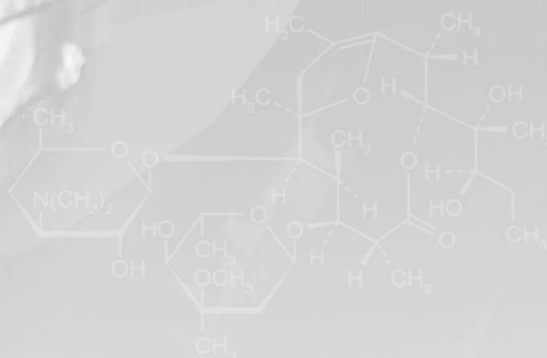


# Pharmaceutical Reference Standards

Strasbourg, France, 9-10 October 2008

**PROCEEDINGS**





# **PHARMACEUTICAL REFERENCE STANDARDS**

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

9-10 October 2008  
Strasbourg, France

## **PROCEEDINGS**



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*Welcome address*

**Dr Susanne Keitel**, Director, EDQM/Council of Europe

Ladies and Gentlemen,  
Dear Colleagues,

Welcome to the EDQM, a place reflecting the image of the Council of Europe, the cradle of European democracy, as it offers an appropriate framework to meet, find common ground, work together and share resources and expertise.

The room in which we find ourselves today is also particularly symbolic, as this is the very place where the European Pharmacopoeia Commission meets three times a year - and of course the theme of our symposium today would not exist without the standards defined by the European Pharmacopoeia for the application of its monographs.

Today's symposium was inspired by frequent discussions on the required properties and use of reference standards held at different levels and forums. We therefore believed that it would be valuable to provide a platform for an international exchange of views on the different aspects related to the subject. The great interest this symposium attracted - we have more than 170 registered participants from 31 countries - proves that this is indeed an important topic for all stakeholders involved.

However, the objective of this symposium is not to reach any conclusion or any particular decision, but in fact to provide a forum for discussion and exchange whereby users and partners can express their point of view, opinion and criticisms in order to optimise the system in this field, a field which is constantly expanding – indeed the ever increasing portfolio of substances available from pharmacopoeias demonstrates this. At the EDQM more than 2000 different preparations are currently available and largely used in more than 100 different countries.

As you may be aware, the mission of the EDQM is based on the very concept of providing a forum for dialogue and exchange. This symposium is therefore a perfect example of such an event whereby representatives and stakeholders from national authorities, regulators, industry, associations, the OMCL network, academia and pharmacopoeias from the world over can make their contribution to a topical issue.

The programme over the next two days will cover both chemical and biological reference standards and will open discussion for the following:

- Is the uncertainty of measurement of the assigned value of a pharmacopoeial reference standard an important parameter to be used for determining conformity to a specification? We are all aware that our US colleagues just announced their first Certified Reference Standard. So is this the direction to take?
- Can International Units be replaced by S.I. Units for the assignment of potency in Biological Reference Preparations used for the control of Biological

medicinal products? If so, in which circumstances can this be achieved and which measures do we need to take?

- The pharmaceutical industry would welcome the introduction of global standards – to what extent is this possible and what impediments must be removed to realise this objective?
- The increasing importance of herbal drugs poses the question of how to establish and prepare standards for herbal drugs and preparations.
- The globalisation of trade increases the need for adequate impurity control. Thus, availability of standards for the control of impurities in pharmaceutical substances and products is becoming even more important to ensure compliance with ICH and pharmacopoeial requirements. But which approaches are possible and should be taken?

In conclusion, I wish all of us a fruitful and constructive symposium and hope that as a result we will all be better equipped to tackle the new challenges that lie ahead in this field, a field which is essential for the future of medicines in Europe and the whole world.

**SESSION 1:  
Pharmacopoeial Reference Standards**

**Definitions and guidelines**

Prof. John Miller, Head of the Laboratory Dept, EDQM/Council of Europe

Prof. Miller's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Session 1: Pharmacopoeial Reference Standards

The presentation includes definitions employed and refers to guidelines relevant to the preparation of reference standards. The status of the standards of the European Pharmacopoeia is also outlined.

**The United States Pharmacopeia (USP) Reference Standards Programme**

Dr William F. Koch, Chief Metrology Officer for the USP

Dr Koch's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Session 1: Pharmacopoeial Reference Standards

The United States Pharmacopoeial Convention (USP) is the official public standards-setting authority for all prescription and over-the-counter medicines and other health care products manufactured or sold in the United States. USP's documentary standards and reference standards are used by regulatory agencies and manufacturers to ensure that these products are of the appropriate strength, quality, and purity. USP's official Reference Standards are highly characterized specimens of drug substances, excipients, impurities, degradation products, dietary supplements, compendial reagents and performance calibrators. USP Reference Standards are established through a collaborative testing protocol that involves USP laboratories, the pharmaceutical industry, and Food and Drug Administration (FDA) laboratories, based directly on official monographs in the *USP-NF*, whose standards and procedures are enforceable by the FDA. USP's standards are also recognized and used in more than 130 countries around the globe, helping to ensure public health throughout the world for almost 200 years.

In 2008, USP took the next step in providing standards of the highest metrological quality by achieving accreditation to International Organization for Standardization (ISO) Guide 34, building on its prior ISO 9000 and 17025 certifications. The resulting new class of USP Reference Standards, the USP Certified Reference Material (CRM), advances the metrological science of analytical measurements of medicines and food ingredients by providing certified property values with associated uncertainties and metrological traceability. USP is developing criteria to identify which of its over 2000 Reference Standards will be promoted to CRM status with the requisite Certificate of Analysis (COA), based on stability,

homogeneity, measurement need, suitability for use, and impact on public health. Harmonization of the USP Reference Standard program, including CRMs, is a key objective as we provide measurement science as a critical enabler for global pharmaceutical, food and health industries.

**The Japanese Pharmacopoeia (JP) Reference Standards Programme**  
Dr Shigeo Kojima, Pharmaceuticals and Medical Devices Agency (PMDA), JP

Dr Kojima's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Session 1: Pharmacopoeial Reference Standards

**System for revising the Japanese Pharmacopoeia**

First edition of the Japanese Pharmacopoeia was published in 1886. The JP is published by the Japanese Government as the Ministerial Notification of the MHLW (the Ministry of Health, Labour and Welfare) under the Pharmaceutical Affairs Law (PAL) of Japan. The Pharmaceutical and Medical Devices Agency (PMDA), a semi-governmental agency, serves as the secretariat for revising and publishing JP. JP Committee is organized in the Pharmaceutical Affairs and Food Sanitation Council (PAFSC) for consulting important matters related to JP, and 15 Expert Committees are organized for making JP drafts in the PMDA.

**JP has a policy to establish Reference Standards (JP-RS) for the assay of drug substances.**

- Not establish RS only for the assay of drug products
- Not establish RS only for other tests, e.g. identification

**Quality required for JP-RS**

Since JP-RS is established for the use as a measure in the assay to judge pass/fail of drug substance, high purity is required. However, it should be considered that excessively high quality will impose burden on its supplier and users, and hinder its stable supply.

**Current SJP criteria to secure the quality of Chemical RS**

- Procure a candidate for JP-RS with enough quality. In some cases that such a candidate could not be obtained, recrystallization of the candidate was carried out.
- Estimate the content of impurities, and calculate the purity of the candidate.
- If the purity estimated above is not less than 99.5%, the candidate can be used as RS with the purity of 100%.
- If the purity estimated above is less than 99.5%, the candidate can be used as RS by using a correction factor reflecting the estimated purity.

-

**The European Pharmacopoeia Reference Standards Programme**

**Chemical Reference Standards**

**Biological Reference Standards**

Dr Ulrich Rose, Scientific Officer, Laboratory Dept, EDQM/Council of Europe

Dr Rose's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Session 1: Pharmacopoeial Reference Standards

European Pharmacopoeia reference standards - Chemical Reference Substance (CRS), Biological reference preparation (BRP), Herbal reference standard (HRS) - form an integral part of the Ph. Eur. monographs and are used for a wide variety of purposes in order to achieve adequate quality control of substances for pharmaceutical use. Where a European Pharmacopoeia reference standard is referred to in a monograph or general chapter it represents the official standard that is alone authoritative in case of doubt or dispute.

Chemical reference substances (CRS) may be used for different purposes, such as identification tests, tests for related substances by High Performance Liquid chromatography (HPLC), Gas Chromatography (GC) or Thin-layer chromatography (TLC) and as assay standards. The candidate standards are tested against a variety of analytical methods where the extent of testing and the number of laboratories involved depends on the intended use of the CRS. Recently, an increasing number of mixtures and spiked samples have been established in order to avoid the use of individual impurity standards. The growing number of chromatographic assay methods requires the elaboration of assay standards with assigned content which is usually realised by a collaborative study.

Biological standards may be qualified by either physico-chemical or biological methods, the latter being indispensable for the characterisation of highly complex molecules or mixtures.

The decision of the European Pharmacopoeia Commission to introduce compendial reference standards for qualitative and quantitative purposes into monographs for herbal drugs and their preparations resulted in a new challenge to establish suitable standards for these monographs.

The different types of standards, requirements, strategies of establishment and production and the correct use will be discussed in this presentation.

***Discussion with the panel of speakers***

**Question from the floor:** It was noted that the number of CRSs had largely increased these last years both at Ph. Eur. and at USP level, JP having a lower number of CRSs. Would this increase continue to be exponential in the future?

**Answer from the USP:** the increase was linked to the appreciation of the importance of reference standards for quantification/identification of impurities; drug products which were

not yet covered, would have to be covered too in the future, as well as food and dietary ingredients and potentially Chinese medicines.

**Answer from the EDQM:** the increase in the number of CRSs was largely due to the establishment of impurity CRSs, as a consequence of the elaboration, or more often of the revision of monographs (change from a TLC method to an HPLC method). An inflection of the curve was not expected. It was also pointed out that since the Ph. Eur. had decided to apply the prescriptions of the International Conference Harmonisation (ICH) note for guidance on Impurities in new drug substances to all organic substances apart from the antibiotics, and since the Ph. Eur. tried to be as transparent as possible in listing the impurities that could be detected by the method(s) in the monograph, the need for impurity CRSs was constantly growing.

**Question from the floor:** What was the purpose of USP in establishing a CRM? Why just for dextromethorphan hydrobromide? A period of validity was stated: what difference did USP make between retest date and expiry date? On which grounds was the period of validity (until 23 September 2013) based? Was there any added value in using a CRM?

**Answer from the USP:** These last years pilot studies had been carried out on a number of USP reference standards and dextromethorphan hydrobromide had been retained because it was the purest one. USP was in the process of establishing criteria defining how to proceed in the future for further CRMs.

The term “period of validity” was used to be in line with the ISO guidelines. It was nonetheless agreed that the term “retest period” would be more appropriate.

Choice of the date of 23 September 2013: the reference standard had shown to be stable for years so no problem was expected and a period of validity of 5 years was decided arbitrarily. Reassessment of the purity was planned and the production of a new certificate would occur if necessary.

Need for a CRM: there was a need to assess the uncertainty since USP wanted its standards to be part of metrological system where measurement and uncertainty were anchored. It was also important for the traceability of the results. Some people might think that this uncertainty was insignificant but this was not the opinion of USP; a CRM would give the analyst more information to propagate on the trueness of the results. The use of the uncertainty of the CRM was not mandatory; it was given for information and it was up to the user to use it or not. The CRM was a pedigree given to the reference standard.

**Comment from the audience:** if the use of the uncertainty value of a CRM was only for information, this should be clearly stated. It was also pointed out that a retest period was completely different from a period of validity: at the date of the retest period, the batch had to be retested while at the end of the period of validity, the batch had to be discarded.

**Question from the floor:** Dextromethorphan hydrobromide CRM was a monohydrate but the certificate of analysis of the CRM stated that “For quantitative USP-NF applications, determine the water content titrimetrically at the time of use and use a calculation value of 1.000 mg of dextromethorphan hydrobromide per mg of material on the anhydrous basis”. The water content was about 4%; the uncertainty of the water determination would contribute to the uncertainty of the CRM and it would vary from one user to the other. Under these circumstances, what was the value of the uncertainty given to dextromethorphan hydrobromide CRM?

**Answer from the USP:** the uncertainty of the water determination would indeed contribute to the uncertainty value of the CRM. The uncertainty value had been assigned on the basis of the tests performed.

**Question from the floor:** How about stability testing of CRSs?

**Answer from the EDQM:** the substances described in the monographs of a pharmacopoeia were not completely new substances, but “old” substances fully documented by companies especially as regards the stability data; a risk analysis was therefore possible; the EDQM set up a monitoring programme with a grid of time based on the stability data provided by the company. The retest period was also based on the use of the CRS: when the CRS was used for an assay it was shorter than for a CRS used for identification. When too few data was available to EDQM (e.g. mixtures of impurities), the retest period was 12 months. If good results were obtained, the retest period might be prolonged.

**Comment from the USP:** USP also had a continued stability for use programme. Attention was also paid to complaints received from users. USP could not tell whether FDA would accept the uncertainty value associated to the CRM. The pharmaceutical sector did not inject new challenges compared to what was done in other sectors such as food, environment, ... The way pharmaceuticals should be treated was the same as for other substances. There was no need to reinvent the wheel.

**Comment from the audience:** if the uncertainty value was strictly applied when releasing production batches, this would probably render the specifications stricter and thus have a big impact on industry, without bringing any improvement to public health.

**Question from the floor:** Was homogeneity a problem for herbal reference standards produced by lyophilisation?

**Answer from the EDQM:** herbal products were not lyophilised but active principles or markers which were clearly defined chemical substances. Homogeneity testing was done in the same way as for other freeze-dried substances.



**SESSION 2a: WORKSHOP I**  
**Chemical and Herbal Reference Standards**

**Certified reference materials: a possible approach for Pharmacopoeias and pharmaceutical industry?**

Dr Steve Wood, LGC Limited (UK)

Dr Wood's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Workshop I: Chemical and Herbal Reference Standards

The pharmaceutical industry requires pure materials, as well as matrix standards, for quantification, identification or for demonstrating compliance within or below set regulatory and/or product specified limits. The requirements for such standards vary depending on the end application; however, manufacture of these materials to the requirements of the appropriate guidance documents produced by the International Organisation for Standardisation committee on reference materials (ISO REMCO) is appropriate for all scenarios to ensure quality and fitness for purpose.

Since its inception in 1975, ISO REMCO has produced a number of guidance documents relating to the production and use of reference materials. The most well known of these is ISO Guide 34 (General requirements for the competence of reference material producers), which sets out the quality system requirements for reference materials production including the organisational and production control requirements and gives guidance on the requirements for preparing, certifying, storing and labelling reference standards for physical, chemical and biological measurement.

In this paper I will describe the different reference material categories and definitions; explain the role of ISO REMCO including current activities to develop additional guidance on the production of reference materials for quality control and for reference materials for qualitative analysis; give an overview of the ISO Guides and Standards relevant to the production of certified reference materials and accreditation of reference material producers; and outline the process of reference material production using the certification of a theophylline pure substance reference material to illustrate the key points in the process.

**Non-compendial applications of standards - Needs and expectations from the industry**

Dr Hanno Binder, Sandoz GmbH (A)

Dr Binder's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Workshop I: Chemical and Herbal Reference Standards

In the first part of the presentation the contributors to the accuracy of the assigned content of a CRS are described. Whereas for the determination of water, residual solvents and counter ions – in case of salts, external standard methods are available leading to accurate results, the

determination of the related substances strongly depends on the methods used. The impact of this uncertainty on testing assay is lower than for related substances.

The next chapter deals with non-compendial use of a CRS. European Pharmacopoeia CRS are used for the analysis of medicinal products. The risk to use a CRS for an assay determination is seen as rather low provided that selectivity regarding related substances and excipients is verified.

When the CRS is used for a test for related substances it depends if the same or a different method is used. In the first case similar considerations as for the assay are valid. In the second case a full validation including peak assignment is necessary.

The 3<sup>rd</sup> part of the presentation discusses the doubts related to Ph. Eur. chapter 5.12 "Reference Standards". Despite the chapter is published for information, some national authorities are applying it in a very strict sense. Two examples are given regarding deficiencies expressed concerning the content declaration of related substances and the second one deals with additional requirements from national authorities for a secondary (working) standard which was calibrated versus the Ph. Eur. CRS.

The final chapter highlights some needs and expectations from industry. 6 examples are given demonstrating the impact for the industry. These examples should form the basis for the discussion section.

### **New technologies in characterisation**

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

Prof. Veit's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Workshop I: Chemical and Herbal Reference Standards

Reference standards must have a purity suitable for the intended use. The demand for pharmaceutical reference standards to be of the highest possible purity results from the common practice of performing assay using the 100 % peak area method. This method only supplies sufficiently accurate results if the reference substance has a purity of > 99.5 %. For substances with a lower purity the respective content determined can only be accurate if the response factors of the impurities and of the analyte are identical. This criterion is met in the rarest cases only. All chromatographic methods for content assignment within the scope of certification are called secondary because the values determined always have to be referred to calibrated response factors. Avoiding all problems described, „direct“ or „relative“ primary methods of measurement conveying a direct traceability back to the SI unit ensure an essentially higher metrological quality. To date, however, these methods are only used for purity determination, for content assignment of pharmaceutical reference substances, however, in exceptional cases only.

The quantitative nuclear magnetic resonance spectroscopy (qNMR spectrometry) is such a primary and highly selective method whose employment would essentially simplify and increase 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 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. Ultimately identity and purity analysis could be performed in one step using the qNMR method. Hence the substance supply required for certification, for instance the very expensive natural products, could essentially be decreased, which would save costs due to the high effort in connection with isolation and purification. Since NMR spectroscopy has the character of a primary method, all prerequisites are fulfilled to be able to perform metrologically high-quality, SI-based certifications for pharmaceutical reference materials.

### **Standards for herbal drugs and preparations** Dr Keith Helliwell, William Ransom Son PLC (UK)

Dr Helliwell's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Workshop I: Chemical and Herbal Reference Standards

The European Pharmacopoeia definitions for *Herbal Drugs* and *Herbal Drug Preparations* encompass a diverse range of plant derived materials. Despite this diversity, the framework of analytical methodology for individual *herbal drug* and *herbal drug preparation* monographs is remarkably similar and may be categorised as follows:

- Identification
- Absence of adulterants and/or substituents
- Limit tests for undesirable constituents
- Assay for constituents of interest (either therapeutically active compounds or marker compounds)

Within this framework of analytical methodology there is a requirement for different types of reference standard. Conventional chemical reference standards may not fulfil the necessary criteria and more robust analytical methodology may result from using a herbal drug or herbal drug preparation as the reference standard.

This presentation seeks to examine the analytical requirements for reference standards in herbal drug and herbal drug preparation monographs by reviewing, with examples, the development of some recent monographs. The applicability of the use of *Herbal Drug Reference Standards*, *Herbal Drug Preparation Reference Standards* and *Chemical Reference Standards* will be discussed together with the proposed nomenclature for these standards.

### Standards for impurities

Dr Andrea Lodi, Deputy Head of the Laboratory Dept, EDQM/Council of Europe

Dr Lodi's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Workshop I: Chemical and Herbal Reference Standards

The presentation covers the general lines followed by the EDQM for establishment and provision of impurity reference standards. It also underlines the specificity of this particular category of reference standards.

Impurity reference standards are more and more frequent in the monographs of the European Pharmacopoeia. This is a direct consequence of the policy on organic impurities adopted by the Commission. In particular, the concept of « specified impurity », introduced in the Ph. Eur. (chapter 5.10) as of January 2005 requires that the specified impurities be unambiguously identified. The vast majority of the Ph. Eur. control methods for organic impurities are based on separation techniques (predominantly LC-UV and GC-FID), which require standards for comparison.

Another element to be considered is that the European Pharmacopoeia Commission has endorsed a policy of progressive revision of the existing monographs in order to bring the related substances section up to speed with the general monograph « Substances for Pharmaceutical Use » and the General Chapter 5.10.

As a result of all this there is need for many more impurity CRS than in the past because the average number of impurities controlled by a single monograph is increasing as well as the number of monographs where related substances are controlled by a selective LC/GC method.

The best approach to identify a peak in a chromatogram is to use authentic samples of the impurity. Nonetheless, in case of unavailability of an appropriate quantity of « pure » impurity, the above approach is not practicable. Alternative solutions such as impurity mixtures or spiked samples may be considered, especially in those cases where the use of the reference standard is only qualitative.

A recent, practical case (Lamotrigine for system suitability CRS) is used to illustrate the challenges and the opportunities that can be associated with the establishment of an impurity CRS.

## **SESSION 2b: WORKSHOP II Biological Reference Standards**

### **International Reference Standards**

Dr David Wood, WHO Family and Community Health

Dr Wood's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Workshop II: Biological Reference Standards

*(Summary done by the EDQM)*

David Wood presented the position of WHO regarding International Reference Standards and biological standardization. WHO standards are established in international collaborative studies with biological assays and assigned a value, usually in arbitrary units (International Units, IU). These are considered primary reference standards. They are validated for the intended purpose but the definition of the unit is not always dependent on a specific method. In examples where a shift to chemical reference standards can be achieved, i.e. the biological standard can be appropriately characterized by physico-chemical methods, then the biological standard is discontinued (e.g. some antibiotics). Over the next five year period, one priority of WHO is to establish genetic reference standards to address an increasing demand. Another main objective is to increase contacts with stakeholders and users in order to promote the use of international standards and to increase input from users on needs and concerns.

### **Needs and expectations for Biological Reference Standards**

#### **Viewpoint from the industry**

Dr Sylvie Uhlrich, Sanofi Pasteur (F)

Dr Uhlrich's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Workshop II: Biological Reference Standards

Biological medicines are materials of complex composition which cannot be fully characterized by physical and/or chemical methods. Biological and immunological assays are needed for complete characterization, especially for assessing the activity of biological products. Such methods are comparative rather than absolute, and biological reference standards support the standardization of biological and immunological assays.

In the vaccine industry, a large part of the reference standards used for quality control are biological reference standards. Although the first choice is to have official reference standards, in-house standards are used when no official reference standards are available or when a homologous reference standard is needed. The difficulties related to the management of in-house reference standards will be discussed.

Reference standards are managed under defined quality management systems. All steps, including supply, characterization, qualification, stability, and inventory, have to be

controlled for in-house reference standards and it is expected to have the same control for official reference standards. A comparison between the management of in-house and official reference standards will be made from the user's perspective, and specific needs regarding quality assurance and new standards will be discussed.

### **Qualification of protein reference standards**

Mrs Anne Munk Jespersen, Novo Nordisk (DK)

Mrs Munk Jespersen's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Workshop II: Biological Reference Standards

The presentation will be divided in two parts.

In the first part of the presentation qualification of a protein reference material will be presented by using Glucagon as an example:

- Traceability – why both a primary and secondary internal reference material?
- Which product chosen for a primary and secondary reference material
- Homogeneity, why is this an important parameter
- Characterization – ID and purity
- How to assign the content
- Mass balance as a confirmation
- Content control - How do you measure the consequence of the change? What happens when you then introduce a new set of primary and secondary reference material for lot release?

The second part will deal with challenges in complying with different Pharmacopoeias and WHO's reference standards at the same time and what we can do for obtaining harmonized global reference standards. An example of on-going work on harmonizing pharmacopoeias reference standards will be given and suggestions for future ways to go for a harmonized world will be proposed.

### **International units or milligrams for well-characterised biologicals**

Dr Adrian Bristow, National Institute for Biological Standards and Control (UK)

Dr Bristow's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Workshop II: Biological Reference Standards

The WHO International Standard for a "biological" may be assigned a value in International units or, less frequently in SI units, usually mg. In the therapeutics field the use of units or mg is almost invariably dictated by the decision to use a biological (IU) or physico-chemical (mg) assay method. This choice is formally made on the basis of criteria set out in ICH Q6B:- "a

*biological assay to measure the biological activity of the product may be replaced by physicochemical tests only in those instances where:* • *sufficient physicochemical information about the drug, including higher-order structure, can be thoroughly established by such physicochemical methods, and relevant correlation to biologic activity demonstrated; and* • *there exists a well-established manufacturing history. Where physicochemical tests alone are used to quantitate the biological activity (based on appropriate correlation), results should be expressed in mass".* The transition of somatropin (rec growth hormone, a 22kD "well-characterised" therapeutic protein) from a biological, value assigned in units to a chemical value assigned in mg is an example of the data which have been held to satisfy these criteria.

In the diagnostic field, the issue is less clear cut, as many methods analytical methods such as immunoassays or NAT techniques are not unambiguously either bioassays or physicochemical assays and similar measurands are often differently calibrated. Metrological paradigms have however been developed in which the use of SI units is essentially linked to the availability of a reference method (prEN ISO 17511). The potential applicability of this concept in the therapeutics field can be illustrated using the history of calibration and traceability of subsequent SI-calibrated growth hormone standards. This example also illustrates the metrological consequences, including design of the value assignment protocol (collaborative study) that follow from choosing SI or IU to calibrate a reference material

### **Place of standards in the context of biosimilars**

Dr Martin Schiestl, Sandoz GmbH (A)

Dr Schiestl's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Workshop II: Biological Reference Standards

The regulatory framework for biosimilar products has been successfully established within the European Union and the first products have been recently approved by the European Commission. Examples are the Somatropin products approved in 2006, followed by Erythropoietin in 2007 and most recently Filgrastim in 2008.

In accordance with innovative biopharmaceuticals, the development of biosimilar products requires different kinds of reference materials. Some are established in house, others are provided by international or regional standard setting organisations.

The presentation focuses on roles and issues of international and regional reference standards. These 'external' standards have been proven to be extremely helpful in many ways. They serve as cornerstones in the biotech world, and provide the unit definitions for the potency. On the other hand, these standards are difficult to characterize and require extensive analytical efforts to ensure adequate description and long term consistency. Sometimes inconsistencies happen and both, the standard setting organisation and its customer can help to improve the situation. Potential measures include the strengthening of the communication lines, the extension of the characterization and also additional control measures to handle the worst case.

In addition to the requirements for an innovative development, the biosimilar path requires a comparability exercise with the reference product, which represents the product of the originator. The development of the biosimilar is therefore triggered by the measured properties of the reference product. In the case that an international standard is not available, the reference product is used to define the potency units of the biosimilar product.

### *Discussion with the panel of speakers*

*(Summary done by the EDQM)*

The presentations and the discussions confirmed that for most groups of biologicals, international standards calibrated in IU will continue to be the mainstream for many years. For selected biologicals such as small-medium sized peptides without glycosylation, a shift from biological (IU) to chemical reference standard (SI) is feasible and has indeed been used successively. However, this process is extremely labour-intensive and thus uncommon. The WHO plans to further investigate strategies on this topic at the next meeting of the ECBS (2009). Development of metrological approaches, involving primary methods for biologicals that are SI traceable, is being supported by the EU through various dedicated groups. Exchange between these groups and WHO/EDQM were encouraged to ensure that the needs of the pharmacopoeial environment and ultimately patients were kept in mind as developments progress.

There is a current trend to develop and/or request product-specific reference standards, e.g. for assay of combination vaccines or shift to immuno-chemical methods for replacement of animal experiments. This will however create a significant challenge to the concept of global international standardisation.

Standard setting authorities as well as industry participants estimated that the assignment of potency unitage to successive batches of reference standards is performed with the minimal discontinuity possible. It was confirmed that a stability testing (monitoring) programme is already in place for official reference preparations. However it was acknowledged that there was a demand from the users for more information on the stability monitoring. It was thus suggested that means to address this demand could be sought, perhaps through inclusion of information in product leaflets or in publications such as *Pharmeuropa-Bio*.

The prevailing preference among industry to use official standards over in-house standards calls for improved communication between industry and standard setting authorities. This implies a two-way flow of information: from authorities to users of information on existing and future reference standards, as well from users to authorities of feedback information on the standards used and early input for the establishment of future standards.

EDQM insisted that reference standards are not established to hinder the development of biosimilar products and that communication with the biosimilar industry is as wanted as with other stakeholders. All parties agreed that cooperation between industry and regulatory bodies is essential for optimised work on both sides.

There is a general consensus that globalisation of the market for medical products requires a sustained need for enhanced harmonisation of standards and methods for biological substances between WHO and regional pharmacopoeias as well as between regional pharmacopoeias.

**SESSION 3:  
Perspectives from the regulators & industry**

**European Union's View point & Expectation**

Dr Jean-Louis Robert, Joint CHMP/CVMP Quality Working Party (QWP, EMEA)

Dr Robert's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Session 3: Perspectives from the regulators & industry

In an application file for marketing authorisation, information on Reference Standards is part of the submission. This is described in Notice to Applicants, section 3.2.S.5 and 3.2.P.6 of the CTD-Q:

“Information on the reference standards of reference materials used for testing of the drug product should be provided.”

**The Russian Federation's Viewpoint & Expectations**

Prof. Dr Valeria L. Bagirova, Scientific Center for Expertise of Medical Products (ZRU)

Prof. Bagirova's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Session 3: Perspectives from the regulators & industry

*(Summary done by the EDQM)*

Review of the system in Russia, of the reference sources for raw material and finished products production in this area. Overview of the fast development of the pharmaceutical industry in Russia since the beginning of privatisation, leading to a growing need of a strengthened and centralised regulation and of reference standards, first imported then in the future established in Russia or by international collaboration.

**Audits and GMP-Inspections, Reference material**

Dr Matthias Heuermann, Landesinstitut für Gesundheit und Arbeit NRW (D)

Dr Heuermann's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Session 3: Perspectives from the regulators & industry

Adequate reference substances are one of the essential fundamentals of analytical test result in GMP-batch release testing. About 25 % of all GMP-inspection observations are classified as QC-laboratory failures in NRW, Germany. Colleagues from Hessen have shown, that in their districts most of the observations in QC-Labs are seen in the area of qualification of equipment, but directly followed by two other important classes of observations: deficiencies in documentation and deficiencies in handling und use of reference standards.

According to the GMP-guidelines special attention should be given to the quality of laboratory reagents, volumetric glassware and solutions and of course to reference standards. Laboratory reagents like reference standards intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardization and the last current factor should be indicated. Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.

All of the GMP-basics have to be described in SOPs and they are part of the quality management system.

Many observations are linked to the following general GMP-requirements.

- Qualified vendor
- Batch number
- Preparation date
- Delivery date
- Opening date
- Expiry date
- Signature
- Storage conditions

According to ICH Q6A a reference standard or reference material should have a quality appropriate to its use. It is often characterized and evaluated for its intended purpose by additional procedures other than those used in routine testing.

Many observations are linked to characterization of standard material and to improper use, outside the intended purpose.

Pharmaceutical industry can use primary, secondary and inhouse standards for GMP-compliance testing. It is a common practise to qualify inhouse standards with the help of primary standards like CRS. Those tests to qualify the inhouse standard have to be conducted and documented like batch release tests.

The following observations have been seen frequently:

- Deficiencies related to the SOP on handling and use of reference material
  - Definitions not clear
  - Usage of reference materiel not clear
  - Characterisation insufficient prescribed
- Deficiencies in characterisation of inhouse standards
- Documentation deficiencies during testing of standards
- Storage conditions not fixed for reference materials
- Storage conditions not fixed for standard stock solutions
- Missing evidence for the expiry date of standard stock solutions
- Deficient documentation of standard solution preparation

- Missing evidence for the expiry date of inhouse standards
- Missing expiry dates of reference material
- Deficiencies in labelling standards (GMP-basics)
- Standard solutions with visible impurities (particles and yeast)
- Insufficient documentation of the standards used for
  - Batch release
  - Release of inhouse standard
- Calculation errors

In general all analytical results of GMP-tests must be traceable to an official standard like CRS. Inhouse standards can be used, but they have to be characterised towards their use under GMP conditions. Traceability of inhouse standards to CRS has to be shown step by step via GMP-compliant documentation. In cases of doubt CRS have to be used.

### **Characterisation of primary reference standards**

Dr Christian Kulinna, Boehringer Ingelheim Pharma GmbH & Co (D)

Dr Kulinna's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Session 3: Perspectives from the regulators & industry

A variety of analytical techniques require the use of reference substances and standards for the identification and quantitation of compounds in medicinal products. These reference materials can be used as internal standards, external standards or for calibration purposes.

Hence, the accuracy and consequently the reliability of analytical test results depend on the quality of characterization for such reference materials.

A secondary standard (working standard) used for routine control is typically characterized to a lesser extent but can be traced back to a primary reference standard that has been more thoroughly characterized.

This presentation summarizes the extent of primary reference standard characterization from an analytical point of view and primarily focuses on non-compendial drug substances (NCE's) in the light of regulatory requirements.

The qualification of a primary reference standard comprises the proof of the proposed molecular structure, characterization of physico-chemical properties and purity determination. The combination of different analytical techniques to achieve such a broad characterization will be examined.

Furthermore, specific considerations like the timing of establishment or definition of a re-test period for primary reference standards will be discussed.

The analytical testing of drug substances and drug products might also require the availability of other reference materials (e.g. impurities) different from the drug substance itself. The extent of analytical qualification for such reference substances, depending on their specific use, is also to be presented.

**Establishment and use of secondary standards**

Dr Mark Bradley, Novartis Pharma AG (CH)

Dr Bradley's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Session 3: Perspectives from the regulators & industry

Topics covered will include the approach taken in Novartis Pharma AG for reference standards including:

- Extent of Testing Compared to Primary Reference Substances
- Selection of Appropriate Material
- Retesting
- Content Assignment
- Labelling
- Storage and Shipment

**Reference standards quality system**

Dr Matthew Borer, Eli Lilly and Company (USA)

Dr Borer's slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Session 3: Perspectives from the regulators & industry

Pharmaceutical reference standards play a critical role in the manufacture and control of pharmaceutical products. This talk explores how reference standards are used in pharmaceutical analytical controls and their unique characteristics compared to materials produced for human consumption. Together, these factors dictate the intended use of reference standards and form the basis for an appropriate set of quality policies. Existing external regulations and guidance are also reviewed. Specific examples of quality system elements such as re-evaluation, specifications, and labeling are explored as examples of how to build an appropriate reference standard quality system.

**Generic industry viewpoint**

Dr Antony Raj Gomes, Shasun Chemicals and Drugs Ltd (India)

India is rapidly becoming a global manufacturing hub for drug substances and drug products. This presentation attempts to give an overview of the generic industry today and provides an insight into the procedures/practices related to pharmacopeial and in-house reference standards. This presentation also touches upon the various approaches for secondary standards that are being practiced. While providing typical examples of technical issues, it also elaborates various solutions that can be considered as general scientific options. This

presentation also elaborates the various challenges that are faced by the generic industry and concludes with the section that deals with various approaches that can be explored by the pharmacopeia keeping the current challenges and futuristic trends in mind.

### *Questions to the speakers*

**Question to Dr Heuermann:** How to establish a secondary standard for assay, if no assay value is given for a primary, pharmacopoeial standard (slide 11)?

**Answer:** If a content value is not given, the primary standard is not intended for assay. It should not be used to establish a secondary standard intended for assay. A user should characterise a standard appropriately. Tests such as water content or residual solvents should be performed.

**Question:** Relevance of ISO guides (for ex. ISO Guide 34) for GMP inspections?

**Answer:** GMP inspections are made against legally valid standards i.e. EU GMP and annexes. Other standards are only “state of the art” literature.

**Question:** Some EU countries require the use of official standards as working standards?

**Answer:** Legally it is possible to justify the use of in house standards as working standards. Stultz, Lilly: first example of a presentation of the expectation of an inspector.

**Question to Dr Bradley:** How secondary standards are established in your Company?

**Answer:** Secondary standards undergo extensive characterisation but rely on primary standards for identification and structure elucidation.

**Question:** How to determine and assure that the transport conditions are appropriate in the case of small quantity RS?

**Answer:** Shipping tests have been done with data loggers at different temperatures, generating data to support the choice of transport conditions. These conditions have been validated to avoid sending data loggers with every parcel. If the temperature needs to be controlled but the substance cannot be frozen, there are expensive controlled temperature boxes for a short period. In vaccines transportation, it is frequent. You may consult the WHO website for more details.

**Question:** Should not the polymorphic form of standards be defined and constant?

**Answer:** Generally speaking, the solid state characterisation is not part of the reference standard characterisation. It is an aspect that is very important during development.

**Question to Dr Gomes:** In the case study you presented, an impurity reference standard has been replaced by a cheaper substance.

**Answer:** This was not a quantitative use, only for system suitability and the method was adapted from an original compendial method to be used for the finished product. This change is acceptable as long as supported by appropriate validation data.

*Discussion with the panel of speakers*

**Question from the floor:** Different units of measurements are used during the establishment phase (e.g. mole/mole, mg/mg).2- Is harmonisation scheduled ?

**Answer from the industry:** For the moment, in the industry, results stated in the CoA are expressed in units which are in line with the corresponding validated methods.

**Answer from the EDQM:** Harmonisation between pharmacopoeias is an important agenda item for the PDG.

**Answer from the USP:** The USP is attempting to follow the highest metrological standards and the international units system.

## CLOSING SESSION

Workshop conclusions' slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008 Presentations - Workshop I & II Conclusions

### **Conclusions - Chemical and herbal reference standards workshop**

Prof. Dr Jos Hoogmartens, Member of the Ph. Eur. Commission and Chair of Group of Experts n° 7 on Antibiotics

First of all I would like to thank Dr Ulrich Rose who helped me with the preparation of this presentation. You can see in the programme that I should speak about conclusions, but in fact I should say that in reality we did not really reach any conclusions. We had very nice presentations, very interesting presentations. We also had a good discussion, but the fact that there were no real conclusions probably allows me to conclude that we should have more of these meetings. Then later on maybe we can come to real conclusions.

The first presentation was given by Dr Steve Wood on 'Certified Reference Materials: a possible approach for pharmacopoeias and pharmaceutical industry.' Dr Wood introduced us to the world of certified reference materials and emphasised the importance of traceability and then he also spoke about ISO REMCO. ISO is of course known by everybody, REMCO stands for Reference Materials Committee. He referred to the different ISO guides that were important for the study and the preparation of reference materials and he also spoke about the production of certified reference materials. After his presentation we had a discussion and I think that one of the points I should emphasise that came from this discussion, is that in the determination of uncertainty the stability studies or at least the results of stability studies should be incorporated.

Then we had a presentation by Dr Hanno Binder on 'Non-compendial application of standards – Needs and expectations from the industry.' So he gave an overview of the different CRS that exist for related substances and then he went on to speak of non-compendial use of a CRS. Where a CRS of course can be used for finished products, although they are not intended for that use but under certain conditions it is possible. Then he also spoke about eventual use of CRS of the European Pharmacopoeia for the use in other methods where a lot of validation is needed by the user before he is allowed to use it for this purpose.

Then he spoke about the use of chapter 5.12 of the European Pharmacopoeia, the use of it and maybe also sometimes the misuse by certain authorities that might go too far in the application of the identification of impurities whereas this is not really necessary as is stipulated in chapter 5.12. He then spoke about the needs and expectations from the industry and I can say that the major points here are the fact that industry is hoping to have more standardisation, more harmonisation of standards in fact, and the conclusion was that this is already on the right track for microbiological references but much less so for other standards. So there is still a long way to go if we want to harmonise.

Then we had a presentation by Prof Markus Veit on 'New Technologies in Characterisation'. You see on my slide that my text is very short, but that doesn't mean that the presentation was not interesting, in fact to the contrary. In fact he introduced quantitative use of NMR, most of us are used to the qualitative application of NMR and he showed very nicely that NMR is a nice technique for the quantitative characterisation of standards and can be used as another, I would not say a second, but just another method for characterisation of standards. We also heard in other presentations that this technique is becoming more and more important.

Then we switched to herbal materials with Dr Keith Helliwell who spoke about 'Standards for herbal drugs and preparations.' He first gave an introduction of the use of reference standards and monographs for herbal drugs and herbal drug preparations and then he moved on to the description of different types of standards. He mentioned the use and the need for herbal drug reference standards. These are standards which are used for identification in fact and he then also mentioned that these identifications by microscopy are becoming more and more difficult because less and less people are able to do it. This is partly due to the fact that at most universities apparently, and this is also true at my university I must admit, students are less and less well-trained for doing microscopic identification. So I think that maybe we should review the situation and do something about it in the future.

Then he also mentioned the need for herbal drug preparation reference standards, which are used for the examination of preparations, of extracts. Then finally a third group, the chemical reference substance, where of course we have the same situation as for the chemical reference substances for other drugs, where pure reference substances are used, which is not the case in the two previous groups, where of course we have to deal with non-homogenous mixtures.

He also referred to the rapid increase in the number of monographs and therefore also the very rapid increase in the need for more reference substances which is of course a challenge because the work that is needed to develop these is quite important.

At the end he also reported on the fact that more and more reference substances are not only used for qualitative purposes as was the case before for herbal drugs, but these reference substances are also used more and more for quantitative evaluation.

Finally we had a presentation by Dr Andrea Lodi of the EDQM on 'Standards for Impurities.' At first he gave a classification of the different impurities that can be found in drugs. He gave information about the role of impurity CRS within the monograph and he also told us how impurity CRS can be established. In the EDQM the preferred option is to have an individual CRS for each impurity. Where necessary, an assigned value can be given when the impurity is too different from 100%.

In the case that individual impurities are not available he referred to the use of drug substance in which the different impurities are spiked and that this mixture can be used for peak identification and also for system suitability testing.

Finally he also gave some information about the strategy used for development of impurity standards in conjunction with the elaboration of the monographs that are in development.

I think therewith I have given the most important information about what was shown yesterday afternoon.

**Conclusions - Biological reference standards workshop**

Dr Maria Sol Ruiz, Vice-Chair BWP/CHMP/EMEA

I will try to summarize the conclusions and suggestions from the session that we had yesterday. Also I would like to thank all the speakers because really very interesting topics were raised and I think the discussion was very good. But also I would like to thank very much Dr Karl-Heinz Buchheit. I am the voice of the conclusions but he did the work. So thank you.

First of all, we have a couple of slides with some general points. So the conclusion for some general subjects was that for most groups of biologicals, international standards calibrated in International Units (IU) will continue to be the mainstay for many years.

For selected biologicals, that is small proteins or peptides and a good example was also given by Dr Adrian Bristow regarding human growth hormone, a shift from biological units to SI units, such as milligrams, is feasible and has been successfully used for human growth hormone. This approach has also been used for insulin, but it was also shown that the case of somatropin was an ideal approach which may not be feasible for many others, but that was a good example.

Another conclusion is that for certain products, such as for instance combination vaccines, product-specific reference standards will become more important and particularly for in vitro potency assays. So this will certainly create a challenge to the concept of global international standardisation.

There was a request from industry to have a batch specific certificate to be sent with each shipment. For reference standards from the EDQM a batch validity statement is already available on the EDQM web site.

Regarding the establishment and use of biological reference preparations it seems that industry in general prefers to use official standards over in-house standards and we heard that around 65% of the cases this is what happens and the concern is regarding the availability in time of these primary reference standards. Industry would like to see earlier involvement in the establishment of reference standards for instance in the discussions on prioritization of the work programme and would also like to be informed earlier as to when a standard will be available.

Regarding the interaction with users of reference standards, there was also a conclusion from the meeting that there is a need for more feedback from users of official reference standards to providers on observations during their use and in particular if any stability issues are identified – that would certainly help to improve the system.

There was also a request to have more information on the stability of reference preparations and the proposal is to include information on how the stability is controlled, either in publications - and for the EDQM, one of the instruments is the publication in 'Pharmeuropa-Bio', and also in product leaflets.

Regarding harmonisation, it is clear, and we also heard it this morning, that there is an on-going need for continued harmonisation with WHO and regional pharmacopoeias in the field

of biologicals, particularly for methods but also for standards. There is also a need for harmonisation between regional pharmacopoeias and it was also made clear that it is a particular problem for reference standards for peptides, labelled in SI units, as the same batch can be labelled with different content in different regions, so this is clearly a practical problem for global companies, but also a problem for patients who receive treatment in one region and then spend some time in another region.

I think those are the main points we identified. Thank you for your attention.

## Final Round Table Discussion

with the participation of: **Prof. Henk J. De Jong**, Chair of the European Pharmacopoeia Commission; **Dr Erling Ehrin**, WHO Collaborating Centre for Chemical Reference Substances; **Dr Susanne Keitel**, Director, EDQM/Council of Europe; **Mrs Suzette Kox**, European Generic Medicines Association (EGA); **Dr Jean-Louis Robert**, Joint CHMP/CVMP Quality Working Party (QWP, EMEA); **Dr Maria Sol Ruiz**, Vice-Chair BWP/CHMP/EMA; **Mr Shigeki Tsuda**, Society of Japanese Pharmacopoeia; **Dr Sylvie Uhlrich**, Representative from the Industry (EVM-EFPIA); **Dr David Wood**, WHO Family and Community Health

The topics discussed during the Symposium covered both chemical and biological reference standards and other related topics such as the uncertainty of measurement of the assigned value of a pharmacopoeial reference standard or the use of S.I. units for the assignment of potency in Biological Reference Preparations.

The round table discussion provided the perfect opportunity to get feedback from representatives from the pharmaceutical industry and licensing authorities whether they would welcome the introduction of global standards – to what extent would this be possible and what impediments would have to be removed to achieve this objective?

In summary, the general trends and positions of all stakeholders attending this symposium provided a very positive feedback regarding the use of Pharmaceutical Reference standards; these standards clearly have their role and utility for users in the field of quality control.

A real need for global pharmaceutical standards exists and this is linked to a further need for harmonisation of assay methods in all the three Pharmacopoeias. As a result, full support is given to the Pharmacopoeial Discussion Group (PDG) and the harmonisation process.

Another very important issue for end users and clients is the commercial availability of reference standards at the time a monograph is implemented. The communication between the pharmacopoeias and their customers should be improved to facilitate and increase the sharing of expertise. At the same time, better communication needs to be initiated regarding changes already made and those to come in Chapter 5.12 (European Pharmacopoeia General Chapter on Pharmaceutical Reference Standards).

*Closing remarks*

**Dr Susanne Keitel**, Director, EDQM/Council of Europe

Dear Colleagues,

As already highlighted in the welcome address, the intention of this meeting was to offer a platform for discussion rather than having the aim of reaching a conclusion on all the different topics covered. And interesting discussions and exchange of opinions we have indeed had!

I would like to express our sincere thanks for all the contributions, especially to the speakers, moderators and panelists. In addition, I would like to take the opportunity to thank all of you who are actively involved in the establishment and characterization of reference standards and materials. We are especially grateful for the donation of materials as this is indeed a most valuable contribution to help establish a portfolio of reference standards destined to benefit all stakeholders, but most importantly patients.

From the perspective of the European Pharmacopoeia, one tangible outcome of this symposium is that clarification on the use of European Pharmacopoeia reference standards would be highly welcomed by users. Hence, we are considering publishing a short communication in “Pharmeuropa” on this topic.

The series of symposia on heparins will be continued next year by a meeting to be hosted by our USP colleagues. Knowing them, I am sure they will come up with interesting topics and I am personally very much looking forward to this meeting.

I wish you all a safe trip home and hope to see you again at one of our next conferences, in our expert working groups or working parties, in the meeting of the European Pharmacopoeia Commission, or at any of our future EDQM events.

## POSTERS

Original Posters' slides are available on the website under the download section <http://www.edqm.eu/site/Download-527.html#966>, click on Events organised by the EDQM - Follow-up previous events - 2008: Pharmaceutical Reference Standards, 9-10 October 2008  
Posters - Posters



**POSTER No. 1**

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**POSTER DETAILS**

<b>Poster Title:</b>	<i>Homogeneity and stability testing of CCQM study materials for purity determination of therapeutic monitored drugs</i>
<b>First Author's Full Name:</b>	Ralf D. Josephs
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**ABSTRACT**

Homogeneity and stability are two key characteristics of any reference material intended for use in interlaboratory studies. Extreme care must be taken during production to prepare materials that are as homogeneous as possible and sufficiently stable for the entire period of the interlaboratory study. The degree of homogeneity and stability can generally be improved by use of suitable manufacturing techniques, for example, appropriate grinding/blending and filling under inert gas/temperature controlled storage, respectively. Nevertheless, careful production by itself is insufficient.

Internationally accepted standards and guidelines such as ISO Guides 30-35 and 43 (for reference materials and proficiency testing in general) and WHO guidelines require affirmative demonstration of homogeneity and stability along with a quantitative assessment of their corresponding uncertainty contributions in accordance with the ISO Guide 98 (guide to expression of uncertainty in measurement, GUM) and ISO 17025. Significant uncertainty contributions due to homogeneity and stability have to be included in the calculation of interlaboratory study reference values and their associated uncertainties. In most cases participating laboratories are only provided with one or a very limited amount of interlaboratory study samples which does not allow them to reliably estimate the uncertainty contribution due to homogeneity. Therefore, between-bottle homogeneity must be examined by the study coordinating laboratory. In addition, stability for the period of the interlaboratory study must be demonstrated and, if necessary, the resulting uncertainty contribution has to be estimated by appropriate statistical approaches. This can be done by regression analysis of the results of a stability study ideally carried out using isochronous measurements. Usually the time frame of interlaboratory studies is very short compared to possible instability so that the uncertainty of stability is generally negligible.

However, homogeneity and stability studies often fail to give satisfactory quantitative information because of poor experimental design, use of an insufficient number of replicates and lack of measurement repeatability.

In the present, work homogeneity and stability studies undertaken for two interlaboratory studies are presented from the perspective of the BIPM Chemistry Section's role as coordinator of organic purity assessment interlaboratory studies carried out within the Organic Analysis Working Group (OAWG) of the Consultative Committee for Amount of Substance - Metrology in Chemistry (CCQM). Both analytes selected for the pilot studies (CCQM-P20.e and P20.f) are produced as pharmaceutical reference standards by EDQM and USP. In addition they are required for the establishment of reference measurement systems for clinical chemistry and laboratory medicine. The two CCQM-P20.e study materials investigated were a high-purity sample of theophylline (CCQM-P20.e.1) and a sample of theophylline spiked with known amounts of the xanthines caffeine and theobromine (CCQM-P20.e.2). The cardiac glycoside digoxin was selected as the CCQM-P20.f study material.

**POSTER No. 2**

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**POSTER DETAILS**

<b>Poster Title:</b>	<i>International comparisons of the assignment of mass fraction composition of pure organic compounds – a model for benchmarking capabilities for the assessment of Pharmaceutical Reference Substances?</i>
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**ABSTRACT**

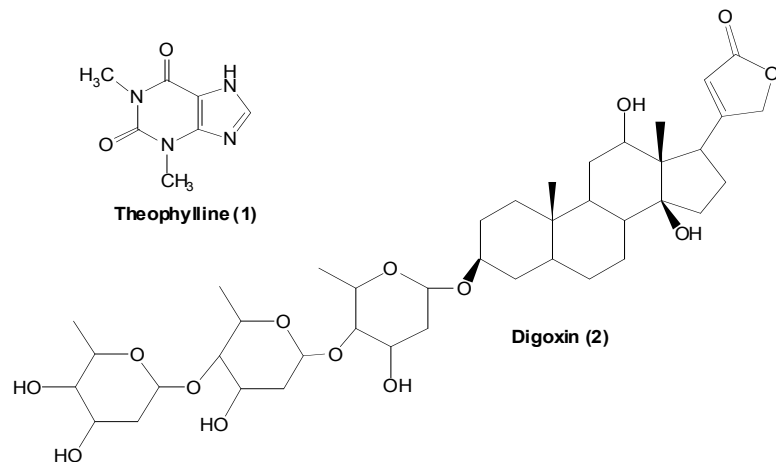
The Bureau International des Poids et Mesures (BIPM) is an international centre for metrology charged with ensuring world-wide uniformity of measurements and their traceability to the International System of Units (SI). The focus of current activity in organic analysis within the Chemistry section at BIPM is the coordination of organic purity assessment studies carried out on behalf of the Organic Analysis Working Group (OAWG) of the Consultative Committee for Amount of Substance – Metrology in Chemistry (CCQM).

BIPM coordinated the final rounds of a pilot study (CCQM-P20) investigating methods for the mass fraction purity assessment of high-purity organic compounds. Participants in CCQM-P20.e were required to purity assess both a high-purity sample of theophylline (1) and separately a sample containing known amounts of the related structure materials caffeine and theobromine. For CCQM-P20.f the cardioactive therapeutic digoxin (2) was studied. Both these compounds are produced as Pharmaceutical Reference Standards by the USP and EDQM. USP and Mexican Pharmacopoeia (MP) Reference laboratories participated in the intercomparison along with various National Measurement Institutes (NMIs).

The aim of the CCQM-P20 series of studies was to investigate and evaluate the scope, applicability and limitations of various methodologies to assign the purity of organic materials. Additionally, these studies allowed the participating NMIs (as well as the USP and MP) to benchmark their capabilities to characterize the purity of their own materials, including the identification and quantification of associated impurities. The CCQM-P20 studies also allowed NMIs with specific Calibration and Measurement Capability (CMC) claims for the provision of organic pure substance Certified Reference Materials (CRMs) to demonstrate their technical capabilities.

The poster summarises the approaches used to perform the purity assessments and the value

assignments, with their associated measurement uncertainties, reported by the participating laboratories in both studies. The study could be used to provide a model for benchmarking studies of the technical capabilities of laboratories responsible for the characterisation of Pharmaceutical Reference Substances.



**POSTER No. 3**

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**POSTER DETAILS**

<b>Poster Title:</b>	<i>Importance of Using Extremely High Purity Stable Labeled Internal Standard for Successful LC-MS/MS Bioanalysis</i>
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**ABSTRACT**

**Novel Aspect**

Importance of identifying the contaminations in high purity stable labeled IS which have a large impact on a low LLOQ.

**Introduction**

Nowadays, the majority of bioanalytical methods use stable labeled drugs as internal standard (IS). Use of stable labeled drugs is well known for its advantages such as reduction of the analysis run time, improvement in the inter-injection reproducibility, reduction of matrix and ionization effects. In general, since the stable labeled internal standards have high isotopic purity, the interference on the LLOQ is negligible. However, extra considerations should be addressed when the LLOQ is close to picogram/milliliter level. The cases of Ursodiol-d5 and Oxycodone-d3 ISs are described in this work. In fact, it was discovered that, even if these deuterated ISs had a high isotopic purity, they could not be used as IS due to the presence of even low level impurities.

**Methods**

Bioanalytical method ranges for the quantification of Ursodiol (with endogenous levels) and Oxymorphone (Oxycodone metabolite) were from 10 to 5000ng/mL and 10 to 5000pg/mL, respectively. For both methods the LLOQ and zero human plasma samples (IS concentrations are 2µg/mL of Ursodiol-d5 and 10ng/mL of Oxycodone-d3) were extracted using a solid phase extraction procedure. Extracts were injected onto a LC-MS/MS (Agilent 1100 pump/autosampler coupled with Sciex/AB API3000 and API5000), employing a turbo-ionspray ionization source. Quantification of the contamination in deuterated internal standard was achieved by comparison of peak area between Oxymorphone and Ursodiol in extracted zero samples with extracted LLOQ samples. Product ion scans were performed on

both stable labeled internal standards (Ursodiol-d5 and Oxycodone-d3) to identify the contaminants.

### Results

For Ursodiol-d5 (isotopic purity 99%), the comparison of extracted zero samples (IS only) with extracted LLOQ samples showed the presence of an interfering peak on Ursodiol SRM transition >20% of LLOQ. Moreover, the Ursodiol-d5 internal standard working solution (2 $\mu$ g/mL) showed the presence of an interfering peak on Ursodiol SRM transition >700% of LLOQ working solution (10ng/mL). The confirmation of Ursodiol presence in Ursodiol-d5 solutions was performed by comparing the fragmentation patterns for both Ursodiol and the interfering peak present in Ursodiol-d5. It was found that the interfering peak has the same cluster ion and fragments of Ursodiol:  $[M+NH_4]^+$  at  $m/z=410$ ,  $[M+NH_4-H_2O]^+$  at  $m/z=392$ , and  $[M+NH_4-2H_2O-OH]^+$  at  $m/z=357$ . These results proved that the main contamination in Ursodiol-d5 is really Ursodiol. Hence, even if the isotopic purity of Ursodiol-d5 is 99%, this standard cannot be used as IS for Ursodiol quantification when the Ursodiol range is 10-5000ng/mL.

For Oxycodone-d3 (isotopic purity 99%), the comparison of extracted zero samples (IS only) with extracted Oxymorphone LLOQ samples showed the presence of an interfering peak on Oxymorphone SRM transition >20% of LLOQ. Moreover, the Oxycodone-d3 internal standard working solution (10ng/mL) showed the presence of an interfering peak on Oxymorphone SRM transition >1600% of Oxymorphone LLOQ working solution (10pg/mL). The confirmation of Oxymorphone presence in Oxycodone-d3 solutions was performed by comparing the fragmentation patterns for both Oxymorphone and the interfering peak present in Oxycodone-d3. It was found that the interfering peak has the same protonated molecular ion and fragments of Oxymorphone:  $[M+H]^+$  at  $m/z=302$ , product ions at  $m/z=284$ , 242, 227, and 198. These results proved that the main contamination in Oxycodone-d3 is really Oxymorphone. Hence, even if the isotopic purity of Oxycodone-d3 is 99%, this standard cannot be used as IS for Oxymorphone quantification when the range for Oxymorphone is 10-5000pg/mL.

**POSTER No. 4**

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**POSTER DETAILS**

<b>Poster Title:</b>	<i>Considerations Associated With The Interactions Between Industry And Compendia</i>
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**ABSTRACT**

The major pharmacopeial compendia rely heavily on interactions with the pharmaceutical industry for supplying monographs and reference standard materials. When these interactions are not forthcoming and timely, negative consequences can result for both industry and the pharmacopeia. These consequences can include lack of appropriate public standards and unproductive use of resources occupied in addressing monograph issues. This presentation will discuss the types of interactions and their consequences to provide support for more proactive, collaborative interactions between industry and pharmacopeia groups.

**POSTER No. 5**

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**POSTER DETAILS**

<b>Poster Title:</b>	<i>Multi-Year Stability of Pre-made Solution Reference Standards</i>
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**ABSTRACT**

When appropriate parameters are chosen in the design, preparation, packaging, and storage of the certified solution standards, long term stability is possible. This poster provides examples of pre-made solution reference standards that exhibit multi-year stability.

Five examples were selected for the purpose of this study to exhibit the stability of pre-made solution standards. The compounds selected included a cross section of products offered including morphine, diazepam, fentanyl, meperidine and fluoxetine hydrochloride. Solution stability was determined by comparison of a stability lot to a freshly prepared solution, the existing lot and a calibration curve. Chromatographic analytical techniques were employed to gather this data. Results of these comparisons are included in this poster.

Analytical reference standards prepared in a solvent that promotes stability and packaged under argon in a flame sealed ampoules can be stable for many years when stored correctly.

**POSTER No. 6**

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**POSTER DETAILS**

<b>Poster Title:</b>	<i>Multi-Compendial Certification of Secondary Pharmaceutical Reference Standards in an ISO 17025/Guide 34 Environment</i>
<b>Initials, last name and institution of all other authors:</b>	A W Nichols, RT Corporation, L Lang, RT Corporation

**ABSTRACT**

**Multi-Compendial Certification of Secondary Pharmaceutical Reference Standards in an ISO 17025/Guide 34 Environment**

**P J Jenks, RT Corporation Ltd, A W Nichols, RT Corporation & L Lang, RT Corporation.**

The certification of a secondary pharmaceutical reference standard to multiple compendial standards in the ISO 17025/ISO Guide 34 environment offers end users unique strengths in quality assurance; it also allows for traceability to the multiple compendial standards through a single standard. Further, unlike compendial standards, a secondary pharmaceutical reference prepared in compliance with ISO 17025/ISO Guide 34 must have its uncertainty value determined, allowing the laboratory to better monitor performance over time. Uncertainty values are key elements in establishing effective quality assurance programs and are a required element in the preparation of Certificates of Analysis according to ISO 17025. Through the proper use of secondary pharmaceutical reference standards an ISO 17025 accredited laboratory user is able to evaluate a compendial standard's performance and quality, data that is not readily available for compendial standards.

Data is presented regarding the qualification and certification of RTC's Ibuprofen PRS™, a commercially available secondary pharmaceutical reference standard that is certified to compendial standards offered by the United States Pharmacopeia, European Pharmacopoeia, and British Pharmacopoeia. This secondary pharmaceutical reference standard has been manufactured and certified according to the relevant sections of ISO 17025/ISO Guide 34 for an inter-compendial comparison that identifies the European Pharmacopoeia Ibuprofen compendial standard as having an assigned content value of 99.7% for the identified batch.

**POSTER No. 7**

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**POSTER DETAILS**

<b>Poster Title:</b>	<i>Development of Generic Protein Biomarker Standards</i>
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**ABSTRACT**

Circulating biomarkers are potentially useful indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic interventions.

In many instances multiple biomarkers need to be considered to give a dataset capable of predicting a phenotypic end-point. Such multiparametric assays, where overall pattern recognition rather than precise analysis of individual analytes form the diagnostic pose new problems for assay QC and validation in terms of determining sensitivity, accuracy, robustness and other performance indicators. This is further complicated by the natural broad dynamic range of proteins in serum which challenges the detection of low-level analytes.

A panel of non-human protein “biomarker standards” has been developed as a tool for the assessment and validation of protein detection platform technologies, to be spiked in to serum and used as a generic standard. To cover a range of proteins the molecular weights of the selected proteins ranged from 10.8-57.8 kDa, with pIs ranging from 5.25 to 9.38. The concentrations of the proteins in the panel range from 50 pg/mL -10<sup>7</sup> pg/mL to encompass the broad dynamic range of proteins in serological samples. Non-human proteins were chosen to avoid detection of endogenous proteins within human serological samples.

The construction of the panel and demonstration of applicability for measuring the performance characteristics of two antibody-based detection methods (Luminex and Meso Scale Discovery) are described.

**POSTER No. 8**

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**POSTER DETAILS**

<b>Poster Title:</b>	<i>Absolute protein quantification and traceability to the SI</i>
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**ABSTRACT**

For complex biomolecules, standards are currently traceable only to uniquely assigned International Units. SI is often only inferred by the amount of “pure” protein weighed out. This lack of SI-traceability has been identified as an issue in achieving consistent measurement within the clinical community<sup>1</sup>. The development of traceable methods capable of fully characterising the amount of material present in each vial are required. Using somatropin as a model, a fully SI-traceable method of quantification has been developed and used to assign SI-traceable values to international standards.

The method developed was based on the traceable quantification of tryptic peptides released from the protein. This required the development of digestion procedures capable of totally digesting the protein to yield molar equivalents of the measured peptides. The protein concentration was calculated from the molar quantities of a number of these peptides.<sup>2</sup> To maintain full traceability, the peptide standards used were fully characterised and quantified by complete acid hydrolysis. The primary method of exact-matching isotope dilution mass spectrometry (EM-IDMS) was employed throughout<sup>3</sup>.

Proof of principle was demonstrated using a purified in-house standard (IS) of recombinant human growth hormone (somatropin) in which four independent peptides were quantified and gave equimolar results under two separate digestion procedures<sup>4</sup>.

Two somatropin standards obtained from EP and WHO were fully characterised using the developed EM-IDMS method. In order to determine the equivalence of the digestion method for the two standards and eliminate the possibility of digestion variation due to differing salts and buffers present, results were compared with standard addition analyses using the fully EM-IDMS quantified in-house somatropin standard and isotopically labelled peptides. To further corroborate the standard addition results, relative quantification via isotope-coded affinity tagging (ICAT), where samples are digested in tandem under identical conditions,

was performed.

A second tagging technique (iTRAQ) was used for relative quantification of the three standards (IS, EP, WHO) with traceable tryptic peptides as internal standards<sup>5</sup>. This yielded greater measurement uncertainties than EM-IDMS but also provided traceable results and was able to give an indication of peptide variability across the protein sequence.

The developed methods are capable of fully characterising the concentration of the primary sequence of the protein present. The uncertainties reported are attainable for simple systems where a traceability chain is possible and fully maintained. This simple comparison exemplifies the challenges posed and the uncertainties associated with primary value assignment of traceable protein standards.

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**POSTER No. 9**

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**POSTER DETAILS**

<b>Poster Title:</b>	<i>The most versatile automated powder dispensing to achieve reliability and traceability</i>
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**ABSTRACT**

Most labs in life-science, chemical, semi-manufacturing, food and academia are facing the dispensing of powders in formulation, development, preparation or repackaging as tedious, difficult, and potentially hazardous process. The use of automation and workflow integration offers the ability to repeat rapidly the dispense of powders precisely and without error. In the powder dispensing process, successful automation needs to demonstrate reliability and traceability, as well as ease of use. We demonstrate automation solutions capable of dispensing of powders with unmatched versatility to overcome wide range of powder types and receptacles.

**POSTER No. 10**

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**POSTER DETAILS**

<b>Poster Title:</b>	<i>Pharmacopoeial Reference Standards and Measurement Uncertainty</i>
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**ABSTRACT**

**Pharmacopoeial Reference Standards and Measurement Uncertainty.**

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World wide reference standards or mutual recognition of pharmacopoeial reference standards and uncertainty statements for assigned values of reference standards are important factors in assuring harmonisation of drug products across the world.

For a number of products (e.g. human insulin), different pharmacopoeial reference standards exist in different regions and the reference standards are not mutually recognised. This means that the labelled content of a batch of drug product may depend on the market the product is shipped to. Furthermore, most pharmacopoeial reference standards are at present not supplied with a statement expressing the uncertainty of the assigned value. Therefore, a manufacturer has no way of knowing how much of the variation in content determinations over time may be attributed to the pharmacopoeial reference standards.

**SPECIFICATIONS FOR DRUG PRODUCTS**

It is important to know the sources of variation in content determinations in different respects, but especially important when specifications and shelf life are considered for drug products. Today, pharmaceutical manufacturers are able to estimate the uncertainty contributions related to the production, the analytical procedure, and the value assigned to in-house reference standards (if used), but the uncertainties of pharmacopoeial reference standards are needed to know all parts of the uncertainty chain.

### **UNCERTAINTY OF THE ASSIGNED VALUE OF A REFERENCE STANDARD**

The uncertainty associated with the assigned value for a sample from a reference standard batch should be valid for the shelf-life period and should be stated as contributions from

- the estimation of the content (the assigned value)
- the homogeneity of the content, i.e., the between-vial homogeneity and, if relevant, the within-vial homogeneity
- the stability of the reference standard during the period of validity (shelf life).

The stated uncertainties should be valid for the value of the actual reference standard sample at any time within the validity period.

### **CONSEQUENCES FOR THE SPECIFICATION INTERVAL**

The uncertainty related to the assigned value of a reference standard has always existed whether stated or not and so have the effects of the uncertainty. Therefore, the specification interval should under no circumstances be narrowed as a result of an uncertainty statement. Uncertainty statements for reference standards should be acknowledged as documentation of the quality of the materials giving the user the possibility of using the information actively, e.g. in relation to production control.

**POSTER No. 11**

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**POSTER DETAILS**

<b>Poster Title:</b>	<i>Analytical Techniques Required to Ensure a Well-Characterised Biological Material</i>
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**ABSTRACT**

Currently, more than half of the drug candidates in the discovery stage are biologics including proteins, peptides, monoclonal antibodies, etc. This poster discusses the tremendous amount of analytical testing required to support a biopharmaceutical product - from discovery, through development, clinical trials, and manufacturing and eventually to the market. Due to the complexity of these large molecules, vast arrays of methods are utilised to fully characterise these complex molecules -significantly more difficult task than typical small molecules. Since biopharmaceuticals are expressed (produced) by living systems, i.e. *E. coli*, yeast, or mammalian cells, there are additional testing matrices associated with viruses and cell lines. Further, the FDA is requiring orthogonal techniques when available to better understand the structure and stability of a biopharmaceutical. The poster will outline the many different techniques required to fully characterise a protein reference standard and why each is important such as.

CEX

SEC-MALS

SEC-UV

RP-HPLC

Western Blot

AAA

Sequencing

CE

Peptide Mapping

Mass Spec

IEF

SDS-PAGE

**POSTER No. 12**

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**POSTER DETAILS**

<b>Poster Title:</b>	<i>The United States Pharmacopeia Reference Standards Process – from Cradle to Catalog</i>
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**ABSTRACT**

The United States Pharmacopeia (USP) establishes reference standards to help ensure the strength, quality, and purity of medicines (drugs, biologics, and excipients) and foods (dietary supplements and food additives). The USP reference standard collection consists of more than 2200 materials ranging from drug substances, related impurities, residual solvents, biologics, excipients, medical gases, botanicals, polymers, Near-IR and dissolution calibrators, photomicrographs, and melting point standards. The reference standards are closely tied with the documentary standards published by the USP. Maintaining and growing the collection takes the concerted effort of many dedicated industry experts, regulatory agencies, USP staff, and the volunteers of the USP Council of Experts. Through this collaborative process, USP strives to produce reference standards of the highest quality and make them readily available to the public.

As part of its public health mission to establish pharmacopeial standards based on the best available science, USP has embarked on developing selected standards as Certified Reference Materials (CRMs). The USP study design for a CRM utilizes a metrologically valid testing procedure for one or more specified properties of the material, with additional testing to provide appropriate data for statistical analysis. A resulting CRM will be accompanied by a certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability.

The intent of this presentation is to familiarize the reader with the USP reference standard development process, from bulk material procurement to QA release, and to introduce the USP CRM program.

**POSTER NO. 13**

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**POSTER DETAILS**

<b>Poster Title:</b>	<i>A study for establishment of Korean national standard for diphtheria toxin and antitoxin</i>
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**ABSTRACT**

The establishment including manufacturing and evaluation, of national standard for the biologics for which quality control have to be performed, is important affairs of NCL. Since 2001, KFDA have performed national standard establishment project.

At present, the potency test of diphtheria vaccine submitted for regulatory release to our administration routinely estimated by *in vivo* toxin neutralization assay in guinea pigs according to minimum requirement of KFDA based upon the requirement of the U.S. The *in vivo* toxin neutralization methods need both diphtheria toxin and antitoxin standards. In order to prepare and establish, the national standards of diphtheria toxin and antitoxin produced candidate material by Kaketsuken, Japan.

KFDA evaluated for the candidates through collaborating study with five Korean vaccine manufacturers and KFDA and calibrated national standard candidates for diphtheria toxin and antitoxin. As the results of collaborative study, the estimated potency of diphtheria toxin and antitoxin was found to have a unitage of 101.8 L+/mL, that of diphtheria anti-toxin is 198 U/mL, respectively.

## BIOGRAPHICAL NOTES

**Prof. Dr Valeria L. Bagirova** is the author of more than 200 scientific articles and 6 monographs on standardisation and quality control of pharmaceutical products. Since 1975 she has worked at the State Institute of Standardisation and Control of Medicines starting as a junior researcher and progressing to senior researcher, Head of Laboratory and presently to Director of the Institute. In 1972 she graduated from the Sechenov I.M. State Medical Academy. In 1998 she became a Doctor of Pharmacy.

**Dr Hanno Binder** obtained his degree in chemistry from the university of Innsbruck/Austria. He studied for his PhD at the same university and obtained his PhD in 1978. During the period 1978 – 1982 he was research assistant at the university of Innsbruck/Austria. He joined Sandoz GmbH in 1982 and from 1982 – 1996 he was appointed as group leader and finally as head of the analytical R&D laboratories, being responsible for the development of  $\beta$ -lactam antibiotics. He changed to Quality Assurance of Sandoz GmbH in 1996 and is now in the position as Head of Quality Management of Sandoz International. Since 1998 he has been member of expert group 7 (antibiotics) of EDQM.

**Dr Matthew Borer** obtained his PhD in Analytical Chemistry from Indiana University, Bloomington, USA. He obtained his Bachelor of Science degree in Chemistry from Bowling Green State University, Ohio, USA. Dr. Borer is currently the senior technical leader for the global reference standard program at Eli Lilly and Company. In this role, he has technical oversight for all corporate reference standard materials that support development and manufacturing. He is also the subject matter expert for the Lilly reference standard quality system. As a recognized expert in the field of pharmaceutical reference standards and associated analytical control strategies, Dr. Borer is a member of the United States Pharmacopeia Expert Committee on Reference Standards. Dr. Borer was also the host for the 8<sup>th</sup> Industry Reference Standard Symposium in May, 2006.

**Dr Mark Bradley** obtained his degree in Chemistry from the College of Technology in Dublin, Ireland. He studied for his PhD in University College Dublin, Ireland. He obtained his PhD Physical/Analytical Chemistry in 1992. During the period 1993 to 1998 he worked initially in a research based role before moving to Quality Assurance in a company working in the medical devices area. In 1999, he joined Novartis in a quality role, and in 2000 was made responsible for the Novartis International Service Laboratory (ISL) which performs release testing of drug substances and drug products and has responsibility for the global Novartis drug substance stability program. Another key function of ISL is in the establishment, certification and distribution of reference materials to Novartis affiliates worldwide.

In 2004, he took an opportunity in Novartis Headquarters in Technical Research and Development, Basel, Switzerland as a Group Head in Pharmaceutical Development. Since February 2008 he has worked as Pharmaceutical Development Unit Manager for Solid Oral Dosage Forms 1, in Novartis Pharmaceutical Development, Switzerland.

**Dr Adrian Bristow** joined the National Institute for Biological Standards and Control in 1979. His current position is Head of the Technology Development and Infrastructure group. His research interests focus principally on characterization of the biological and physico-

chemical properties of biological and biotechnological medicinal substances, and on principles of Biological Standardisation.

In addition to his work at NIBSC, Dr Bristow has been a member of the biologicals expert groups of both the European and British Pharmacopoeias for over 20 years, and is also a member of the steering committee of the EDQM Biological Standardisation Programme. He also attends regularly the WHO Expert Committee on Biological Standardisation, and has a central scientific role in developing and coordinating the NIBSC/WHO Biological Reference Material Program.

**Dr Karl-Heinz Buchheit** obtained his degree in pharmacy from the Johann-Wolfgang-Goethe University in Frankfurt/M. (Germany) and his PhD in pharmacology in 1984 from the same university. From 1984 until 1999 he worked for Novartis /Sandoz in Basel (Switzerland) as research scientist and group leader in preclinical pharmacology. Since December 1999, he is Deputy Head of the Department Biological Standardisation, OMCL Network & HealthCare at the EDQM (Council of Europe, Strasbourg, France) and secretary of the Steering Committee of the Biological Standardisation Programme.

**Ms Monica Caphart** is a Senior Compliance Officer in FDA's Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, Center for Drug Evaluation and Research (CDER). She began her FDA career in 1989, as an analyst in the Northeast Regional Laboratory, transferred to the Office of Regulatory Affairs as a Scientific Coordinator, before moving to CDER in 1993 as a Compliance Officer. In 1997 Monica was selected as DMPQ's technical/regulatory specialist on pharmaceutical laboratory CGMPs. In 2000 Monica was awarded a Mansfield Fellowship (a program whose focus is to enhance US/Japan government relations) which enabled her to study Japanese for a year, followed by a year at the Ministry of Health, Labor and Welfare, where she learned about Japanese GMPs. She's a member of FDA's Foreign Inspection Cadre and a training resource for FDA. Monica holds a Bachelor of Science degree in Chemistry and a Master of Science degree in Pharmacology. She is currently seconded to the Inspections Sector of the EMEA as a Visiting Expert until the end of November 2008.

**Prof. Henk J. de Jong** studied chemistry and physics with a major in analytical chemistry (1970) at Leiden University, The Netherlands. A PhD at the same university on hyphenated chromatographic-spectrometric techniques (1973) was followed by a post-doc period at Montpellier University (France), where he worked on the use of radioisotopes in studying drug metabolism. After returning to Leiden University (1974) he became professor of pharmaceutical analysis. From 1980 till 1984 he was dean of the Pharmacy Faculty at Leiden University. In 1984 he moved to France to join Servier, a privately owned, French, research based, internationally operating, pharmaceutical company, as head of pre-clinical development, from 1994 till 2000 he managed worldwide Regulatory Affairs then International Scientific Relations. At present (since september 2006) he is Senior Advisor Pharmaceutical Sciences. Next to this he continues work at Leiden University where he is professor of Pharmaceutical Quality. He is chairing chemical expert groups in France and at the European Pharmacopoeia and was elected chair of the European Pharmacopoeia Commission for 2007-2010.

**Dr Vincent Egloff** received his degree in Pharmacy and his Masters in Pharmaceutical Industry from the University of Strasbourg, France (1984). After two years as a research assistant at the University he worked in several French pharmaceutical companies in the field

of quality control and regulatory affairs. He was nominated expert for the French Pharmacopoeia in 1990. He joined the European Pharmacopoeia in 1992 first as a Pharmacist/analyst, then as Head of the Quality Assurance Unit and is presently Head of the Reference Standards and Samples Division.

**Mr. Antony Raj Gomes** is Head-Quality Management (Vice President) of Shasun, one of the leading Indian Generic API/Formulation manufacturer. Has a Post Graduate Degree in Analytical Chemistry and a Post Graduate Diploma in Industrial Analytical Chemistry with a work experience of about 19 years in the field of Pharmaceutical Quality.

He is elected to the '*United States Pharmacopeia-Reference Standards Expert Committee*' as a Member to serve for the period of 2005 – 2010. He is elected as a member of the '*Indian Pharmacopoeial Expert Committee for Antiretroviral Monographs*'. He is also the co-chair of '*USP-IP advisory panel for monographs and reference substances*' - a scientific collaborating panel between both pharmacopoeias. He is member of the Indian advisory council of Drug Information Association (DIA) and the recipient of IDMA (Indian Drug Manufacturer's Association) '*Eminent Pharmaceutical Analyst*' award for the year 2006.

**Dr Keith Helliwell** obtained his PhD, B. Pharm, M.R. Pharm SJ in 1975 at The School of Pharmacy, London University on an alternative poppy species to *P. somniferum* as a source of opiates.

He 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).

**Dr Matthias Heuermann** has gained his PhD thesis in pharmaceutical analysis at the University of Münster, Germany. Since 1995 he was working in the OMCL of Northrhine Westfalia (NRW), now a part of the NRW Institute of Health and Work. Analytical testing of human und veterinarian drugs was one of his tasks. Beside his laboratory work he was GLP inspector until 2005. Since 1995 he is involved in GMP inspections, mainly focused on the QC laboratories and QA systems. Experiences from national and international GMP inspections and from his OMCL work were brought into several working groups of the general OMCL network of the European Directorate for the Quality of Medicines (EDQM). Since December 2004 he is the head of the OMCL of NRW.

**Prof. Dr Jos Hoogmartens** (°1945) studied at the Katholieke Universiteit Leuven, Belgium. In 1966 he obtained a degree in chemistry, in 1969 a degree in pharmacy and in 1972 a PhD in pharmaceutical sciences. He has been teaching Pharmaceutical Chemistry and Drug Analysis at the Université de Kinshasa (Congo) (1972-1976), at the Université Catholique de Louvain, Belgium (1988-1997) and at the Katholieke Universiteit Leuven (1977- ) where he is a full professor since 1988. He has been a temporary collaborator of the National Institute of Biological Standards and Control, London (1975, 3 months), of the British Pharmacopoeia

Laboratory, London (1976-1977) and of Janssen Pharmaceutica Belgium (1997-1999, senior director analytical development).

He was member (1985-1997, 2004- 2007) and is chairman (2007-) of Ph. Eur. Group 7 of experts (antibiotics) and is expert of the WHO (1996- ). He is chairman of the Belgian Pharmacopoeia Commission (2000- ) and member of the European Pharmacopoeia Commission (1992- ).

**Mrs Anne Munk Jespersen** studied Biochemistry at the Danish Technical University (DTU) for Engineers and received her Bachelors Degree in February 1981. From 1981 to 1986 she worked as Candidate Stipendiate at the Chemical Department, Carlsberg Laboratory working with fermentation, purification and characterization of a beer maturing enzyme. From 1986 to 2000 she worked as Research Scientist at Novo Nordisk A/S working with HPLC on human growth hormone, preparing and maintaining in-house hGH reference materials, and preparing hGH monographs and international reference material. In January 2001 she was assigned Reference Material Coordinator for hGH, glucagon and FVIIa, expanding the monograph work to all three products. April 2002 she was appointed Principal Scientist. In 2005 she was elected member of the USP Expert Committee B&B: Proteins and Polysaccharides and in February 2008 she was elected member of the USP Expert Committee on Reference Standards.

**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 EMEA 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.

**Dr William F. Koch** received his Bachelor of Science degree in chemistry at Loyola University of Chicago, and was conferred a PhD in analytical chemistry at Iowa State University in 1975. He joined the United States National Institute of Standards and Technology (NIST) as a postdoctoral fellow in 1975 and established a career at NIST in chemical metrology both as a scientist and in management, retiring from the United States Federal Government in 2007 as the Deputy Director for Chemical Science and Technology. Dr. Koch joined the United States Pharmacopoeial Convention (USP) as its Chief Metrology

Officer in 2007 and now oversees the organization's research and development laboratories and the analysis, production, and distribution of USP Reference Standards.

**Dr Shigeo Kojima** graduated from Kyoto University, Faculty of Pharmacy and joined the National Institute of Health Sciences (NIHS), the Ministry of Health, Labour and Welfare (MHLW) in 1966. He started his carrier as a researcher in the NIHS and received his PhD degree from Kyoto University in 1979. He became the director of Division of Drugs, NIHS in 1993, and contributed to establish ICH quality guidelines as the ICH Quality Coordinator of MHLW during 1993-2005.

Dr. Kojima is currently the senior advisor of the Pharmaceuticals and Medical Devices Agency. He is a member of the Pharmaceutical Affairs and Food Sanitation Council (PFC) in Japan and is contributing to review quality aspects of registration applications of new drugs, and to revise the Japanese Pharmacopoeia.

**Mrs Suzette Kox** is Senior Director Scientific Affairs of the European Generic medicines Association (EGA) since 2001 and EGA coordinator for the EGA Biotechnology & Biosimilars Committee, the EMEA-EGA Working Group and the EGA Safety & Pharmacovigilance Working Group.

Previously she worked for 10 years in regulatory affairs and management for the German generic company *ratiopharm* and was Chair of the EGA Regulatory & Scientific Affairs Committee and Member of the EGA Board and Executive Committee.

Suzette is also Member of the Science Committee of the International Generic Pharmaceutical Alliance (IGPA) and of the DIA Euro Meeting Programme Committee, and belongs to the visiting faculty of the School for International Training (SIT): Department Development Studies and Public Health in Geneva (accredited college in Vermont).

Before joining the generic industry, she followed a hospital and retail pharmacy career. Along with a degree in pharmacy (Paris) she holds a postgraduate diploma in anatomy-pathology.

**Dr Christian Kulinna** graduated in 1990 from the University of Cologne and received his PhD in chemistry in 1994 from the University of Essen, Germany. After a postdoctoral stay at the Risø National Laboratory in Denmark, he joined the Bayer AG, Leverkusen in 1996, responsible for formulation analytics.

In 1998, Dr Kulinna continued his career at Boehringer Ingelheim Pharma GmbH in the field of drug substance analytics. In 2003 he was appointed head of the analytical drug substance development group in Biberach, responsible for the analytical characterization of drug substances (NCE's) within preclinical and clinical development. Main activities within his group are analytical method development and validation, conducting early stability and stress stability studies, characterisation and release of drug substance for clinical trials, as well as the qualification of reference standards and substances.

**Dr Andrea Lodi** received his M.Sc. in Chemistry and his PhD in Physical Chemistry from the University of Bologna, Italy. He is a Chartered Chemist. He started his career at Henkel, Italy as Head of the R&D Analytical Laboratory. Between 1985 and 2000 he was with Glaxo, Italy where he held several positions in R&D Pharmaceutical Development working in the field of chemical and pharmaceutical development of new chemical entities. In 2000 he joined the European Department for the Quality of Medicines & HealthCare (EDQM) as Deputy Head of the Laboratory Department.

**Prof. John Miller** is head of the Laboratory Department of the European Directorate for the Quality of Medicines, Council of Europe, Strasbourg, France, and is also a visiting Professor to the Department of Pharmaceutical Analysis at the University of Strathclyde, Glasgow, United Kingdom. He is a registered pharmacist, a member of the Royal Pharmaceutical Society of Great Britain and is a Chartered Chemist, member of the Royal Society of Chemistry. He has worked in the pharmaceutical industry, a contract research institute, and an official medicines control laboratory. He has many years of experience in pharmaceutical analysis and the establishment of pharmaceutical reference standards..

**Dr Jean-Louis Robert** studied chemistry at the University of Basle (CH) and obtained his PhD from there in 1976. He had a post-doctoral training at the Pharmaceutical Institute of the "Eidgenössische Technische Hochschule" (ETH) in Zurich (CH). He spent one year with a pharmaceutical company before joining the National Health Laboratory (LNS) in Luxembourg. In his current position he is, Head of the Department of Control of Medicines, an official medicine control laboratory at the LNS.

He is a member (co-opted) of the Committee for Human Medicinal Products (CHMP) at the European Medicines Agency (EMA) in London and chairman of the CHMP/CVMP Quality Working Party.

Within the International Conference on Harmonization (ICH), he is rapporteur for the Guideline Validation of Analytical Procedures, EU-topic leader for the Common Technical Document-Quality (rapporteur for step 4 and the implementation working group), rapporteur for the revision of the guidelines on impurities Q3A and Q3B, member of the EU Q8 team (pharmaceutical development) and Q10 (pharmaceutical Quality System). Currently he is chairing the ICH IWG of Q8, 9 and 10. At the European Pharmacopoeia, he is a member of the Commission and of the group of experts 10 B (synthetic products). Currently he chairs the Steering Committee of the CEP. He serves as a pharmaceutical expert at WHO.

**Dr Ulrich Rose** is responsible for the establishment/monitoring of the Ph. Eur. reference substances and the special revision programme of the European Pharmacopoeia in the Laboratory Department of the EDQM in Strasbourg.

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. 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 30 publications.

**Dr Maria Sol Ruiz** is the head of the Biotechnology Unit at the Spanish Medicines Agency. She is the Spanish representative in the BWP (Biologics Working Party), member of the GTWP (Gene Therapy Working Party) and a co-opted member of the CHMP (Committee for Human Medicinal Products) at the EMA (European Medicines Agency). She also participates in several working groups related to biotechnological and biological products both at the EMA and at the European Pharmacopoeia. She has been involved as an assessor in the TSE Certification system at the European Pharmacopoeia since the beginning (2000-present) and she has been the chairperson of Technical Advisory Board of this TSE Certification scheme since then (2001-present).

**Dr Martin Schiestl** obtained his degree in chemistry with focus on analytical sciences from the university of Innsbruck/Austria. He characterized therapeutic proteins for his master and PhD thesis at Biochemie GmbH and obtained his PhD in 1996. He joined Biochemie/Sandoz in 1996 and has been working since then with increasing responsibilities in the quality development of biopharmaceuticals. Since 2005 he is heading the analytical and pharmaceutical development group at Sandoz Austria. He is member of the Expert Group No. 6 for Biological Substances at the European Pharmacopoeia since 2003, and member of the Expert Committee for Proteins and Polysaccharides at the United States Pharmacopoeia since 2005.

**Mr. Jean-Marc Spieser** studied Pharmacy at the University of Strasbourg and obtained his Masters Degree (postgraduate) in Applied Industrial Pharmaceutics at the University of Montpellier in 1973.

After different positions in the Research and Pharmaceutical Industry he joined the Technical Secretariat of the European Pharmacopoeia Commission at the Council of Europe in Strasbourg. Jean-Marc Spieser is currently Head of the Department of Biological Standardisation, OMCL Network & HealthCare (DBO) at the EDQM, a department which manages:

- the OMCL Network including for the time being about 90 participating Official Control Laboratories all over Europe involved in both the human and the veterinary field. In 1994, he initiated the inter-communication between Official Medicines Control Laboratories (OMCL) within Europe by developing a real European Network governed by general common policies and operational guidelines, especially in the areas of: Quality Assurance; market surveillance for pharmaceuticals commercialised in Europe through both systems (centralised and decentralised); and batch release activities by Official Control Authorities for biologicals.
- the activities of the Biological Standardisation Programme aimed at:
  - developing and validating new methodologies and particularly those *in vitro* methods which are alternative methodologies to *in vivo* animal bio-assays and
  - establishing the European working standards and reference materials for biologicals (hormones, vaccines and blood derivatives).
- the Blood transfusion and Organ transplantation activities.
- and since January 2008, the activities related to the protection of patients from counterfeit medicines and pharmaceutical crime.

**Dr Sylvie Uhlrich** graduated in 1983 from Paris National High School of Chemistry and received her PhD in Biochemistry in 1986 from University of Paris-Sud, France. She was appointed in 1986 by Institut Merieux as Research scientist.

She developed her carrier as senior scientist in Analytical science and assay development at Sanofi Pasteur. She is currently Global Analytical Franchise leader at Sanofi Pasteur.

**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 ass. Prof. 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 LAT GmbH, 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 Pharmacopeia Expert Committee on Pharmaceutical Chemistry. He teaches at the Universities of Frankfurt and Berlin, Germany and the University of Florida, Gainesville, USA.

**Dr David Wood** qualified with a PhD in Virology in 1984 from the University of Manchester, UK. After initial work in diagnostic virology in Manchester, he transferred in 1988 to the UK National Institute for Biological Standards and Control with responsibility for batch release, standardisation and research on poliovirus vaccines, hepatitis A and yellow fever vaccines. While at NIBSC he became closely involved with WHO activities working both on global standards for biological medicines, and also with the polio eradication initiative, which is now very close to the goal of eradicating wild type polioviruses. In February 2001, he transferred to WHO initially co-ordinating the research agenda for development of post-certification polio immunisation policy and also standardization of virus vaccines. In June 2003 he assumed overall responsibility for all WHO biological standardization activities. He is Secretary to the WHO Expert Committee on Biological Standardization. From January 2006, as Coordinator of the Quality, Safety and Standards Team, he is responsible for all aspects of regulatory support provided by WHO to countries and UN agencies for biological medicines, including the vaccines pre-qualification scheme. He is also responsible for a laboratory network of WHO Collaborating Centres for biological standardization.

**Dr Steve Wood** obtained his degree (1978) and D.Phil (1982) in chemistry from the University of Sussex, UK. In 2003 he joined the reference materials production team at LGC Limited, was appointed team leader in 2005 and successfully led the team to ISO Guide 34 accreditation (Production of Reference Materials) in 2006. He is the UK representative at the International Organisation for Standardisation Reference Materials Committee (ISO REMCO), secretary of both the UK Reference Material Working Group and the British Standards Institute Reference Materials Committee and LGC's representative on the European Reference Materials co-operation.

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