especially emphasize, however, that by using this method not only the purity for content assignment can be determined but also the content of (identified, proton-containing) impurities and that very comprehensive information on their identity can be derived from the NMR spectra. This might also be of particular importance for the detection of pharmacologically active impurities in compounds used in pharmacological testing. Ultimately identity and purity analysis could be performed in one step using the qNMR method. Hence the substance supply required for certification, the very expensive natural products, could essentially be decreased, which would save costs incurred by the high effort in connection with isolation and purification. Since NMR spectroscopy has the character of a primary method, all prerequisites for performing metrologically top-quality, SI-based certifications for pharmaceutical reference materials are fulfilled.

Some other methods are used infrequently, however, on a case by case basis when advantages are evident. In this context, for instance, capillary electrophoresis has recently been used more extensively as an alternative separation technique in order to avoid the use of acetonitrile.

### Quality control of herbal drugs - emerging methods and approaches

Prof. Matthias Hamburger, Institut für Pharmazeutische Biologie, University of Basel (CH)

Prof. Matthias Hamburger's slides are available on the following link:

<http://www.edqm.eu/en/Proceedings-of-International-Conferences-83.html>

Recent Conference Proceedings - Herbal drugs and herbal drug preparations, 25 September 2009 - Session 1: Progress in analytical techniques applied to herbal drugs or herbal drug preparations: concrete case examples.

Herbal drugs are materials with a high degree of tissular and chemical complexity and heterogeneity. Combinations of methods are needed for a full assessment of the quality aspects, but until recently, suitably sophisticated and adequate methods were often lacking. Over the past decade, several methods have emerged which allow to overcome current deficits. The presentation will review a selection of methods and applications in the areas of extraction, separation and detection.

Classical extraction methods which are typically used in the quantitative assays of herbal drug monographs have several drawbacks. They are usually time-consuming, may not be exhaustive, and hence lack of reproducibility. Recent methods such as Pressurized Liquid Extraction (PLE) and Microwave-assisted Extraction (MAE) overcome some of these limitations, since they are fast, exhaustive, reproducible, and can be automated with commercial equipment. We exemplify some advantages of instrumented extraction methods by a comparison of PLE with current extraction protocols used in the quantitative assays of various herbal monographs.

HPLC with UV absorbance detection has been established as quantitative assay in herbal analysis. However, major natural product classes such as isoprenoids are difficult to analyze due to weak chromophores. The Evaporative Light Scattering Detector (ELSD) may overcome current limitations in the analysis of important compounds such as saponins. ELSD signal can be mathematically related to the amount of nebulized analyte, and recent equipment is sensitive and robust enough to enable the development of validated assay protocols.

Quantitative chromatographic assays require access to reference compounds. Compound purity is usually assessed by chromatographic assays, eg. HPLC. However, this may not correspond to the true content, as solvent of crystallization, moisture, salts and inorganic impurities are not measured. Quantitative NMR (qNMR) is probably the best approach for determination of the content of a reference, provided that the acquisition and processing parameters are correctly selected. This will be exemplified with a comparison of HPLC and qNMR analysis of glucosinolate references. qNMR can also be favourably used in certain cases for a quantitative assay of herbal drugs. A case in point is the quantitative determination of indigo in the Traditional Chinese Medicine herbal drug *Indigo naturalis*. Comparison of qNMR and the HPLC assay of the proposed *Indigo naturalis* monograph for the European Pharmacopoeia will be shown.

*Discussion with the audience*

**Dr Michael Wierer:** Thank you for your talk. I have a remark concerning the detectors you mentioned. We, the European Pharmacopoeia Secretariat, share your enthusiasm for ELSD applications. In fact we have already a monograph on Sesam oil refined (corrected by the author) where this is used. However, one of the disadvantages is the question of volatility, so we have to switch the mobile phase. Therefore it is somehow the same limiting factor as for HPLC-MS detection. The second point is: would you think that it is already well-known or applied in the industry? So we have some hesitation from our expert groups to adopt these kind of methods, knowing that in daily practice they are not present everywhere. What is your view on that?

**Prof. Matthias Hamburger:** Obviously there are certain limitations and I've shown what is possible in terms of mobile phase addition additives, and what is not possible. Non volatile additives are not possible, but I think even with this limited selection one can in our experience, resolve, I would say really the major part of issues. Sometimes it's just maybe a question of looking a bit further to find suitable mobile phase additive. Just an example, you mentioned LCMS. We had the same problem with our glucosinolate analysis. For sulphated compounds, sometimes even two sulphate groups, you need ion pairing. Typical ion pairing reagents are non volatile and therefore not suitable for LCMS. If one looks sufficiently far away there is a solution. We were able to find the volatile ion pairing reagent which worked perfectly well so the peak shape was absolutely perfect. So I think it's just the matter of how far we try to look. So in my opinion, for this issue I do not really see a problem but obviously it's not the absolute thing.

Regarding the second question, we have two ELSDs and we use them routinely not only for quantitative purposes but also in a different setting for our lead discovery purposes so we run all sorts of samples where we really do not know much and in our opinion it's extremely useful. Now I think, in terms of cost, an ELSD is not expensive. It's comparable I would say to a diode array detector, 20-30 000 Swiss Francs. What's that? 15-20 000 Euros. So, an affordable operation. It's robust. I think it's maybe more hesitation to engage into something novel. The issue of volatility also. I mean the new generation of instruments they now can operate at a very low temperature. You can go down to 45 degrees with the recent generations of instruments. So there's not this problem that one had in the first generations of instruments where compounds that were not really, let's say, non volatile like a brick, but even very moderately volatile even were evaporated and not detectable. In the early generation it was rather selective I would say. I do not think this is a problem. The operation is really very simple, our Masters students use it without any problem!

**From the floor:** Just to add because you asked why there was a kind of lack of distribution of these instruments. I think from an industry point of view, my experience is that in early times we did not have regulatory acceptance from the authorities. I do not know if this has changed now. In the industry there is still the feeling that authorities will not accept a non-linear calibration model. Maybe authorities may comment on that, but there is still some hesitation to use this method because it is still unclear as to whether it will really be accepted by authorities.

**From the floor:** I also would like to comment. My question is related to the fact that none of you mention near infra-red spectroscopy and I know in the regulatory field it's a trend for

chemicals, because it's very fast method which you can do on-line. Even imagine the matters which will be introduced in the far future. So my question is there no future for this technique in the whole area?

**Dr Markus Veit:** I think one of the reasons for that is that the validation of near infrared (NIR) spectroscopy is quite a difficult thing and it's quite an effort to do that. Again, there is from my experience on the regulatory side and the assessment, a lack of knowledge on how to assess this data. From my experience there is a need, and this is also true for other methods, really to make an on-going education of assessors in most sophisticated methods.

**Prof. Dr Brigitte Kopp:** There are several researches at the institution of analytical chemistry at the University of Innsbruck and I think there will be a method for the future in this way.

**From the floor:** I would like to go back to the Evaporative Light Scattering Detector (ELSD) - just to add a comment and some experience. We have been using ELSD for some herbal drugs and herbal products. Two examples were shown by Prof. Matthias Hamburger: Ginkgo biloba and Ginseng. ELSD was really established in our laboratory quality control and it is relating to Ginkgo biloba it is used in the United States Pharmacopoeia and the Chinese Pharmacopoeia for Ginkgo biloba, but for example our experience is certainly positive but recently for Ginkgo biloba the new European Pharmacopoeia monograph introduced refractive index detection which is not so innovative, let's say. Our experience is that now we are going back to refractive index detection and reducing the activities with the ELSD.

**Dr Michael Wierer:** It's always a problem to find a compromise between what is the interest and obviously there are many producers who have well established methods which are in the registration dossiers and therefore sometimes it is to find a compromise. Apparently this came from another Pharmacopoeia and was well-established before. So often this is a request from stake-holders during the public comment period, to go over to a method which is already in use and this has to be balanced against the advantages of a novel technique and that's exactly what we have here.

**From the floor:** But for Ginkgo there are not too many dossiers.

**Dr Michael Wierer:** It came from a Deutsches Arzneibuch (DAB) monograph.

**From the floor:** My comment is also directed to the ELSD methods. One thing you showed us was the precision. The precision was lower than 3.6% relative standardisation but we have to keep in mind that we have to do a recovery rate and we have to compare two measured values. If we have this precision for both of the values, our active pharmaceutical ingredient (API) and our finished product we have a problem to meet the requirements of +/- 5% and the recovery rate for the release. Do you see any chance to come to better precision or otherwise this test is to be kept in mind by the authorities and be respected?

**Prof. Matthias Hamburger:** This is a very valid point. I cannot specifically comment on this example here, but maybe our colleague from Indena who was involved in this work could comment. I think quite a bit in ELSD depends on the equipment that one uses. I think that's probably the key issue. I mean this paper here was published in 2000 so that was already I would say three generations back in ELSD development. We have also in our laboratory two generations of detectors and the difference is really appreciable. So I would say with a new generation I would expect the data to be significantly better. Also another point is the peak broadening that's also an issue with the earlier detectors, it can be significant with the new

ones, a very slight peak broadening but it's really not significant compared to the UV which we always use in line. First Diode Array Detector (DAD) and then the ELSD. So I think that's certainly an improvement.

**From the floor:** You presented Principle Component Analysis (PCA) as a method for identification purposes, would that be ok to put into a dossier? Would that be accepted by the authorities?

**Dr Matthias Hamburger:** I promise you not!

**SECOND SESSION :**  
**Introduction of new assay methods in the European Pharmacopoeia  
and regulatory implications**

**Update from EDQM**

Dr Michael Wierer, European Pharmacopoeia Department, EDQM, Council of Europe

Dr Michael Wierer's slides are available on the following link:

<http://www.edqm.eu/en/Proceedings-of-International-Conferences-83.html>

Recent Conference Proceedings - Herbal drugs and herbal drug preparations, 25 September 2009 - Session 2: Introduction of new methods in the Ph. Eur. and regulatory implications

The first part of the lecture presented the reasons for updating existing assays by the introduction of more reproducible, instrumental methods which can also be automated. The example of standardized Horse Chestnut dry extract was given and it was explained that a change of the analytical method might for a given sample lead to different results due to an increased selectivity when using HPLC. This would have regulatory implications for marketing authorisation (MA) dossiers which had been approved with reference to the existing method: in particular the link to the posology as described in literature, e.g. HMPC monographs might be less accessible and would potentially require a change of SPC and labelling of medicinal products. However, the European Pharmacopoeia Commission had recommended a mechanism for transition to guarantee a smooth changeover (see *Pharmeuropa* 20.3). Similar cases were envisaged for on-going projects on Rhubarb and Senna.

The presentation also highlighted the current working proposal for "other extracts" to allow the use of methods and analytical markers different from those mentioned in specific monographs in order to be in line with the reflection paper on analytical markers as published by the HMPC.

Furthermore, recently adopted texts such as the general method for the determination of ochratoxin A in herbal drugs and the test for aristolochic acids in herbal drugs were presented. The latter was used in monographs on herbal drugs (used in Traditional Chinese Medicines) which bear a risk of being adulterated with aristolochic acid containing species. The general test for aristolochic acids in herbal drugs should not be used as assay method for species producing aristolochic acid as secondary metabolites.

Participants were informed on the recently adopted general limits for certain heavy metals in herbal drugs: cadmium (max. 1.0 ppm), lead (max. 5.0 ppm), mercury (max. 0.1 ppm). The respective general method would be revised to embrace in future Inductively Coupled Plasma - Atomic Emission Spectrometry (ICP-AES) and Inductively Coupled Plasma - Mass Spectrometry (ICP-MS).

The HMPC and EDQM are collaborating closely in the field of herbal drugs and herbal drug preparations by mutually participating to its respective meetings. Items discussed were for example:

- establishing a link between established and modern analytical methods
- classification of particular extracts
- choice of relevant markers
- harmonisation of solvent ranges for extraction between HMPC and Ph. Eur. Monographs

**Introduction of new assay methods in the European Pharmacopoeia and regulatory implications - Industry Viewpoint**

Dr Barbara Steinhoff, Association of the European Self-Medication Industry (AESGP)

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Recent Conference Proceedings - Herbal drugs and herbal drug preparations, 25 September 2009 - Session 2: Introduction of new methods in the Ph. Eur. and regulatory implications

The use of modern analytical methods ensures consistent quality of herbal drugs and herbal drug preparations according to the most recent scientific knowledge. As far as available they should be included into European Pharmacopoeia (Ph. Eur.) monographs. The established dosage recommendations of HMPC and ESCOP monographs, however, are usually based on the established conventional, mostly unspecific pharmacopoeial methods. These monographs do not mention the analytical method used. For this reason, a close link between HMPC/ESCOP monographs and Ph. Eur. monographs is of high importance for regulatory and manufacturing practice. This subject is of particular relevance for "standardised" extracts which are characterised by a defined content of a particular substance/group of substance, e.g. hydroxyanthraquinone derivatives in Senna or flavone glycosides in Hawthorn.

By using new analytical methods, different, typically lower assay values are obtained due to their higher selectivity and specificity. The result is a gap between standardisation and the published dosage recommendation. In industry, there are experiences available on the differences in assay values obtained with modern, more selective methods (e.g. HPLC) as compared to established methods such as photometric assays. However, performing the assay with the (new) Ph. Eur. method and in parallel with the established method (in order to make reference to the HMPC and ESCOP monograph) would result in additional, unnecessary work.

As a solution it has been proposed to introduce conversion factors between the new and the established analytical method [1]. In a further contribution, a conversion factor for silymarin has been proposed which was determined in a laboratory comparison for a Milk thistle extract [2]. From the European herbal industry's viewpoint, such a conversion factor should be taken over into the Ph. Eur. monograph once it has been determined in daily practice of the companies. This would permit taking advantage of technical and analytical progress and at the same time to make reference to the dosage given in HMPC and ESCOP monographs which are related to the established method. As recent examples, the draft Ph. Eur. monographs on Aesculus might serve [3,4] which intend to establish a "smooth transition" for authorised products and which would permit industry to use both methods in parallel while collecting data on both analytical methods.

Conclusion: In order to establish a link between Ph. Eur. monographs for standardised extracts using modern analytical methods such as HPLC and the dosage recommendation in HMPC/ESCOP monographs which are mainly based on established methods (e.g. photometry), a conversion factor should be determined and included into the respective Ph. Eur. monographs.

### References:

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- [3] Horse-Chestnut. *Pharmeuropa* 2008;20(3):477-481.
- [4] Horse-Chestnut Dry Extract, standardised. *Pharmeuropa* 2008;20(3): 481-483.

**New practical experience with instrumental methods recently introduced into the European Pharmacopoeia**

Dr Bernhard Klier, PhytoLab GmbH Co KG (D)

Dr Bernhard Klier's slides are available on the following link:

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Recent Conference Proceedings - Herbal drugs and herbal drug preparations, 25 September 2009 - Session 2: Introduction of new methods in the Ph. Eur. and regulatory implications.

During the last two years there have been a few new instrumental methods introduced into the European Pharmacopoeia (Ph. Eur.).

In chapter 2, analytical methods, methods for determination of Aflatoxin B1 (2.8.18.), Ochratoxin A (2.8.22.) in herbal drugs are described. In the monograph pesticides residues (2.8.13.) the requests for qualitative and quantitative analysis have been described instead of a method. This takes into account the usage of different methods in pesticide residues laboratories. A test for aristolochic acid (2.8.21.) and pyrrolizidine alkaloids in herbal drugs are in preparation and the determination of heavy metals in herbal drug with ICP-MS is planned. With these new monographs modern methods for analysis of contaminants in low concentration are described.

In individual monographs illustrations for the microscopic identification of the herbal drug have been added to the microscopic description. These illustrations support trained and untrained laboratory technicians by interpretation of microscopic pictures.

By introducing new extract monographs to Ph. Eur. the development of new assay methods was necessary. These HPLC assay methods should be applicable for both extract and herbal drug. There have been some difficulties to overcome by introducing more specific methods (HPLC) and by considering extract definitions also.

For "other extracts" an analytical marker is required. In the monographs of Valerian root and Valerian preparations, one single method could be used causing different HPLC chromatograms and different definition of the marker substance. In the case of Melissa the photometric assay in the monograph Melissa leaf was changed to HPLC causing lower levels of marker substance and no correlation factor to photometric values.

In "standardised extracts" an assay of an active substance is required. Changing the method and the definition of the active substance there is no correlation given to HMPG monograph any longer. In the draft monograph for Horse Chestnut the new method is described in parallel hoping to get a correlation factor between both methods.

"Quantified extracts" consist of active markers (contributed to therapeutic activity) and in some cases of analytical markers additionally. The monograph St. John's Wort dry extract quantified contains three markers within definition. As the adjustment of content in quantified extracts could only be done via mixing of extracts the production of a conforming extract became more difficult.

The new light scattering detector allows to quantify substances which show no characteristic UV-absorbance (e.g. triterpenic acids in *Cimicifuga* rhizome).

On the one hand the introduction of new instrumental methods into the Ph. Eur. yields a harmonisation of methods and is very helpful for the quality control in herbal drugs; on the other hand a few regulatory questions have to be resolved and additional work has to be done by marketing authorisation holders.

**Regulatory implications of the introduction of new assay methods in the European Pharmacopoeia**

Dr Burt Kroes, Medicines Evaluation Board (NL) & Chairman of the European Medicines Agency (EMA) Committee on Herbal Medicinal Products (HMPC) Quality Drafting Group

Dr Burt Kroes's slides are available on the following link:

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Recent Conference Proceedings - Herbal drugs and herbal drug preparations, 25 September 2009 - Session 2: Introduction of new methods in the Ph. Eur. and regulatory implications

*Discussion with the audience*

**Dr Ulrich Rose:** Thank you. So we have seen that there are quite a number of regulatory implications when we change the assay method in the European Pharmacopoeia. Maybe it would be best not to change!

So, are there any questions?

**Dr Markus Veit:** I would like to ask two questions and maybe Dr Michael Wierer is the right person to answer them. Firstly, I would like to comment that I appreciate the approach to make active markers non mandatory because this has caused a lot of problems. For example we are faced with a lack of regulatory acceptance not to use stability markers for finished product analysis. A good example is the monograph for *Plantaginis folium* where we have an assay for acteoside, which is used as a stability marker in order to detect not properly stored or dried drug material. Acteoside is only suitable as marker for the stability of the herbal drug and not an appropriate marker for quality control of the finished product. However and we are often requested by the authorities, not here in the room, but from Europe, to use acteoside also as marker for the analysis of finished products. Maybe it would be nice to not only make them non mandatory, but also to state on their properties if there is a stability marker. Maybe this can be indicated, that this marker is used as a marker to prove stability or not appropriate for processed drug material. That is the first comment.

I also have a question. We are really facing a lot of problems with new regulation defining that cut herbal drugs need to comply with the monograph. There is only one example valid where we do have two limits for cut and normally broken herbal drugs, which is Valerian root and if you will apply that in future also for all other monographs lacking distinct specifications for cut material, in some cases there will be no herbal drug available on the market really to comply. You have to start with very high amounts of markers in the beginning if you would like to stay within the limits after you have cut this material. So that will cause a lot of problems in the future. How will you face that? Is there any intention to make again like in Valerian, two types of specifications for cut and broken herbal drugs? What will be the future?

**Dr Keith Helliwell:** I appreciate what you're saying. I understand your problems. The Valerian was done for a very specific purpose because on the market, traders were actually mildly cutting the Valerian root, so you could not distinguish between cut and whole, and then applying the old cut limits to it. So in fact they were selling sub-standard material. What we have done with the Valerian, we have cut it for a specific purpose, which in this case is for tea and again if we open up the other monographs because Valerian is 'another plant', if you want to look at it like that, then you could use other markers for your stability. I don't think there is really a desire to go down that route. It has been mentioned that one or two herbal drugs that contain essential oils may be equally applicable, but I don't think it's going to be a huge category, to be quite honest.

**From the floor:** For producers of herbal teas it will be a problem. We already did a lot of analysis on that because you not only have to make sure for batch release to stay within the limits, but you also have to make sure of the stability of what is no longer a herbal drug, they are finished products to comply with these specifications. This will be a big problem in the future and I don't know how to resolve that. There are quite a few herbal drugs containing essential oils produced for teas.

**Dr Keith Helliwell:** Are you telling me that at the moment you don't do any stability studies at all on teas?

**From the floor:** Of course we do, that's the reason why I have concerns.

**Dr Keith Helliwell:** So what are you using at the moment for your stability studies on tea cut from Valerian?

**From the floor:** It is defined that the herbal drug has to comply with the specifications given in the monograph, this is mandatory but tea is a finished product and teas are not mentioned in the European Pharmacopoeia, so own limits could be set and justified and approved and set by the authorities. Now the authorities have limits which are mandatory for finished products also.

**Dr Keith Helliwell:** I understand your concerns. It was for a specific purpose and perhaps we need to think again about the problem. It's not going to go away, I don't think.

**From the floor:** I have one question. What will the policy of the EDQM be when there is no correlation between the two methods?

**Dr Michael Wierer:** I think this was maybe not too clear in the presentation so far as there are different options. I would say if there is a clear correlation, then we could take the option to introduce a correlation factor for example, and that would be a simple conversion from the new method to the old. But the method that we have proposed, analysing in parallel and then looking at results and then maybe setting a new content range would be a little different. That would be exactly for the case where you test the same material, using both methods. You say the range is like this with the old method and the new values are within this range and all the materials that would have complied with the previous range are acceptable as quality standard for the future. This is not a fixed correlation and it would have an implication on the labelling. This is the worst case. I think it has to be distinguished, where for example the conversion factor is possible and those cases where you can't make the correlation. Still we would say that the material was acceptable and so far is acceptable with the new method - a differently defined acceptance range. That is my personal view.

**Dr Ulrich Rose:** The problem with the conversion factors is of course you need both methods to have sufficient repeatability and reproducibility which is a problem for the Horse Chestnut where the HPLC is ok but the old photometric method of the German Pharmacopoeia is not very easily reproducible and here it is very difficult based on the analytical results to fix a conversion factor. One possibility which has not yet been discussed but I'm wondering if it could not be discussed is also to keep photometric assay as it is in the old monographs, provided that it gives sufficient repeatability and reproducibility and to use chromatographic profile in the kind of tests for related substances. To determine a profile by HPLC for instance, where you can also indicate the composition we would like to have. The same approach has been used for antibiotics where it was too difficult to switch from a micro-biological assay to a HPLC assay so the micro-biological assay was kept and the HPLC method finding the chromatographic profile was introduced. So you have both methods combined in one monograph and the definitions, which means the content range, does not have to be changed. This has not yet so far been discussed, but it might be possible for some of you.

**Dr Michael Wierer:** The disadvantage is that you then run two methods instead of one.

**Prof. Fritz Kemper:** With my question I am addressing the moderator as well as all speakers this morning. Nanotechnology is approaching in all sectors of daily life and I have the first reports that nanotechnology is also used in herbal medicinal products. And made only to avoid competition on the market or something else which doesn't fit into our discussion here, but do you think that nanotechnology and its consequences could play a role in what we are discussing here in Vienna today? For my field of toxicology, it plays an enormous role.

**Dr Burt Kroes:** I think indeed what you mention that nanotechnology could indeed affect the bio-availability of a constituent but let's say in case of a toxic constituent the applicant from a regulatory point of view always has the obligation to demonstrate the safety of his products. So if we have a new method of production or a new method of applying a new pharmaceutical form then in that case safety has to be demonstrated for that specific preparation. If it doesn't affect the specifications of the product itself then it probably will not have to be changed but as mentioned already the European Pharmacopoeia is mandatory so what you have to do is demonstrate that the method you are using is comparable to the one described in the European Pharmacopoeia.

**Dr Michael Wierer:** Some other information from recent discussions where we have participated in the field of heavy metals and some toxicologists have in fact mentioned the same as Prof. Fritz Kemper that this may dramatically change the uptake of heavy metals to, for example the brain, which has been demonstrated as being negative for children's intelligence in for example, mercury. So in this respect I think it is even more important that good methods for controlling heavy metals in herbal drugs are prescribed and so at least at that conference the toxicologists very much welcomed the Ph. Eur. approach to make these limits mandatory. But there is even a tendency of requiring stricter limits in future for this reason. It is not only the medicinal products that contain nano particles, tomato ketchup or toothpaste may contain nano particles for technological reasons for instance and these may affect the whole cycle of uptake of heavy metals. So I think it's a valid point. Thank you.

**From the floor:** I have a question concerning the markers. You mention the active and analytical markers and my question is what are the criteria that put a marker in one or the other category, because there's obviously a lot of major consequences in terms of the product specifications and analytical need in particular. So in the Hypericum monograph and I'm sure that certain pharmacologists would not agree that the flavonoids and hyperforin are just analytical markers. So that's one point. The other, how are you going to handle the situation when let's say, an analytical marker based on pharmacological evidence all of a sudden becomes upgraded to an active marker?

**Dr Burt Kroes:** I can respond. We were asked to draft a statement, a discussion slide, and it's exactly the same question I had, what are the criteria for a marker? For instance I know that for Hypericum hypericin is used because it gives a nice red spot on the liquid chromatography (LC). That's the only reason why people started to quantify the amount of hypericin. So I think definitely we need some criteria to establish when something is considered an active marker but furthermore as explained in the monographs we see that some preparations have different uses and when you put the active marker mandatory the question is then should it also be applicable for something which is used topically? It's not taken orally. So that is a question which needs to be addressed in classifying these markers as well.

**Dr Barbara Steinhoff:** From my point of view, this is a very good example where a close co-operation between the EDQM and the HMPC is necessary because the decision on whether a substance is an active or more an analytical marker depends of course as you said, on the pharmacological data available and it should be thoroughly assessed by the experts for instance from the HMPC to which group this substance belongs. Therefore an exchange of information between EDQM and HMPC is required.

**Dr Michael Wierer:** I think from the Secretariats point of view there was a discussion many years ago at a symposium when the general monograph on extracts was prepared. I was not present at this symposium but Dr Keith Helliwell was present at that time. The general understanding is that we include only such preparations into the European Pharmacopoeia which have been authorised by member states. So basically the monograph should reflect decisions made by the regulators in Europe. So basically it should not be the expert group that reads the literature and decides whether the extract is classified in this or in that class. That's what we want to make sure with the collaboration with the HMPC. That we only classify them as quantified if this is agreed by the regulators. I understood that there was a link to be made to clinical studies that have been performed for the quantified extract. It is undisputed that there is a change of use of the different contributions from the different constituents but this is normal. For me the criteria would be successful clinical studies or authorisations in member states. Part of the discussions and divergences that we also have reflects that this has been handled differently in different member states.

**Dr Markus Veit:** But that causes a lot of problems and I would like to stress what you said, Dr Barbara Steinhoff. I think it's very important to involve medicinal and pharmacological assessment which is not present in the EDQM at the moment. There is a need to collaborate and also to reflect the pharmacological research and what is going on because there is increasing knowledge on compounds and this must influence categories of active markers and active constituents. There might also be the opposite too, that an active marker is no longer regarded as an active marker. That could happen also. Melissa is also a good example with rosmarinic acid. There are a lot of compounds which are not really, in my opinion it's always I doubt if you really need a big category quantified extracts. That's my personal opinion. There are only a few examples in my opinion which are valid for this category.

**From the floor:** I would like to come back to the question regarding the existing classification with three categories which are standardised, quantified and other preparations. In my point of view the cut off between the first two categories standardised and quantified is something quite easy to place, but between the second and the third categories quantified and other categories, there is really a grey zone. This classification was set-up maybe 10 years ago and so far, as far as I know, there is no official classification and for industry it's something quite difficult in a situation working on herbal medicinal preparation in which category it is, and could you clarify is there a project to clearly define and classify herbal preparations, herbal substances? The difficult question in my point of view is between the second and the third categories.

**Dr Keith Helliwell:** Thank you very much indeed for that question – something that concerns us all. You're quite right. When we had our meeting over 10 years ago, when we first defined the categories initially there was only going to be 2 categories: standardised and other. But due to pressure from manufacturers, some of whom who had spent a large amount of money on clinical trials, etc, in order to determine results, we introduced the category quantified

extracts, and I agree with Dr Markus Veit, it is always going to be a very small category, particularly as national authorities can't agree whether clinical trials are valid or not. We're now taking a serious look at the Ph. Eur. at this classification. Ten years ago we didn't have the benefit of the wisdom of the HMPC. The Pharmacopoeia only deals with quality and I think we will only continue to deal with quality. We certainly won't be having people that are pharmacologists etc actually assessing from that point of view. I think now we need to more clearly define the role of the HMPC and the European Pharmacopoeia and depend on the HMPC to actually define into which category the extracts or plant material actually come so that we in the European Pharmacopoeia can then produce good quality monographs. What I would hate to see, though, is having many active or analytical markers defined for each plant material. This would give the European Pharmacopoeia a terrific headache if we had to have different monographs based on different markers. I think we need to have a pragmatic and sensible approach but certainly there is a move now to redefine the extracts and the categories. I'm in the process of writing a paper which I hope will appear in *Pharmeuropa*, probably early next year, which outlines all of the problems that there are, all of the items which actually need to be resolved. So it's a timely reminder and something we have to do. I hope that in the next two or three years we'll manage to get greater clarification.

**Dr Burt Kroes:** Can I comment on this. I think the HMPC is more than happy to collaborate with the EDQM. But I think one thing that is very crucial in this question is that we have to set up definitions for what we consider to be standardised. We need to be clear what a standardised product is. I think what we have to do before we classify these products, we have to establish clear definitions, what is known as a specific activity, what is an active marker, for instance should it be biodegradable, should it be active in a certain dose etc.. so I think when these issues are clarified, it will be much easier to classify these extracts or markers.

**Dr Linda Anderson:** Just really to echo what Dr Keith Helliwell and Dr Burt Kroes have said. I think there's a very clear need here for collaboration between the HMPC and the EDQM and also what we have to bear in mind since the meeting 10 years ago, we've now got traditional directives and a lot of the products we're talking about are traditional extracts which may have to be handled in a very different way and maybe we have to start a dialogue particularly with, I was going to raise them this afternoon, looking at the community list entries where we are trying to simplify things, trying to get some clarity and simplification for industry and maybe we need to be clear that what we mean there by analytical markers, active markers and so on and things really have perhaps moved on in an historical way and we have to look forward to Dr Keith Helliwell's paper because if we're going to get the answers to the questions as well, maybe we need this next month. Sooner rather than later. Very important.

**From the floor:** I have a specific question regarding heavy metal content. Is there an idea for time-line when we see ICP-AES and ICP-MS?

**Dr Michael Wierer:** I think the revision has just been started with group 13B. On the other hand that is already practiced in industry so I think that would take us two or three years to get that to the final adoption. On the other hand I think if manufacturers are now already using this, they have proper validation and there shouldn't be a problem for this to be accepted because in general we have a method in the European Pharmacopoeia for both techniques, but not validated on herbal matrix.

**THIRD SESSION :**  
**Update on recent discussions and developments**

**Reference Standards for Herbal Drugs and Herbal Drug Preparations**

Dr Ulrich Rose, Laboratory Department, EDQM, Council of Europe

Dr Ulrich Rose's slides are available on the following link

<http://www.edqm.eu/en/Proceedings-of-International-Conferences-83.html>

Recent Conference Proceedings - Herbal drugs and herbal drug preparations, 25 September 2009 - Session 3: Update on recent discussions and developments

Reference standards of the European Pharmacopoeia are integral parts of the monographs and represent the official standards that are alone authoritative in case of doubt or dispute. They are required to achieve adequate quality control of substances for pharmaceutical use and pharmaceutical preparations.

The types of reference standards used in monographs for herbal drugs and herbal drug preparations include constituents with known therapeutic activity (CRS = chemical reference substance), active or non active markers (CRS) and herbal extracts (HRS = herbal reference standard). The use of these primary standards may be qualitative in system suitability tests, for identification of constituents in a chromatographic system, in tests for adulterations or quantitative as assay standards.

The ways of establishment and the rationale for using CRS or HRS in different monographs will be discussed in this presentation, examples are given.

More recently, also powdered drugs, such as long pepper or aristolochia serpentaria have been described as herbal reference standards.

**Characterisation of constituents by group determinations – a pragmatic approach for Herbal Drugs and Herbal Drug Preparations**

Dr Anton Biber, Deutsche Homöopathie-Union GmbH & Co. (D)

Dr Anton Biber's slides are available on the following link

<http://www.edqm.eu/en/Proceedings-of-International-Conferences-83.html>

Recent Conference Proceedings - Herbal drugs and herbal drug preparations, 25 September 2009 - Session 3: Update on recent discussions and developments

The consistent quality of herbal drugs and herbal drug preparations is assured by the detailed definition and use of the starting material, the constant production process as well as the specification. Specification is defined as a list of analytical procedures and acceptance criteria to which a herbal drug/preparation should conform to be considered acceptable for its intended use.

In the last years, more and more monographs on herbal drugs and herbal preparations have been introduced in the European Pharmacopoeia and up to now more than 170 monographs are available. The monographs are structured (Ph. Eur.) as a monograph on a chemical defined substance: Definition, Characters, Identification, Tests and Assay (wherever possible) are described. Depending on the knowledge of a specific herbal drug or preparation, the analytical characterisation described in the "Assay" is done by the constituents with known therapeutic activity, by active markers or by analytical markers. Wherever possible, liquid chromatography or gas chromatography are the methods of choice, but often group determinations are performed as the "active" constituents are not known or the substances with known therapeutic activity are a mixture of related substances for example:

Ultraviolet and visible absorption spectrophotometry

Flavonoids (Birch leaf, Elder flower, Passion flower, Calendula flower, Hawthorn leaf and flower)

Hydroxyanthracene derivatives (Aloes, Cascara, Frangula bark, Senna leaf, Senna pods)

Alkaloids (Cinchona bark)

Determination of Tannins (2.8.14) (Dried bilberry fruit, Hamamelis leaf, Rhatany root, Tormentil, Oak bark, Pelargonium root)

Volumetric titration

Belladonna leaf, Hyoscyamus leaf, Stramonium leaf, Ipecacuanha root, Kelp

Determination of Essential oil (2.8.12)

Sage leaf, three-lobed, Ginger root, Eucalyptus leaf, Angelica root

These group determinations, which are easy to perform without the use of expensive reference substances, are sufficient in many cases.

For the analytical characterisation of homeopathic mother tinctures we looked for an easy and robust quantitative method and used the determination of flavonols after hydrolysis as described in the monograph on Ginkgo leaf (Ph. Eur. monograph 1828). According to Annex I of directive 2001/83 these determinations cannot be considered as an assay. An assay in homeopathic mother tinctures is only required in case of toxic compounds.

Results (Table 1) demonstrate that the method is useful and suitable to analyse a lot of samples in short time, whereas the flavonoid determination by spectrophotometry described in the monographs mentioned above is very time consuming. Further the HPLC method is more specific than spectrophotometry and the results deliver a pattern of flavonols, which are characteristic for a herbal drug.

Table 1  
Flavonols (% , calculated as quercetin) after hydrolysis in homeopathic mother tinctures

Mother tincture (manufactured HAB)	according quercetin	Flavonols (%)*			sum
		kaempferol	isorhamnetin		
Allium cepa	0.0156	0	0		0.0156
Ceanothus americanus	0.1731	0.0076	0		0.1807
Clematis recta	0.0209	0.0094	0		0.0303
Drosera	0.1125	0.0035	0		0.1160
Eupatorium perfoliatum	0.0277	0.0126	0		0.0403
Galega officinalis	0.0154	0.0175	0.0030		0.0359
Ginkgo biloba	0.0348	0.0288	0.0050		0.0686
Haplopappus baylahuen	0.0360	0.0194	0.0114		0.0668
Iberis amara	0.0107	0.0082	0.0030		0.0219
Ononis spinosa	0.0075	0.0316	0		0.0391
Populus tremula	0.0207	0.0068	0		0.0275
Sambucus nigra	0.0223	0.0030	0.0067		0.0320
Solidago virgaurea	0.0147	0.0095	0		0.0242

\* quantitation limit 0.0030%

As traditional Chinese and Ayurveda medicine become more and more popular, there is a great interest to establish monographs of these drugs in the Ph. Eur. as well. The determination of flavonols as outlined above may be a pragmatic approach to characterise part of these plants.

Therefore the description of the method as a general method in the Ph. Eur. should be considered. Detailed description of preparing the test solution may be given in each individual monograph.

**Update on methods and limits for the microbiological quality of herbal medicinal products**

Dr Keith Helliwell, William Ransom and Son plc (UK)

Dr Keith Helliwell's slides are available on the following link

<http://www.edqm.eu/en/Proceedings-of-International-Conferences-83.html>

Recent Conference Proceedings - Herbal drugs and herbal drug preparations, 25 September 2009 - Session 3: Update on recent discussions and developments

*Discussion with the audience*

**Dr Markus Veit:** Dr Keith Helliwell, first of all thank you very much for all your work and your colleagues. I think it is a very pragmatic approach and we are very glad to have that in Europe but now the question: will this go back to the Pharmacopoeia Discussion Group (PDG) or who convinces the USP about your concept?

**Dr Keith Helliwell:** I don't think I can answer that. I don't know who can answer that. Would you like to, Dr Michael Wierer?

**Dr Michael Wierer:** I can only say that so far herbal or herbal drug preparations have not been the subject of any discussions with the PDG. It is not on the PDG work programme, it was out of the scope, in particular the Japanese colleagues have different views in that area. So we have never been approached to put that on the work programme.

**Dr Markus Veit:** There are considerable problems with the USP presenting this specific specification criteria to them because they do not accept them at all. They insist to have the categories which are in 5.1.4.

**Dr Michael Wierer:** We have signed off the text specifically telling them that there will be specific European provisions for herbals and they have accepted them, so you should convince them to put that on the table for addition to the work programme.

**Dr Keith Helliwell:** Yes because basically in 5.1.4 as it was, will no longer exist. It's no longer an official text or won't be after 1st April. They're going to have to change their minds I think.

**From the floor:** Regarding clarification in the micro-biological quality. If I correctly understood your presentation nowadays 5.1.4 does not exist anymore and 5.1.8 is not in force, but will be next April. What is the situation today?

**Dr Keith Helliwell:** I confused you. 5.1.4 exists at the moment and has done since 1 January 2009 so theoretically herbal medicinal products should have complied during 2009 with the figure of  $2 \times 10^x$ . However, it doesn't seem logical and I don't know how the regulatory authorities have dealt with it. It doesn't seem logical to change from 1 January 2009 to  $2 \times 10^x$  from  $5 \times 10^x$ , only to change back. Everyone knew what we were looking at because we had it in the draft texts to change then back to  $5 \times 10^x$  next April. I think most regulatory authorities, and maybe someone can answer who is dealing with it, have taken the pragmatic approach and said, "we're going to stick with  $5 \times 10^x$  during the intervening period," knowing that the MQH working party was actually going to adopt this text in due course. Does anyone from a regulatory authority want to speak and say what approach they've actually adopted? So basically  $5 \times 10^x$  – the intention was the try and apply that and we did speak at one time at the European Pharmacopoeia of doing a special notification but because we'd spoken to the HMPC and they knew about it in general, we assumed that we didn't have to go that way.

**Dr Michael Wierer:** Maybe there are questions now for the other presenters?

**From the floor:** I have a question concerning the reference standards. You make the re-test monitoring of the reference standards, what's the deviation from the starting value you accept in the content?

**Dr Ulrich Rose:** We have to distinguish between single compounds and extracts with assigned content. For the single compounds for instance where we assign the content as it is – which means 100% with the calculation I have shown you what taking account of water content and impurity and solvents we accept deviation in the monitoring of 0.5% of the assigned value. That means 0.5 % for the total, for the sum of water, impurities and so on. This is fixed as such in our internal procedures. There is no official guideline, you have to fix something in your own procedure. When the deviation is higher we do further testing and when we confirm that there is really a change the value due to whatever degradation or change in water content or whatever, then we have either to assign a new content, this depends on the specifications within the monograph or we establish a new batch. For the extracts for instance our way of monitoring is a bit more difficult. I haven't explained this in detail, but during the establishment, we establish at the same a kind of inactive marker, which is an external standard, a pure compound of whatever e.g. methylparahydroxybenzoate, something very simple but very stable. We establish a response factor between the active ingredients or the analytical matter which we determine in the extract and this external standard, and here we determine the response and this we use also in the monitoring. Otherwise it's quite difficult to monitor these standards and extracts because we don't have absolute values for this.

**Dr Michael Wierer:** Further questions? I have a question for you Dr Anton Biber. When we discussed the content determination for a flavonoid containing drug, to switch from spectrophotometric routine determination to an HPLC, your approach was proposed and we were asked why, if we switched to HPLC, why we should then not analyse the glycosides and why should we perform something with the hydrolysis. Could you explain the advantage of group determination compared to determining the glycosides directly?

**Dr Anton Biber:** As I explained, the group determination can be used as a universal method as you determine the aglyca: quercetin, kaempferol and isohamnetin. If you have established a method like the rutin determination you would not change to this method. The proposal is more if you have new monographs or new plants then this should be an option and not to do a lot of research into finding markers. Then it will be an option to do determination of flavonoids.

**Dr Markus Veit:** But I think there is a risk and I have discussed this already very briefly with Dr Anton Biber. Because if you measure only the aglycons, you may miss the glycosides because the occurrence of aglycons in a mother tincture is related to the manufacturing process, the homoeopathic manufacturing process of these kinds of products. Because these are mainly resulting from enzymatic degradation and this is not complete in all cases so there is a large variance depending on enzyme activity and I think you cannot use this concept without considering glycosides at the same time. That's my opinion.

**From the floor:** We tested this method of homoeopathic mother tinctures and maybe you are right about enzymatic activity but the proposal is a general proposal to do in dry extracts and it works. So I think it may be not so bad.

**Dr Markus Veit:** But in normal dry extracts outside of homoeopathic preparations you should not have too much aglycons only in certain plants. Normally there are not genuine in

plants there are no aglycons, they are all artefacts. Only some flavonoids which are accumulated at the surface of plants and that is the case of Ginkgo. In these cases you do have aglycons in extracts. For hypericum for example, if you have aglycons in hypericum extract, this extract was not manufactured in the right way. So that is an artefact.

**From the floor:** I think there is a misunderstanding. We measure the flavonglycoside after hydrolysis.

**Dr Markus Veit:** So that's a misunderstanding.

**Dr Michael Wierer:** I understood that you perform as a standard the hydrolysis and then determine them as the aglycons. My question in fact was why not to measure the intact glycosides compared to the measurement after hydrolysis?

**Dr Anton Biber:** The answer was, if you have a plant containing mainly rutin you will measure rutin but if you have 5 or 6 or 7 flavonglycosides it's easier to perform hydrolysis to reduce the analysis to the 3 aglyca

**Dr Michael Wierer:** Comments?

**From the floor:** I would like to pick up a note from Dr Anton Biber. He said that an assay must only be performed when toxic compounds are concerned and of course when we discuss homoeopathic tinctures we have a batch to batch difference and all the problems that we have with natural products and plants. This is not different from phytochemicals or phytopharmaceuticals. However I see a big difference in that by definition in a homoeopathic product it is not the compounds that are the active principles and so I have a general question: why should I do an assay on specific compounds or some determination when those compounds are not considered as acting principles? The result of an assay would say nothing about the quality of that homoeopathic medicinal product?

**From the floor:** You may have noticed we avoided the word "assay" specially because of the reasons you noted. This analysis is a kind of characterisation of a plant for herbal preparation – that's the purpose. It's not a quantitative assay to find specific properties of herbal starting materials or a mother tincture or herbal preparations.

**Dr Michael Wierer:** I think we should restrict the discussion in this meeting to the analytical aspect. I know what is behind the discussion and there are different opinions on that but I think at least the presentation could be as well applied in the normal herbal monographs as well and as such I think it is a valuable proposal.

**Development of the HMPC's work programme**

Dr Burt Kroes, Medicines Evaluation Board (NL) & Chairman of the European Medicines Agency (EMA) Committee on Herbal Medicinal Products (HMPC) Quality Drafting Group

Dr Burt Kroes's slides are available on the following link

<http://www.edqm.eu/en/Proceedings-of-International-Conferences-83.html>

Recent Conference Proceedings - Herbal drugs and herbal drug preparations, 25 September 2009 - Session 3: Update on recent discussions and developments

**Update on EDQM's work programme including a progress report on Traditional Chinese Medicines (TCM)**

Ms Melanie Bald, European Pharmacopoeia Department, EDQM, Council of Europe

Ms Melanie Bald's slides are available on the following link

<http://www.edqm.eu/en/Proceedings-of-International-Conferences-83.html>

Recent Conference Proceedings - Herbal drugs and herbal drug preparations, 25 September 2009 - Session 3: Update on recent discussions and developments

Currently about 2100 monographs are published in the European Pharmacopoeia; out of these about 10 % (215) are monographs on Herbal drugs and Herbal drug preparations.

For the 7<sup>th</sup> Edition of the Ph. Eur. it is intended to present the monographs on Herbal drugs and Herbal drug preparations in a separate section of the Pharmacopoeia. The publication in a separate section will facilitate the identification of monographs on Herbal drugs and Herbal drug preparations and will allow a better handling of the book. This change does not imply any change in the status of the monographs.

The monographs on Herbal drugs and Herbal drug preparations have recently been revised and will be published in Ph. Eur. supplement 6.8 (January 2010).

Definitions for "whole", "fragmented"; "broken" and "cut" have been introduced in the monograph on Herbal drugs. A reference to the general method on ochratoxin A (2.8.22) has been included in the monograph. Maximum limits for cadmium (1.0 ppm), lead (5.0 ppm) and mercury (0.1 ppm) have been decided and will be presented in the monograph on Herbal drugs. Where necessary limits for other heavy metals may be required or limits differing from the general requirements may be introduced into specific monographs.

The terminology in the monograph on Herbal drug preparations has been changed in order to clarify the scope of the monograph with respect to the monograph on Herbal drugs.

The European Pharmacopoeia has started to publish illustrations of powdered herbal drugs. These drawings complement the descriptions given in the microscopic identification sections. 27 illustrations have already been published in the Pharmacopoeia. In the Ph. Eur. supplements 6.7 and 6.8 another 7 powder illustrations are going to be published. About 15 powder illustrations are currently published in the Pharmeuropa volumes 21.2 and 21.3.

More than 80 monographs on Traditional Chinese Medicines (TCM) are on the work programme of the Ph. Eur. Five monographs on TCM herbal drugs have already been published in the Pharmacopoeia, namely Bistort rhizome, Notoginseng root, Safflower flower, Sanguisorbia root and Schisandra fruit. Furthermore, two monographs have been adopted by the European Pharmacopoeia Commission and will be published in the next volumes of the Ph. Eur. Another 11 monographs have already been published in Pharmeuropa. The work on about 45 monographs is ongoing. A general chapter on TCM is under preparation.

*Discussion with the audience*

**Dr Michael Wierer:** I have a question for Ms Melanie Bald. Maybe most people are aware of the high value of arsenic that was accepted for kelp and maybe you can explain why it is acceptable to have such a high value in kelp.

**Ms Melanie Bald:** I think here it is organically bound and will not be liberated, so a rather high level is acceptable for this plant.

**From the floor:** I have a question. You made this comparison of monographs and differences. Now, the first question concerns the example of Valerian. In that EMA monograph the extraction solvents that are described, is that based on commercially available products or what is actually the basis for this?

**Dr Burt Kroes:** Before we draft a monograph we do a survey amongst the member states and the extracts included in a monograph are those mentioned by the member states. In the case of traditional products we also look in handbooks to see if there is some data of traditional use in the European Union (EU). If there is sufficient data of use in the EU as well as posology because that's important it will also be included in the monograph.

**From the floor:** I was surprised to see the sentence 'no single or main active ingredient has been identified – the state of the art.' How recent is the literature which is being reviewed for these monographs?

**Dr Burt Kroes:** Indeed this is not a recent monograph. It was one of the first ones published. That was indeed the outcome of the assessment then and that's not saying it's not effective, because it has a well-established indication. What you're saying is that the assessor could not identify a single ingredient which was responsible for the activity.

**Dr Michael Wierer:** In fact when you presented that I also had in mind that this may be only an apparent discrepancy between both ways of writing monographs because in fact that some compound is defined as generally accepted minimum quality criterion here to measure the sesquiterpenic acids. I think most of the people in the audience agree that this is what you do when you analyse this product. It is not in contradiction that you have analysed the literature and could not find one common single main active ingredient. Because somehow this is like another extract so this is a marker which is commonly accepted. That's my understanding.

**Dr Burt Kroes:** I agree but I think this clarifies that the marker you are using is probably analytical marker and should be classified as such in the monograph. To say that we have to at least merge these two monographs in order to classify markers in the monographs of the European Pharmacopoeia.

**Dr Michael Wierer:** A second point and this is very illustrative here. The European Pharmacopoeia Commission has decided now to broaden the range for the ethanol to take account of the lower limit, so that no product that may comply here is excluded from our monograph. On the other hand the methanol extracts were accepted in a member state not part of the EU so in fact our monograph is a bit wider here but I think it's not a problem as long as it's not brought to EU with reference to your HMPC monographs. So I think overall maybe the outcome of the dialogue is that we go more transparent in why and how we set these criteria.

**From the floor:** I have a question for Dr Burt Kroes or Dr Michael Wierer. So if I understand correctly could I interpret the EDQM monograph as more for the quality and the EMA monograph as more therapeutic application? So they are totally different?

**Ms Melanie Bald:** Yes this is correct.

**Dr Burt Kroes:** My intention was to clarify that the starting point of drafting the monographs are different. With the EDQM the quality prevails and at the EMA we look at the quality aspects also the monograph and the contents of the monograph are different. We don't put in specifications like you have with identification etc. So because of that there are some differences but I'm not implying that the one on the right is better than the one on the left. I think we need to have some kind of co-operation where they are more in-line with each other.

**Dr Keith Helliwell:** Thank you for the presentation on what the HMPC does. We spent a long time today discussing European Pharmacopoeia updating monographs. Is there any provision within the HMPC work programme to update your monographs in due course, as may be required because of advances in what actives may be found to be or what the therapeutic indications are? Or is it forever set in history?

**Dr Burt Kroes:** There is a procedure in place at the HMPC for updating monographs. There is also a guidance document for that but it is something which was drafted by the Orgam group so I am not fully aware of the contents of that document but I know for Rhubarb there were some questions and also from Valerian and from interested parties. Because of that the monograph will probably be updated shortly but the difficulty of the work we are doing at the HMPC is not funded by any organisation. People have to do it in their spare time and that's the difficulty with the work being done at the HMPC now.

**Mr Klaus Reh:** I think I can give an explanation. We have fixed procedures, the HMPC secretariat published for stakeholders four years after publication. The normal time frame is to have in five years a new updated monograph and if we have other reasons, for example pharmacovigilance or new marketing authorisations or so on, HMPC can decide earlier to update the monograph. So it's sure we have a new monograph every five years.

**Dr Burt Kroes:** I have to mention that Dr Klaus Reh in the audience is a member of the HMPC Orgam group.

**From the floor:** I have a question regarding the TCM monographs. I mean this is a relatively small number compared to all the herbal monographs that are in the Chinese Pharmacopoeia. How is the selection being done of those drugs that should be monographed and is there co-ordination or harmonisation with the on-going activities in China? As far as I know from my relatively frequent visits to China, things are moving very dynamically there and especially they are introducing many new methods because they do not have our historical burden so they are a bit less inhibited by our past.

**Ms Melanie Bald:** Concerning the first question, this was due to public health issues in monographs chosen and due to their importance on the European market. Concerning the second question I would rather give this to Dr Michael Wierer concerning the collaboration with the Chinese authorities.

**Dr Michael Wierer:** In fact as Ms Melanie Bald said, we have been asked to draft these monographs because we knew that they were in use in Europe without any appropriate source of information on how to analyse them. We know how Chamomile looks like and what European plants look like but we didn't have a big reference on these drugs and of course we took things like Stephania (root) where we were afraid of the adulteration first. Of course it was decided to look first in the Chinese Pharmacopoeia to see whether this could be a starting basis for our work, but unfortunately many of the monographs at least when we started our work still used chloroform and solvents which we wish to avoid. Some of the monographs didn't have assays at all. The Ph. Eur. Commission very much insisted on drafting monographs that have an equal level of quality, like our normal European monographs and in fact that's why there is no special class they are in the same alphabetic order and so we should apply the same standards.

What's going on in China for us that is completely new and personally I know that there are different movements in China. Some want to modernise traditional Chinese medicines, some want to go more traditional. It's a bit difficult at this point of time. We still have a long work load with those that are on our first priority list. We are trying to establish links with China and the Chinese Pharmacopoeia. It is not an easy task.

**Dr Susanne Keitel:** If I may add to that. We are in the process of, and are very interested in establishing links with the Chinese Pharmacopoeia because why should we re-invent the wheel and they have got the expertise. But you know that China is not that easy to understand from the outside. I mean Europe is not easy to understand for outsiders, sometimes not easy for us to understand it. If I ask here how many of us understand the differences between the European Union and the Council of Europe, I'm sure that not all of us are aware of them. So the same applies for China on a different level. We are in touch with Chinese authorities and I am confident that we will manage to establish the correct links to get support from their side as well.

**Prof. Dr Brigitte Kopp:** Maybe I can add something about the Chinese Pharmacopoeia which will be published in 2010. I know several new monographs and they are really equal to the European Pharmacopoeia monographs or the United States Pharmacopoeia. So they have done a lot of work in the last five years.

## FOURTH SESSION

### **Round-table discussion with the participation of representatives from the regulatory authorities, associations and industry**

Dr Linda Anderson, Medicines and Healthcare Products Regulatory Agency (MHRA)

Prof. Matthias Hamburger, Institut für Pharmazeutische Biologie, University of Basel (CH)

Dr Susanne Keitel, Director, EDQM, Council of Europe

Dr Burt Kroes, Medicines Evaluation Board & Chairman of the EMA's HMPC Quality Drafting Group

Prof. Dr Fritz Kemper, Chairman, European Scientific Cooperative on Phytotherapy (ESCOP)

Prof. Dr Brigitte Kopp, representative from the Society for Medicinal Plant and Natural Product Research (GA)

Dr Frank Waimer, Dr Willmar Schwabe GmbH Co. KG (D)

**Dr Susanne Keitel:** I would like to start by presenting the three additional panellists who have not already spoken today. I would like to start with Dr Linda Anderson who is a quality assessor at the MHRA. Dr Linda Anderson was the UK delegate to the Quality Working Party and since a number of years is now member of the HMPC and the Quality Drafting Group. Then we have Dr Frank Waimer, Head of Quality Management at Dr Willmar Schwabe GmbH Co. KG in Germany.

And no need to introduce Prof. Fritz Kemper. I think all of you have known him for a long time.

As a starting point for our round table discussion, we have asked our panellists to give us their opinion as to whether there is interest from the side of European Pharmacopoeia stakeholders to introduce new methods as presented by the speakers in the first session, considering all the information we have heard today. Also related to this is the issue, we would appreciate if they addressed the question 'when are new methods mature enough to be employed in European Pharmacopoeia monographs?'

Secondly, we would like to discuss the implications of the introduction of new assay methods for industry and regulators. We would be interested in getting feedback on the methods and approaches discussed today and especially on a potential need for a transition period. Hot topics we discussed earlier today were, for example, correlation factors and more specifically the problems related to the dosage as presented in the Summary of Product Characteristics.

As regards the third session, the question is whether stakeholders are happy with the recent developments in the areas of micro-biological quality and reference standards. Last but not least, any advice on further improvement or areas where the European Pharmacopoeia should take the initiative to respond to the stakeholders needs is highly welcome. This is the basket of questions we have asked our panellists. So can I ask you, Dr Burt Kroes, to start?

**Dr Burt Kroes:** I have drafted two statements, one dealing with session two, which was more or less discussed this morning. My question is, 'do we need analytical markers or even active markers in the European Pharmacopoeia?' And also I think the criteria for active markers should be clarified, should be laid down somewhere.

The other question is, 'how do we deal with markers if there are some HMPC monographs which have different indications or even different methods of administration, like oral or external? Is it sufficient to have one marker or should the HMPC or the EDQM monographs

contain for different applications different markers in the monograph?' This is open for discussion.

**Dr Linda Anderson:** I think some of these issues are really the hub of what we're focusing on today. I don't think we'll have the answers yet but I think we need to look very carefully again at the development of terminology for analytical markers, active markers and so on. There needs to be more clarification and then we need to look at where they're placed in the monographs and what options and alternatives applicants can have, rather than assuming that you must do certain types of assays, certainly if they're analytical markers or active markers, that's what needs to be done. We almost need to start fresh with new eyes but not lose the experience that we have. This is a very important topic, not least because of the risk that industry will categorise extract in the wrong way if you start to standardise an extract and then you find when you come to a regulatory level that we don't accept standardisation because you've used an active marker. This is a major problem. So we need to be very clear in order to ensure that the monographs are appropriate in the European Pharmacopoeia but also not to put industry back to the drawing board each time they've tried to progress.

**Dr Susanne Keitel:** Further comments on the topic raised by Dr Burt Kroes?

**Prof. Matthias Hamburger:** Well, I already raised the issue this morning but I really think that one has to define a set of criteria to classify these markers. I think obviously it's really important to bring the analytical side which is, in the end, meant to deliver quality, but to bring it together with the, let's say, the pharmacological knowledge, this one has to be the current state of the art. So obviously I think only a set of criteria that are defined and then a review of the evidence can make a meaningful classification. Some of the examples that we had this morning don't make me feel very comfortable, to say the least. I think it's important because otherwise one fixes something for years which does not actually match with the current knowledge and that's the problem in my opinion.

**Dr Susanne Keitel:** You are referring to the importance of linking efficacy parameters to the criteria which are relevant for quality. As a side note, the advantage of the European Pharmacopoeia compared to the HMPC monographs of course is that we don't have an Organ group so we don't have a work plan which only foresees revision every five years. Therefore if we come across a problem we are almost free to put it on the work programme again. But clearly your point is very valid.

**Prof. Dr Brigitte Kopp:** We made the decision if it's an analytic or active marker, maybe five years ago and so the research has changed and now an analytical marker could be an active marker and vice versa. A good example of this is analytical markers and active markers in Valerian roots. We are really blocked with this definition.

**Dr Susanne Keitel:** Coming back to what we already discussed this morning – the importance of revisiting the definitions and having the correct ones.

**Dr Linda Anderson:** I just have a few slides – some ideas about the introduction of new analytical methods. One of the things which wasn't directly spoken about this morning was the concept of possibly having during the transitional period dual labelling. This type of labelling for the Milk thistle is already adopted in a few member states to cover the two different methodologies but what we as regulators have always to think about is that once you decide to change declarations maybe we have to then try to capture it in our guidance documents as well.

Also I have just a few thoughts on the need for transparency. I think, and again I'm just repeating what I said earlier, I think we have to make clear in the HMPC monographs at the time that they're adopted and subsequently revised if needs be if there are constituents accepted with therapeutic activity. This is one of the very critical things for enabling standardised extracts to be produced and we do then need further clarification on active markers to enable, if there is a desire for quantified extracts, to be clear about those. Certainly in the UK we have seen a muddle with manufacturers who start off thinking they've got a standardised extract and they have to change it to a quantified extract. This is a major headache and they have to change their method of production. So we need clarification on that level.

The next slide to finish off: I think the collaboration between the EDQM and HMPC is very timely. I think we need to get this well under way. The example of Valerian, we have on the EDQM side methanolic extracts but not captured in the HMPC monograph. We happen to know just from our own experience in the UK that there are methanolic extracts being used in EU member states, so clearly when the Valerian monograph was promulgated, it wasn't comprehensive in terms of the extracts used in member states. This happens because we're dealing with a lot of information and there's a time now to try and go back and stratify what's covered in the HMPC monograph and what should then be covered in an EDQM monograph. I think there's a real priority to make sure we cover the commodities that will fit in the traditional list because this was an opportunity from the European Commission to make a very simplified scheme for manufacturers for these very traditional products. Ideally you want to have public objective standards that are absolutely as clear as they can be. So I think there should be a priority to make sure all of those are covered because we haven't got very many right now and so this could be an opportunity to catch up.

Lastly I wanted to say now that we have much more experience in Europe with this new class of traditional products we need to tap the experience of industry and regulators to make sure the outcome is adequate, particularly for that group of products. I think the well established products need something more sophisticated, but for the traditional products, where we have traditional methodologies the analytical methods need to be fit for their purpose. They don't have to be very expensive or involved so that we can enable industry to move forward with that group of products.

Those are some thoughts I had.

**Dr Susanne Keitel:** Thanks a lot for these statements. So a sort of dual standards for well established versus traditional medicines as regards the quality?

**Dr Linda Anderson:** Not dual standards because I think the way we view quality with herbal products is very much about getting the starting material right, of the right quality, identification especially and controlling potential impurities. However, at the end of the day if you have a traditional product with no constituents with no therapeutic activity, maybe very limited information on active markers, there is no point chasing around for very sophisticated methodology as long as you have methods that are fit for their purpose. I just want to make sure that we don't, as the British say, 'throw the baby out with the bath water'. I want to make sure that we have good quality products in that category that we can trade across the European Union.

**Dr Susanne Keitel:** Thank you. Any comments from your side on the statements by Dr Burt Kroes or Dr Linda Anderson?

**Dr Michael Wierer:** I need to comment that I think the question of the markers is mainly important for the preparations, for the extracts. I think at a level of herbal drugs you can't know what is the future fate of what is produced out of that, which indication will it finally be used for. Do we agree that the discussion is mainly about preparations?

**Dr Linda Anderson:** My personal view is that, at the level of the herbal drug we are actually using the term marker incorrectly. I think what we should be talking about, and this is rather provocative, its constituents that are characteristic. Often we are not talking about one thing anyway in terms of identification but we are trying to find something that characterises the quality of the commodity. I think if you compare for example, the Valerian with lemon balm, and we had a very good example this morning, where we're talking about both having analytical markers, where you could argue if you were being provocative, like Dr Keith Helliwell sometimes, that what happened with Valerian, was that we chose the wrong marker, we chose something unstable. Having said that, the valerianic acids are characteristic of Valerian and in terms of identification and possibly the quality level they do characterise that material. That is why I think we almost have to go back a step and think again about what we are trying to achieve at each stage and not to think that everything is necessarily linked, and do not anticipate what happens at the next level. I think we've also got some confusion about where we use markers for analytical purposes in the finished product. That can be anything at a regulatory level. It doesn't matter what you measure if you're trying to define your quantity in the finished product. We don't really mind if you measure any secondary metabolite as long as it is an appropriate analytical marker. So, again there's a confusion with what we're trying to do.

**Dr Markus Veit:** First of all I would like to comment that in the first instance I like the approach to consider not defining markers in the European Pharmacopoeia for these botanical drugs, for the herbal drugs, because maybe you're right. We need to have a proper quality control, but that could be achieved also with any other marker and maybe not with the one defined in the European Pharmacopoeia. It is the responsibility of the applicant really to show in their application that they chose the right marker. Maybe we should think about that. I like that.

But I would like to comment on the other statement related to have 'fit for purpose' methods for traditional products. From my point of view the problem is that the analytical challenge for traditional products is quite large compared to well-established used products because you have very often multi-component products and combination products and even products where you extract drugs all together in one extract and so on. It's quite a challenge to analyse these products. The opposite is true, in my experience you need more sophisticated methods to fulfil requirements which are defined in guidelines in Europe, where you need to make sure you did your homework, which is defined in the regulatory documents, and that's a problem.

**Dr Linda Anderson:** I don't disagree with the complexity. I think the problem is trying to balance, particularly at a cost level, as a regulator we don't have to worry about cost, but we do have to worry about regulatory impact of cost and if you choose the most sophisticated methodologies then very often for a multi-component herbal tea this is just impossible. So the companies will go away and sell dietary supplements or just food commodities where they don't have to do the testing. I think the rational is to build quality in so that you have European Pharmacopoeia starting materials. We've said in our document on combination products that we recognise that although you could, with very heroic methods, maybe do a very complex combination with an assay on each component, it's realistic to test at different stages and apply more routine. When I say routine we're talking about liquid

chromatography, it's just not liquid chromatography with mass spectrometry and quantitative NMR, that's the state we're at.

**Dr Markus Veit:** I appreciate your approach, but the reality is different because even in the traditional quality guideline there is a statement that you can use less selective methods only if you can prove that you are not able to do your homework with the normal equipment and to make group determination and so on. You are only allowed to do that, if you read the guideline carefully, if you fail to make the determination with a more selective method. That's a problem for the applicants. I'm happy if we have an application to the MHRA, but if I go with the same dossier to another agency in Europe they will not accept that and that's a problem the applicant is faced with. There are different standards between different countries in the EU and I think it's very important that there is a level which is defined through guidelines and at the moment the level is quite high.

**Dr Linda Anderson:** I think one of the things we're trying to achieve within Europe is harmonisation of assessment criteria as well. We've actually been working very hard particularly on combination products and how different member states would approach them. Again it's very important but the combinations guideline never sought to look at heroic methods. It was to look at what seemed to be a routine type of approach to analysis. It wasn't that you would have to go to something that would be 10,000 GBP a sample, or whatever. Or approach a university first. That wasn't what was intended and if it reads like that then we've written it wrong and we should explore and revise it.

**Dr Susanne Keitel:** You now have homework for you and your colleagues in the Quality Drafting Group in the HMPC to harmonise. Prof. Dr Brigitte Kopp any statements for us?

**Prof. Dr Brigitte Kopp:** I have two points I want to mention. It concerns my work in the expert working group 13B. The one point is that we have until now no standardised method for the extraction of drugs for the assay methods and it came to my mind during Dr Matthias Hamburger's presentation that maybe PLE methods should be the choice for the method of extraction. My second point is that all our HPLC methods in the European Pharmacopoeia monographs are described with columns which are not really available and I think we have to harmonise using the short and small columns, so there must be a revision of our HPLC methods because we cannot say yes we can use the small columns. We don't know if it will work. I think this will be important for the next time for our expert groups.

**Dr Susanne Keitel:** Dr Michael Wierer, any comments?

**Dr Michael Wierer:** I did not quite understand when you said the columns are not available. I think what is important is that in view of the shortage of acetonitrile, we have realised we could use shorter columns to achieve similar results. So we could go to employ columns with internal diameters which are about 2.1 mm. The next step would then be as you mention HPLC, but there different people need different instrumentation and again, the question is as you have so high pressures do we want to put in a public standard a method with very specific, expensive equipment or, and I heard this as feedback from the expert group on chromatography, shouldn't we first open up to replace the 250 mm or 150 mm with 4 mm internal diameter columns by the ones with 2.1 mm? I fully agree that when we produce new monographs we should look into that proposal. Although in the presentation this morning we

saw that you can save a lot of diluent we should not forget the sample preparation still needs acetonitrile so this is only half of a solution.

**Prof. Matthias Hamburger:** Let me please add a comment to this. First for the HPLC, 25 cm column, this is really not a standard for today. This is chromatography from the 1980's. The problem is that most of the modern stationary phases are not available in these columns. These are still the old Lichrosphere type columns. Nobody in industry or academia is typically using these columns. I think one should really go to a 10-15 cm column of smaller diameter because that can be handled by the currently available HPLC equipment. You correctly say that UPLC is a major step, a quantum leap with completely new instrumentation and also certain problems in sample preparations related to it. I think the column issue can be solved relatively pragmatically.

As for extraction I mean in environmental analysis PLE is established. There are validated protocols available and I think that one should also in some way make this step. Again I think as far as I see, industry is using PLE quite a lot and I don't know exactly how widely it's used, but as far as I've seen, several companies use it so it really has been around for more than 12 years. As a result it's becoming in a way a standard method. The same is true for LCMS. Twenty years ago this method was very exotic and it really didn't work, I would say, now it has become a standard method that everyone's using. So in extraction, which is a bit less high tech, we can make this step. I would really advocate this.

**Dr Frank Waimer:** I think there's one comment from industry in that you have to think about the fact that there are a lot of small and mid-size companies involved, especially in the herbal industry. For those they're not talking about having 20 HPLC devices in their laboratories and then they buy additional LCMS - they very often have one HPLC, or if they're very lucky two. So still going in the direction of highly sophisticated methods even if they're established in the research and development is a big investment and a big step for small and mid-size industry, which has to be kept in mind when changing to different methods.

**Dr Susanne Keitel:** This brings us back to the problem we already discussed this morning in the first presentation where the question was raised in the direction of the European Pharmacopoeia "why don't you implement?" and concern was voiced that we need to be aware of our stakeholders. This is one of the reasons why we're here and why we're asking for your feedback on these proposals. So thank you for this comment.

**Prof. Fritz Kemper:** I think that this is the point in the discussion where I should raise my voice. For those who do not know me, I'm an old medical doctor, in the 60<sup>th</sup> year of his professional life, and I have followed with great interest today this event. First of all I want to give my sincere thanks to the EDQM for the idea to establish this Symposium as some kind of "state of the art". I think it was the right time, the right moment in the right place. Besides this I feel a little bit like a consumer's advocate. As for the accuracy of analysis, HPLC, LCMS or whatever else, we should not go so far as to make use of what is technically possible. We should go a pragmatic way to a limit of what is necessary to guarantee consumer's expectations regarding quality, efficacy and safety because most of these products, "herbal medicinal products" (HMP), are products for self medication and that means that the choice for the well-educated citizen leads to a special preparation. But there are also two other ways: a medical doctor's supported recommendation to take such a drug or the pharmacist's advice. I repeat myself: We have to meet the expectations of the consumer. If we do so, and in this sense this is the real aim of this conference, we should do it smoothly. That means even conversion factors should be applied, but only there where necessary and this is my opinion.

**Dr Burt Kroes:** Just a small comment that I think the method described in the European Pharmacopoeia does not enter any development in the chemical sense. In principal the method described in the European Pharmacopoeia is not compulsory. You have to demonstrate that your method gives a comparable result to the European Pharmacopoeia, but once you have established that you can use your own method instead of the European Pharmacopoeia method.

**Dr Susanne Keitel:** Thank you for the clarification. However if the method described in the European Pharmacopoeia is more sophisticated, it's difficult to establish that a more simple method will lead to the same result. I think it's more the other way round, defining, as has been stated, 'adequate methods' which serve their purpose in the European Pharmacopoeia and then leave it to industry to apply, if they wish so, more sophisticated methods would then be the more correct way.

**Dr Frank Waimer:** I have some slides. Thank you very much for the invitation. I really followed the discussion with great interest and got the impression that we are on the right track to solve all these problems. I think we learned today that herbal monographs of the European Pharmacopoeia are the basis for registration quality and also stability control in industry. We all accepted and we all want European Pharmacopoeia methods to be state of the art. They don't need to be cutting edge of science, but they must be state of the art, and so I think it's very important that we have a thorough assessment if there are changes in European Pharmacopoeia monographs of what consequences are for industry. This covers everything, new methods, new measuring techniques, new specifications, even new nomenclature or new standards of substances. Everything we saw today has an impact on our daily work. Maybe registration, stability studies and coming back to equipment, investment, personnel, you have to employ the whole pharmaceutical GMP documentation and as well validation or even declaration. So I think it is important, I got the impression that we are all learning that we have to make a very thorough impact assessment taking into account all aspects a change in a European Pharmacopoeia monograph will have.

Again yet another Horse Chestnut slide today, but I do think it is the best example and the proposal which has been made by the EDQM to find a transition scenario is an excellent solution. It gives time to think, it gives time to establish reliable data and to make proper decisions. It gives industry and players on the market time to implement these methods and have experience in these methods. Especially if you look at Horse Chestnut this is usually a delayed release form and so you have to think about how to adopt this method to the finished dosage form to the special requirements there. I have one example to show how far the impact can go of a change in the monograph. If you look at the actual declaration of the product, and this is a specific problem in standardised and quantified extracts, we have today a declaration on a package of a Horse Chestnut product which contains 50 mg TTG calculated as water free (wf) Aescin (UV). I have no comment on the methods; I just put it on for clarification. If you look at the new method in the European Pharmacopoeia, what will be on the label and on the package is one tablet contains 29 mg TTG calculated as wf Aescin (HPLC). I'm very thankful that you make the remark that herbal medicinal products are an OTC product. If I were a customer I might be surprised when I go to buy my normal package of a Horse Chestnut product to find only half of the expected amount and maybe the pharmacist would be a bit overwhelmed by that very specific analytical task, so as a customer I might come to the conclusion that it's better to take two tablets - to be on the safe-side and get in the approximate range of where I was before. Additionally you have to see that these products are

not only European products but world-wide products. They are marketed in Russia or China or South America. Also, we have a common understanding in Europe and people from regulatory affairs understand what happens here, but if you have to deal with registration authority somewhere in the world, it may be rather difficult to explain this very meticulous task.

We also saw options on how to solve that one could be a conversion factor or you proposed something completely new, like using a different reference standard like protoaescigenin and having a labelling of a difference substance which may make it easier for the customer to understand that something has changed.

So these are just some ideas and I'm looking forward to a discussion on this, which I think was very crucial today.

**Prof. Fritz Kemper:** We need more WEU preparations: Well-Established-Use. There is a misunderstanding between Dr Linda Anderson and myself. However, I don't think we have enough time to discuss this now.

**Dr Susanne Keitel:** I think Dr Frank Waimer has really brought it to the point. He has described again the problem we have discussed today. I mean I wouldn't purchase the 29 mg – you're just increasing prices without telling me! Any comments what would be your favourite option here, how should one tackle this situation? You are happy with both?

**Ms Silvia Munoz-Botella:** I have another question: which is the real dose a patient should take? 50 mg or 29 mg?

**Dr Frank Waimer:** All clinical studies, all data has been gathered, with the old analytic, so the product used contained 50 mg as seen determined by the UV method. So that would be the gold standard, which has shown clinical efficacy. Yes, it's difficult. Also there's another element in competition, if you think about such a transition state, how would you trigger the time point when you change the declaration? If I were someone marketing their product, I would try to delay that maybe the competitor was changing his declaration earlier.

**Dr Markus Veit:** Dr Frank Waimer thank you again for a very good presentation. The point is very good. I would like to add that this whole procedure there is no increase in safety, there is no increase in efficacy – just an increase in quality of this product. It's only different testing and nothing else. So I think it's very important to keep that in mind and really to think very carefully before we start such a procedure, if it is really necessary. The impact is really large and in terms of a global regulatory strategy for companies who act globally, this really puts some more problems on the table. That's my experience.

**Dr Susanne Keitel:** Can I interpret this as you advocating no change in method?

**Dr Markus Veit:** No but carefully evaluating beforehand what the impact is. I think there are cases where this would be necessary and we need to have modern methods for quality control of herbal medicinal products and respective starting materials. But at least this example shows that if we do that with already established products it has a really large impact. To do that with new projects and new extracts, that's ok. But to do that with established products it has a large impact and we should think about it carefully before doing anything.

**Dr Susanne Keitel:** But following this again would lead to different standards for older established products, compared to something that is developed new?

**Dr Markus Veit:** It is not a different standard. It's a different method and with the photometric method, we have a large experience and I think they add no value or quality to these products by testing them by HPLC. That is my point of view.

**Dr Susanne Keitel:** To summarise from our side. We see that there is a need to improve methodology but we're very aware of the impact this can have, especially on the status of products that have already been authorised and we are very careful in the decision that we take. So, this is reassuring.

**From the floor:** I would also like to be a little bit provocative and support Dr Markus Veit. We heard so many concerns about the changes in analytical methods from the consumer side, patient side, from the industry, the regulators, so who is really happy with the change? Is it only so that we can say the monograph in the European Pharmacopoeia is state of the art? That is the only benefit I see here. Why do we need that? We have clinical studies with products which were standardised with the old method. We do not have safety concerns with those products. They have been on the market for decades. What is the need for this change?

**Dr Susanne Keitel:** We have already heard some comments about the two methods, compared their variability. I would just like to tell you an anecdote while the microphone is being given to Dr Michael Wierer. I went to India recently to attend a meeting organised by the EDQM and the World Health Organisation (WHO) which focused on the quality of APIs. There we had a discussion on potential different standards in India – one the export standard, the good quality for developing countries, and then the quality for their own market. In this context a gentleman from the Ministry of Trade who said, 'You don't have to eat basmati rice every day; ordinary rice is ok for us.' Somebody else said, 'Twenty years ago I used to clean my trousers using benzene, of course I wouldn't want to do it today. But see - nothing happened, I'm still alive.'

So I do understand that you are provocative but there are several angles to this discussion.

**Dr Markus Veit:** But there is no difference in the quality of the products by testing them in a different way.

**Dr Michael Wierer:** I am afraid that performing a collaborative study with the old method might demonstrate the contrary due to the inherent large variability of this spectrophotometric assay. Publishing this could be dangerous as it might question the data in the literature which make reference to this old method. So in my opinion you can't really say that there is no problem.

**Dr Burt Kroes:** Since people are very provocative I would like to continue this discussion. The other question we could also ask is whether we need the amount. This is very complicated what you propose for the consumer. The question is, do we need the marker on the label? I know we are the author of the declaration guideline, but you could imagine for instance the SPC, a technical document, the people who read it are supposed to know the contents of the document. The solution should not be at the European Pharmacopoeia but maybe you could find a solution at a different level.

**Dr Keith Helliwell:** That is music to my ears! When we had the meeting in Geneva a few weeks ago and also in an article I wrote for *Pharmeuropa* about a year ago. I proposed an

alternative method of declaration. All these problems could be solved if we just had an extract with an agreed reference content of constituent. Then it wouldn't matter if you altered the assay or not, because you're still putting in a tablet or a preparation, the same quantity of extract made by the same process. So if you were to declare it as 60 mg of senna dry extract ARC and we all knew what the ARC was because it would either be in an HMPC specification or a European Pharmacopoeia specification. Then it wouldn't matter if that agreed reference content changed from 10% to 2%. It wouldn't matter in the slightest because it would still be referred to an agreed content reference extract. So if the HMPC is prepared to alter its declaration, which I think is incorrect anyway for standardised extracts then we would solve the problem and you would not have to worry about ratios. What Dr Michael Wierer was saying this morning about all that would be required then would be the range for the old extract and the range for the new extract coincided, you could then encompass them so that you weren't ruling out any extracts that already existed. This is a very simple solution and it would save all this hassle. Everything could go on in the background, the public would not know any different because the label wouldn't alter.

**Dr Linda Anderson:** I think it would solve a great many problems. There are some products that are labelled in terms of the content, for example senna products, some are labelled as 7.5 mg of sennosides and there is no reference to amount of extract, so you've still got to manage a marker place that would have different types of labelling. Maybe you have to get over that and move on to something else. It may be something to think about.

**Dr Susanne Keitel:** Thank you Dr Keith Helliwell for solving all the problems! I would like to hand over now to Prof. Dr Fritz Kemper who wanted to present something to us.

**Prof. Fritz Kemper:** The symposium is coming to an end. First of all in the name of all participants many thanks to EDQM for the idea and for organising this fruitful symposium. I may also go on with the remarks I made a few minutes ago. I think we all are gratefully indebted for the opportunity to express our thoughts not only in this panel, but also in the audience, and to listen for a couple of hours to questions which were raised by experts in the field and given in part some hints as to solve these problems. I think all this was under one roof and this umbrella was herbal medicinal products. There is this enormous traditional value not only acknowledged in Europe. I think as a go home-message look into the consequences of what we heard today. I think, from my point of view, there is more and more need for a better co-operation between those dealing with the subject. It is not only a matter of money behind that, we have to avoid double proves or whatever else, we have to co-operate – we have to look at what one is doing and how can it be applied to my own knowledge and back. We should be open. Here in this panel discussion we saw manufacturers, administrators, and scientists dealing, and I remind you, with the same subject. Let me say goodbye to all of you. This is most probably one of my last statements in public not without reminding you, this is a volume which all of you have in your library, but this has a child, since 2009, that is supplement 2009 of ESCOP monographs which has been made to the very best of our knowledge and with our best intentions to live up to consumers expectations.

**Dr Susanne Keitel:** Thank you very much Prof. Fritz Kemper. Before I close the session I would like to express our sincere thanks to Prof. Dr Brigitte Kopp for organising this event. And with that I would to thank you all for your patience, for staying here on a Friday afternoon until 5.30 pm – thank you! We have very much appreciated your lively participation and lively discussions. I would like to wish all of you a safe trip home.

## BIOGRAPHICAL NOTES

**Dr Susanne Keitel** is a licensed pharmacist with a PhD in pharmaceutical technology. Her work experience includes 10 years in pharmaceutical development in industry, with five years as Department Head of “Pharmaceutical Development/Oral Dosage Forms” at the former Schering AG, Berlin. From 1997 to 2005, she held the position of Division Head Pharmaceutical Quality at the Federal Institute for Drugs and Medical Devices (BfArM), Germany. She additionally served as Acting Head of the Division European Procedures from November 2003.

Since July 1, 2005, Susanne Keitel has been Head of EU, International Affairs at BfArM, a position involving representation of BfArM in a number of EU gremia. As a member of the Joint CHMP/CVMP Quality Working Party (QWP) since 1998, she was elected Vice-Chair of this group early in 2005. She has been a member of the EMA Paediatric Working Party, representing QWP, and has been actively involved in the International Conference on Harmonisation (ICH), where she acted as the EU topic leader and rapporteur for the ICH guidelines on stability testing and pharmaceutical development. On a national level, Susanne Keitel has been Chair of the German Pharmacopoeia and the German Homeopathic Pharmacopoeia since 2001. She also lectures in the postgraduate course “Master of Drug Regulatory Affairs” at Bonn University. She took up the post of Director of the European Directorate for the Quality of Medicines & HealthCare (European Pharmacopoeia and European Network of Official Medicines Control Laboratories/OMCL) - Council of Europe in October 2007.

**Prof. Dr Markus Veit** obtained his degree in pharmacy from the University of Frankfurt (Germany) in 1986. He studied for his PhD at the University of Würzburg (Germany), obtaining his PhD in 1990. During the period of 1990 - 1997 he was research assistant at the University of Würzburg (Germany). From 1997 to 1999 he was assistant professor in Pharmaceutical Biology at the University of Würzburg (Germany). From 1999 to 2002 he was Scientific and Managing Director of the German Central Institute for Pharmaceutical Research (ZA GmbH), from 2002 – 2006 Scientific and Managing Director of a private contract R&D institute. Since 2006 he has been Managing Director of i.DRAS GmbH (International Drug Regulatory Services). Since 1999 he has been Scientific Director of the German Pharmaceutical Manufacturers Research Association and Member of the German Pharmacopoeia Expert Committee on Pharmaceutical Chemistry. He teaches at the Universities of Frankfurt and Berlin, Germany and the University of Florida, Gainesville, USA.

**Prof. Matthias Hamburger** obtained a degree in Pharmacy from the ETH Zürich (Switzerland) in 1980, and a PhD in Pharmacognosy/Phytochemistry with Prof. K. Hostettmann at the University of Lausanne (Switzerland) in 1985. From 1985-1987, he was Postdoctoral Fellow with Prof. G.A. Cordell at the University of Illinois at Chicago (USA). From 1988 to 1993, he was a Senior Researcher and Privatdocent at the Institute of Pharmacognosy, University of Lausanne. From 1993-1996, he was involved with establishing the Center for Natural Products Research (CNPR) (Singapore), a industry-oriented high-throughput screening operation and joint venture of Glaxo-Wellcome and the Singapore Science and Technology Board. He acted as a Group Leader of Sample Supply and

Fermentation, and as Coordinator of worldwide sourcing and external collaborations. From 1995-1996, he was in addition involved with consulting activities in Switzerland in the area of phytopharmaceuticals and OTC products. From 1997-2004 he was Professor and Chair of Pharmaceutical Biology, University of Jena (Germany), from 2000-2002 Vice-Dean of the Faculty of Biological and Pharmaceutical Sciences. In April 2004, he took the current position as Prof. of Pharmaceutical Biology at the University of Basel (Switzerland); in 2009 he became Head of the Department of Pharmaceutical Sciences.

Prof. Hamburger has published over 130 research and review articles, numerous book chapters and proceedings, and co-edited a book. He served as Editor-in-Chief of the international journal *Planta Medica* and is presently Review Editor; he serves on the Advisory Board of several other journals, such as *Chemistry & Biodiversity* and *Fitoterapia*. He is member of various international and national scientific societies, and serves on the Board of Directors of the Society for Medicinal Plant and Natural Product Research. His main research interests are in the areas of natural products lead discovery, in the validation of herbal drugs and phytopharmaceuticals, and in integrated chemical and biological analysis of natural products and extracts.

**Dr Michael Wierer** obtained his degrees in pharmacy and food chemistry from Munich University, Germany. He studied for his PhD also at Munich University in the laboratory of Prof. Dr. Hildebert Wagner and obtained his PhD in 1988. Since 1988 he held several positions in medicines testing laboratories in Germany. In 1997 he was appointed head of the OMCL of Northrhine-Westphalia at Münster. He served as a member of the German Pharmacopoeia Commission and co-ordinator of the German OMCLs. In 2001 he joined EDQM, where he was responsible for several programmes of the European OMCL network and as scientific administrator of several group of experts to the European Pharmacopoeia. In 2006 he was appointed as deputy to the head of the European Pharmacopoeia Department.

He serves as the EDQM observer to the EMEA Committee on Herbal Medicinal Products (HMPC) and the joint CHMP-CVMP Quality Working Party.

**Dr Barbara Steinhoff** works as a scientist at the German Medicines Manufacturers' Association, Bundesverband der Arzneimittel-Hersteller (BAH), in Bonn. She studied pharmacy at the University of Bonn from 1978 to 1982 and received her doctor's degree after working on isolation and structure of tannins in brown algae at the Institute for Pharmacognosy in Bonn. From 1987 to 1990 she worked in the fields of quality control, regulatory affairs and drug safety for companies in Hannover and Münster. In 1990 she joined BAH in Bonn, where she concentrates especially on herbal and homoeopathic medicinal products as well as questions arising from the Medicines Law, e.g. requirements for quality, safety and efficacy, also in the international field.

From 1991 to 2002, Dr Barbara Steinhoff was secretary to the Scientific Committee of ESCOP, the European Scientific Cooperative on Phytotherapy, and has been elected co-chairperson in 2002. Since 1995 she is deputy member of the German Pharmacopoeia Commission and since 1996 member of the German Homoeopathic Pharmacopoeia Commission.

Since its foundation in 1991, Dr Barbara Steinhoff is a member of the AESGP (Association of the European Self-Medication Industry) Committee on Herbal Medicinal Products and thus been involved in various projects of the World Health Organization (WHO), also in co-operation with WSMI (World Self-Medication Industry), such as the preparation and discussion of the "Guidelines for the Assessment of Herbal Medicines" (1991), "Model Monographs on Selected Medicinal Plants" (1996 to 2006) and "Good Agricultural and Collection Practice, GACP" (2002/2003).

**Dr Bernhard Klier** obtained his degree in pharmacy studies from the University of Erlangen in Germany. He studied for his PhD at the department of Pharmaceutical Biology, the University of Erlangen and obtained his PhD in 1992. In 1992 he joined Martin Bauer.

Since 1993 he has been at PhytoLab GmbH & Co. KG, an affiliate of the Martin Bauer group, in matters quality control and test for contaminants of herbal drugs.

He is currently quality control manager and qualified person (QP) at Martin Bauer.

Since 1995 he has been member of the expert group “herbal drugs“ of the German Pharmacopoeia and since 2004 member of the group of experts No 13B (Phytochemistry B). He also attends the working party group MQH (Microbiological Quality of Herbal Drugs) and the working party group PST (Pesticides in Herbal Drugs).

**Dr Burt Kroes** obtained his degree in pharmacy from the University of Utrecht in the Netherlands. He studied for his Ph. D. at the same University. He obtained his Ph.D in 1990. From 1990 to 1997 he was assistant professor at University Utrecht, Department of Medicinal Chemistry, section Biogenic Medicinal Products (Pharmacognosy).

Since 1998 he is senior manager regulatory affairs/ assessor at the Medicines Evaluation Board (CBG-MEB) of the Netherlands and university lecturer at the Faculty of Pharmaceutical Sciences of the University of Utrecht.

He has been member the group on certification of herbals (since 2002) of the European Pharmacopoeia and a member of the Herbal Medicinal Product Working Party (1998-2004), alternate member of the Herbal Medicinal Product Committee (HMPC) of the EMA (since 2004) and chair of the Quality drafting group of the HMPC (since 2007)

**Dr Ulrich Rose** is involved in the establishment/monitoring of the Ph. Eur. reference standards as well as in the elaboration and revision of monographs in the Laboratory Department of the EDQM in Strasbourg. More recently, he is particularly responsible for the establishment of herbal reference standards for monographs on herbal drugs and preparations. Before joining the Council of Europe in 1991 he was assistant professor and lecturer for pharmaceutical analysis and physico-chemistry at the Johannes Gutenberg University in Mainz where he undertook research work in structure-activity-relationships and chiral separation of dihydropyridines. At the same university he obtained his PhD in pharmaceutical chemistry in 1985.

For his research work Dr Ulrich Rose received the Award of the Johannes Gutenberg University in 1985 and the Award of the Emil and Paul Müller Foundation in 1987. He is author of more than 30 publications.

**Dr Anton Biber** obtained his degree in food chemistry from the University of Karlsruhe in 1978. During 1979 and 1984 he was a research assistant at the University of Würzburg and received his PhD. Then he joined a research group at a private institute in Munich and worked on bioavailability and metabolism of tobacco smoke constituents.

From 1987 to 2004 he was Head of the Bioanalytical Department of Dr Willmar Schwabe GmbH & Co. KG, Karlsruhe and was involved in bioavailability and analytics of herbal drugs and preparations.

Since 2004 he is Head of the Analytical Development of Deutsche Homöopathie-Union GmbH & Co. KG, Karlsruhe and member of the expert group “Analytics“ of the German Homeopathic Commission.

**Dr Keith Helliwell** (PhD, B.Pharm, M.R. Pharm.S)

PhD obtained in 1975 at The School of Pharmacy, London University on an alternative poppy species to *P. somniferum* as a source of opiates.

Joined William Ransom & Son plc in 1977 as Head of Research and Development, became Director of Technical Services in 1989 when assumed responsibility for all of the laboratory and non-production technical functions of the company. From 1994 until retirement from full time employment in 2005 additionally responsible for overseeing the manufacture of all plant extraction products. Since 2006 employed, on a part-time basis, by William Ransom & Son plc as Senior Technical Advisor – Natural Products.

European Pharmacopoeia: Chair of Group of Experts 13B (Phytochemistry B), Chair of Working party MQH (Microbiological Quality of Herbal Drugs), nominated UK expert to Group of Experts 13A (Phytochemistry A).

British Pharmacopoeia: Member of the British Pharmacopoeia Commission, member of Expert Advisory Group: HCM (Herbal and Complimentary Medicines).

**Ms Melanie Bald** studied Pharmacy at the University of Bonn (Germany) and became a pharmacist in 2002. From 2002 to 2005 she worked for the Federal Institute for Drugs and Medical Devices (BfArM) in Germany. As scientific assessor she was responsible for the evaluation of dossiers for marketing authorisation in the fields of homeopathy and anthroposophy. She joined the European Directorate for the Quality of Medicines & Health Care (EDQM) in 2005, where she is in charge of the two Phytochemical groups of Experts and the Working Party on Traditional Chinese Medicines (TCM).

**Prof. Dr med. Dr h.c. mult. Fritz H. KEMPER** obtained his degree in medicine (approbation) in 1950 from the University of Cologne/Germany, followed by an education in internal medicine at the Universities of Cologne and Frankfurt (1950 – 1958) and in Pharmacology & Toxicology, University of Münster and abroad. Full Professor for Pharmacology and Toxicology (1969 - 1993), now Professor emeritus.

Consultant of the Scientific Committee on Consumer Products (SCCP), the European Commission, Brussels. Chairman of the Board of Directors of the European Scientific Cooperative on Phytotherapy (ESCOP).

Honorary member of the

- Cosmetic Commission and the Commission for Synthetic Materials of the Federal Institute for Risk Assessment (BfR, Berlin)

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- Scientific Committee for the Evaluation of Food Additives and Ingredients; German Research Organization (SKLM-DFG, Bonn)

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