



European Directorate for the
Quality of Medicines & HealthCare

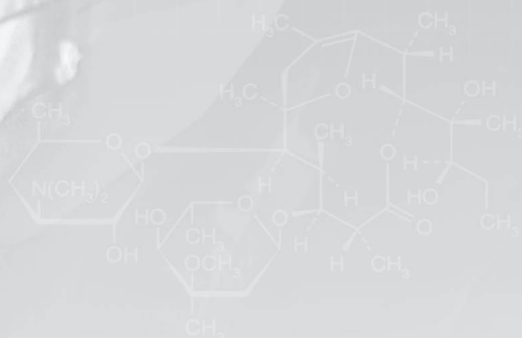


COUNCIL
OF EUROPE CONSEIL
DE L'EUROPE

European Cooperation and Synergy in Quality Standards beyond the European Pharmacopoeia

Strasbourg, France, 15-16 June 2007

PROCEEDINGS



EUROPEAN COOPERATION AND SYNERGY IN QUALITY STANDARDS BEYOND THE EUROPEAN PHARMACOPOEIA

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

15-16 June 2007
Strasbourg, France

PROCEEDINGS

TABLE OF CONTENTS

SESSION 1: General introduction

How to handle the quality of extemporaneous and small-scale preparations at a European level? Problems and issues for hospitals and community pharmacies to consider

Mr V'Iain Fenton May, National Pharmacopoeia Authority (UK)..... 7

Quality standards for extemporaneous preparations

Dr Pieter H. Vree, National Pharmacopoeia Authority (NL)11

GMP for preparation of medicines in small quantities and the annexe for cytotoxics in the Swiss Pharmacopoeia

Prof. Dr Stefan Mühlebach, Swissmedic (CH)17

The view of hospital pharmacists

Quality standards for the preparation of medicinal products

- *Dutch hospital pharmacies*

Dr Paul P. H. Le Brun, Central Hospital Pharmacy (NL).....19

The need for new standards

- *Danish hospital pharmacies*

Prof. Dr Vagn Handlos, Rijshospitalet (DK)23

- *View of French hospital pharmacies*

Dr Patrick Rambourg, CHU Montpellier Pharmacie St Eloi (F)25

SESSION 2: Licensing

The German system of standard licenses and standard registrations (Standardzulassung)

Dr Thomas Zapf, BfArM (D), Prof. Dr Stefan Mühlebach, Swissmedic (CH)29

Standard licences and Formulae magistralis - The European perspective

Prof. Dr Dietrich Schnädelbach, BfArM (D)31

Licensing of German standard preparations

Dr Susanne Keitel, BfArM (D)35

Viewpoint from an inspector

Ms Gudrun Eichler, Staatl. Gewerbeaufsichtsamt Hannover (D)39

SESSION 3: National Experiences of Formularies

The British experience

Dr Gerard Lee, MHRA (UK)43

The Italian experience

Prof. Maurizio Cignitti, ISS (I)47

The French experience

Prof. Jean-Claude Chaumeil, University of Paris V (F)51

The Belgium experience in relation with the Therapeutic Magisterial Formulary

Mrs Paule Jacquain, Agence Fédérale des Médicaments et des Produits de Santé (B)53

SESSION 4: The specific case of radiopharmaceuticals manufactured extemporaneously in hospital radiopharmacies

General introduction

Prof. Alfons Verbruggen, Laboratory for Radiopharmacy, Universitair Ziekenhuis Gasthuisberg Radiofarmacie (B)59

Current practices for preparation of radiopharmaceuticals in hospitals and PET centres: experience and considerations from the field

- **Radiopharmacy practice in the UK**

Prof. Stephen Mather, Imperial Cancer Research Fund Department Nuclear Medicine, St Bartholomew's Hospital, London (UK)63

- **Spain**

Dr Ivan Penuelas, Unidad de Radiofarmacia, Clinica Universitaria de Navarra, Pamplona (E).....65

Guidelines for Good Radiopharmaceutical Practice (from the Radiopharmacy Committee, European Association of Nuclear Medicine)

Dr Clemens Decristofo, University Klinik für Nuklearmedizin (A).....71

EU Guidelines to Good Manufacturing Practice

Annex 3: Manufacture of Radiopharmaceuticals

Dr Elisabeth Norbygaard, Danish Medicines Agency (DK).....73

Posters

- Analysis of pharmaceutical preparations made up in pharmacy by near infrared spectroscopy79
- Control methods of preparations in hospital: investigation in hospital pharmacies and project to development of reference frames81
- Chromatographic methods suitable for a Podophyllotoxin monograph83
- Pharmaceutical compounding in Sweden85
- Quality assurance of extemporaneous preparations in Germany in the frame of round robin tests87
- Guidelines and standards for the quality management system in community pharmacies: the German experience.....89
- Formularies: the Dutch Experience91
- Formularies: the German Experience93
- Supervision of extemporaneous and small-scale preparations in German community pharmacies95
- Quality aspects of automated medication dispensing system97
- Standards for compounding in German hospital pharmacies.....99

Biographical Notes101

List of Participants.....107

SESSION 1: General introduction

How to handle the quality of extemporaneous and small-scale preparations at a European level? Problems and issues for hospitals and community pharmacies to consider

Mr Vlain Fenton May
SMPU (UK)

Mr V'Iain Fenton May's slides are available on page 2 of the Symposium,
Session 1: General Introduction
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

This is the first symposium held under the auspices of the European Pharmacopoeia discussing unlicensed medicines. One may ask why are we here to discuss extemporaneously dispensed medicines when we have a pharmaceutical industry which supplies licensed products which are assured to be safe by the competent authorities of member states.

Not all patients are equal to the average person we are not all equal in height and weight. Some cannot swallow due to inborn difficulties or difficulties following surgery. Some patients are allergic to ingredients widely used such as lactose colorants etc. On some occasions it may be safer to prepare a ready-made product to be given to a patient rather than to expect hard-working extremely busy healthcare workers who have no real experience in handling pharmaceuticals to make rapid calculations and aseptic manipulations to a powder, or concentrate, supplied. Unfortunately so few need these products that there is no commercial basis for their manufacture and therefore those patients most in need will never be satisfied by a fully licensed product.

From research in the UK it is obvious that there is a large number of products which are unlicensed and used in patients. There is also no uniformity in demand and the top 10 varies from year to year.

We must examine the legal status under which a pharmacist would carry out this function. The role of a pharmacist is quite clearly enshrined in the the EC directive of 65/65 and I give this to show how far back this was enshrined in law within Europe now the directive has been updated under 2001/83 and the pharmacist's function defined in Article 5 and further amended in 2003.

Each member state has enshrined those rights in their own laws but they have given it their own interpretation and each of us operates in a slightly different legal environments. It is this environment that the pharmacist must know and understand in order to operate safely both for themselves and for the patients they serve.

Now we must consider the patient's needs, as that is the prime objective of all healthcare professionals.

The patient expects to receive a medicine that is

- of a guaranteed quality
- that is therapeutically effective
- that is the same no matter where it is dispensed

Now we must consider the standards that should apply to these medicines. Many of our colleagues are pressing for standards that are relevant to the needs of the product and the patient.

Before drawing up these standards we have to think of

- single preparations for an individual patient
- large batch made with the anticipation of the needs of many patients that are expected in clinics or outpatient departments

There are many local standards available which have been independently drawn up by colleagues working in this area. Currently under discussion is the draft from the Pharmaceutical Inspectors Convention which is being designed in order to try and define the universal standard that hospital pharmacists may work to supply extemporaneous and bulk prepared products for their patients.

We must consider the risk/benefit ratio of making these products. We may look at an item dispensed for an individual patient, by its very nature, there is little or no quality control applied to a single dispensed product but the effect of having something go wrong is going to be significant to the patient who receives it but in global population terms a very small risk.

The extent of preparation/manufacture ranges from that single item to batches of 200-2000 items. If we take that through its logical conclusion and we have a hospital who produces a large batch of a particular product then we can afford to implement a much greater degree of quality control and assurance into that product however the greater is the batch size so are the significance on a population of an error and the more that is made the greater should be the import and quality and here we could draw some form of safety care that we can see how risky a product could be.

The risk assessment can be further refined by considering the technical risk (which will include the manipulative difficulties, the chemical and physical stability of the entity) and the clinical risk (which will include the therapeutic safety profile). These together can be used to target the resources of local interest groups.

Now we should consider the needs of the products

The outcome of any quality system must be to supply

- A uniform, quality assured product.
- A product which has no batch to batch variations.
- Of significance for a mobile population is a product which will have the same characteristics no matter where it is dispensed.

Patients living in one town may wish to go on holiday and have their medicines dispensed wherever they be; patients may move town; children may be moved by their parents from one town to another due to job changes. One would expect the medicine made in the next

village to be of the same therapeutic and quality standard as that dispensed in the previous village.

It should be noted that the GMP concept of a validated system does not sit well with these special products. Only when they become large batches, and regularly made, could anyone afford the investment that is required to validate the systems and products.

We as a European peer group must assist in producing acceptable standards for the whole of Europe to guarantee the protection of the patient; to guarantee the protection of the professionals making the products and to ensure the continuance of a needed service.

There are decisions that must be taken at a European level.

The setting of the standards for the raw materials. The European pharmacopoeia satisfies many of the needs but not all of them. There is a need for a European Forum to allow for a faster processing of special needs. These products of which we are speaking are often needed immediately and there is no time for a two-year discussion on what quality that will material should be.

The finished extemporaneous products will remain specific to member states for many years. In the UK we find patterns and different usage from hospital to hospital. I am certain this will also be found across member state boundaries

But, there is a need for:

- intra state corporation so that each hospital or dispensary within a member state can work from the same quality level
- an interstate co-operation where we can come together and help each other in the formulation of variants and to share the difficulties which faced by most formulation pharmacists
- support and encouragement from the European pharmacopoeia commission the development of local level of a uniform standards

In summary

We must be aware that patient health depend on the extemporaneously prepared and manufactured products.

The practice will continue to be needed.

There is a duty to draw up and agree on relevant standards

There is a duty to ensure that all medicines dispensed are effective, reproducible and of the right quality.

Those responsible for initiating this meeting and EDQM for allowing it to take place should be congratulated for understanding this need and to helping us to move forward in the future.

Quality standards for extemporaneous preparations

Dr Pieter H. Vree

National Pharmacopoeia Authority (NL)

Dr Pieter H. Vree's slides are available on page 9 of the Symposium,

Session 1: General Introduction

http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

Preparations in community (6,5 million recipes/year) and hospital (2,5 million recipes/years) pharmacies are still an essential element of pharmaceutical care in The Netherlands, as in most other countries. It comprise both officinal and magistral preparations.

In my country both community and hospital pharmacies are preparing:

- dermatological products (the vast majority in community pharmacies);
- modifications of commercially products to the need of special patients, e.g. adjustment of dosage or dosage form;
- commercial products ready-for-use;
- sterile products for home-care;
- replacement therapy for medicinal products withdrawn from the market;
- prescriptions of a medical doctor (magistral preparation).

Sterile preparations constitute the main production in hospital pharmacies. Also diagnostics (radiopharmaceuticals) and experimental products could be mentioned here. A special place have the extemporaneous sterile preparations. By tradition most of these products were made on the wards by nurses. However thorough investigations indicated that patient safety is not duly met in these wards, e.g. because of mistakes, miscalculations and contamination. So, hospital pharmacies are already or will be asked to take over these duties.

Officinal pharmacy preparations are mainly produced in a wide variety, but on a small-scale. Usually they have a short(er) shelf-life. There are also preparations made for one patient only (the magistral formula), e.g. cancer patients, infants, diagnostic procedures and so on. Characteristics of these preparations are e.g.: ready-to-use, calculations included, made with aseptic techniques.

Some people may predict that the amount of pharmacy-made preparations is declining. But over more than ten years, at least in the Netherlands, the number has been stable and tends to increase. It may be expected that the need for this type of extemporaneous preparations will further increase. The scientific knowledge about the genetic and environmental factors, causing variability in patients promotes individualising of pharmacotherapy. Tailoring of dosage schemes and dosage forms may be the result.

In hospitals tasks that traditionally took place on the wards have been transferred to the pharmacy or specialised preparation-units. Other hospitals are underway to bring pharmaceutical handling from the wards to the pharmacy. Furthermore: expansion of home-care for an increasing number of elderly people is an issue in many countries.

Another point of view is whether the pharmaceutical industry will be ready to offer a full range of dosage forms. The recent past has learned us that some drugs or dosage forms have becoming orphanised also in case there is still a need for patients. Last but not least terrorist threat initiated reconsideration of the production function in (hospital) pharmacies in case of emergencies.

The conclusion should be that production facilities in pharmacies are still needed and may be increasingly valuable.

Regarding the legal aspects of this type of medicinal products, pharmacy-made preparations are excluded from EC-legislation but are subject to national legislation. Article 3 of Directive 2001/83/EC as amended by Directive 2004/27/EC states:

This Directive shall not apply to:

- Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).
- Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula).

However the European Pharmacopoeia gives the official standards for medicinal substances and pharmaceutical preparations in all participating countries. Countries still having a national pharmacopoeia may lay down further requirements there in, other countries may have additional provisions in the Medicines Act, a by-law or decree or refer to the Ph. Eur. The way in which quality standards have been laid down in national legislation varies from country to country. Some countries also include a chapter on GMP-rules in their national pharmacopoeias. In the Netherlands there is no national pharmacopoeia anymore. In 1993 the Pharmacopoeia Act was withdrawn.

A decree based on the Medicines Act states that all pharmacy-made medicines shall comply with the European Pharmacopoeia.

Two types of quality standards can be distinguished: product-related standards, such as mentioned in pharmacopoeias and formularies, and process-related standards, such as good manufacturing practice rules.

This presentation focuses mainly on product-related characteristics and particularly explains the significance and relevance of the general monographs of the 6th edition of the European Pharmacopoeia for pharmacy-made preparations.

General monographs are applicable to all products in the class defined, irrespective of whether there is an individual monograph or not. Especially the general monograph on “Substances for pharmaceutical use” has great significance. All substances, also those for which there is no monograph in the Ph. Eur., used in prescribed medicines have to fulfil the criteria mentioned there. Those requirements have a huge impact on daily practice in pharmacies.

Without entering into full details I will mention some general monographs that are of special significance for pharmacy-made preparations.

- Dosage forms monographs
- Monoclonal antibodies (relevant for university hospital pharmacies)
- Radiopharmaceutical preparations
- Substances for pharmaceutical use

The general monograph on substances for pharmaceutical use refers to texts as control of impurities, residual solvents, residual catalysts, genotoxic impurities, and microbiological quality. When relevant to the substance these texts have also to be observed.

If there is an individual monograph, this has to be always read in conjunction with general monographs. Substances and preparations that are the subject of an individual monograph are also required to comply with relevant, applicable general monographs. It can not be emphasised enough that the applicability of general monographs has a big impact on daily practice in pharmacies. Medical doctors in the Netherlands still prescribe for good reasons pharmaceutical products with active substances that can not be found in a current pharmacopoeia. Also these substances have to fulfil the criteria of relevant general monographs of the Ph. Eur. At present, information is not yet available about the possible implications are of that strengthened quality standards.

Professional associations at national and European levels might be stimulated to draw up an inventory of substances not mentioned in any current pharmacopoeia, but still in use in pharmacies.

In my opinion national authorities should bring about individual monographs for those substances or take the initiative to promote the drafting of new monographs by professional bodies as the local society of (hospital) pharmacists or a professional laboratory. If more countries express the same need for a monograph the European Pharmacopoeia Commission is the forum to discuss the need for the development of such a monograph.

Regarding GMP, the Netherlands Association of Hospital Pharmacists took the initiative, thereby stimulated by the Health Care Inspectorate to draft a GMP-guide for Hospital Pharmacies, a so-called GMPz, (English: GMPH).

The Health Care Inspectorate compared this guide with the current standards for industry and after a professional debate the GMP-z was acknowledged as the state of art practice guide.

Inspectors program periodic visits to the hospital pharmacies and issue in case of compliance with the GMPz-standard an official opinion. When that standard was brought about the Dutch inspectors took the initiative to set up an expert circle on Hospital Pharmacy within the PIC/S. This working group developed a new Guide, which follows the structure of PIC/S document regarding GMP as already developed for industrial manufacture. At the moment draft 2 of this document is released for consultation under professionals.

I will discuss now the relation between product-related and process-related quality standards. The text of pharmacopoeia monographs contains on various occasions requirements that refer to good manufacturing practices.

Also the reverse is true. The draft PIC/S guide states: “GMP is that part of quality assurance which ensures that products are consistently prepared to quality standards.”

One of those quality standards is the current edition of European Pharmacopoeia. In my talk I will not go further into GMP-rules. I select only those GMP-aspects that are commonly referred to in texts of the monographs of the Ph. Eur.

The first item I have chosen is “validation”.

All the methods that are described in the Ph. Eur. are validated methods, but there is still the need to check whether that method works properly in the laboratory of the pharmacy, so-called in-house validation. You may better call this performance testing. If an alternative method is used for the Ph. Eur. method, then it has to be validated against the official method.

The second item is “in-process-testing”.

In the production section of an individual monograph there are tests mentioned that are not applicable on the final product, but given for the control of the process. This is an important GMP aspect and should be reviewed by the responsible pharmacist before release of the product or the intermediate.

The same holds true for “parametric release”.

My next example is especially relevant for pharmacists in their pharmacies.

The Ph. Eur. describes for identification purposes tests named “second identification test set”. These tests are given for pharmacies that do not have the equipment to apply the “first identification test set”. The “first identification test set” can be used in all circumstances, but the “second identification set” only under the condition that the substance or preparation is fully traceable to a batch certified to comply with all the other requirements of the monograph. No doubt that this is also a relevant GMP-aspect.

Last but not least: the Ph. Eur. states that the quality standards represented by monographs are valid only where the articles in question are produced within the framework of a suitable quality system.

I now raise the question whether it is possible or not to comply with these quality standards. In other words: what should be the compliance strategy of the authorities. I can only speak for The Netherlands.

The Ph. Eur. is the official standard and so it has to be considered as mandatory. In exceptional cases deviations from the standards can be justified, e.g. if there is shortage of essential medicines and in case of emergencies. During inspection rounds the Health Care Inspectorate may ask for justification. If authorisation is requested, in urgent cases authorisation can be given afterwards. When new standards are put in place usually a transition period is introduced. Professional associations will be asked to set up an implementation plan.

Regarding process-related quality standards: the GMP for hospital pharmacies is a guidance document. It has no legal status. The general approach is:

- Practice what you preach.
- Apply or explain.

In the Netherlands the Health Care Inspectorate, section Hospital Pharmacies, operates an inspection program that includes a schedule for visiting hospital pharmacies and pharmacies with extended production facilities. The GMPz is the current standard.

A hospital pharmacy may apply for a GMPz-opinion issued by the Health Care Inspectorate. Such an opinion is demanded in case a pharmacy delivers pharmaceutical products on prescription of a medical doctor through another pharmacy. As mentioned before the PIC/s has drafted an international standard for pharmacies, that was recently under consultation with professional associations.

If the (hospital) pharmacy prepares investigational medicinal products an authorisation has to be given after a full (industrial) GMP (Annex 13)- inspection.

So in summary the take home messages are:

- Ph. Eur. VI contains relevant and significant quality standards for pharmacists
- General Monographs apply also to substances for which there is no individual

- monograph
- Monograph on Substances for pharmaceutical use is of special significance
- Texts as Control of impurities, residues are also relevant
- Hierarchy of first over second identification series
- Condition: a quality system should be in place
- Preparing aseptic products asks for quality improvements: from wards to pharmacies
- Strong need for tailoring quality standards to specialised small-scale production units
- Ph. Eur. and GMP are complementary standards
- Ph. Eur. refers to GMP and vice versa

References:

1. http://www.edqm.eu/site/The_European_Pharmacopoeia_6th_Edition-681.html: European Pharmacopoeia, 6th Edition, 2007
2. <http://www.picscheme.org/index.php>: PIC/S Guide to Good Practices for Preparation of Medicinal Products, 23 Aug 2006
3. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs/en/an13final_24-02-05.pdf: GMP Annex 13 Manufacture of investigational Medicinal Products

GMP for preparation of medicines in small quantities and the annexe for cytotoxics in the Swiss Pharmacopoeia

Prof. Dr Stefan Mühlebach
Head Pharmacopoeia (CH)

Prof. Dr Stefan Mühlebach's slides are available on page 18 of the Symposium,
Session 1: General Introduction
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

Abstract:

In Switzerland the pharmacopoeia consists of the European Pharmacopoeia and the national pharmacopoeia (Pharm. Helv.). The Convention on the Elaboration of the Ph. Eur. was signed by the Confederation of Switzerland as a founding member in 1964. The pharmacopoeia prescriptions are compulsory for all professionals involved in the manufacture, quality control, authorisation, distribution and stocking, delivery including labelling, and the use of therapeutic products. The federal law on Therapeutic Products was introduced in 2002 only, replacing the regional (cantonal) laws for medicaments and medical devices in Switzerland. The national law aims at the protection of human and animal health by authorising only high quality, safe, and effective therapeutic products on the Swiss market. Secondly it obligates the responsible persons to apply the scientific state of the art, which is finally demonstrated by the regular update of the pharmacopoeia.

The manufacture of drugs includes industrial products committed to the PIC GMP. It comprises also preparations of medicines in small quantities e.g. in retail pharmacies or hospitals, important for the individual therapeutic care of patients. Such manufacture requires in Switzerland only a cantonal authorisation. The lack of suited guidelines on good manufacture and the need for a national harmonisation of requirements was the starting point to establish a compulsory GMP for preparation of medicines in small quantities in the national pharmacopoeia. Such prescriptions are at present clearly beyond the scope of the Ph. Eur. and have to be defined on national levels.

The general chapter was introduced in the supplement Ph. Helv. 9.4 in 2005. A first revision and the annex on cytotoxics followed in 2006 (Ph. Helv. 10). The layout was identical to the PIC GMP but respected the differences between fully licensed drugs and those outside the authorisation (ad hoc manufacture, formula magistralis, small scale production distributed to a very restricted number of patients) pharmaceutically cared by a defined responsible person. A major focus is given to the appropriateness (minimal requirements) and the personal responsibility of the authorisation holder. An individual risk assessment has to be carried out and to be documented. Beside a legally binding text, additional comments are given in a commentary section in the pharmacopoeia including helpful documents like protocols for hygiene measures, production or packaging, and product release.

Cytotoxics represent a high risk ready-to-use preparation with often toxic products. It includes aseptic preparation steps and is mostly individualised to a single patient. Therefore, patient safety but also protection of product and of those involved in preparation and administration had to be considered. The Swiss pharmacopoeia defined these rules together with their users and authorisation specialists. They include state of the art techniques like working in clean room area using safety laminar air flow cabinets and

isolators. The minimal requirements in equipments and premises were stated. Specific aspects to be respected in addition to the general chapter on good manufacture practise for preparation of medicaments in small quantities were included and indications on risk assessment defined.

The view of hospital pharmacists
Quality standards for the preparation of medicinal products
Dutch hospital pharmacies
Dr Paul P. H. Le Brun
Central Hospital Pharmacy (NL)

Dr Paul P. H. Le Brun's slides are available on page 30 of the Symposium,
Session 1: General Introduction
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

The goal of my presentation is to discuss with you how the quality standards for small-scale preparation of medicinal drugs in Dutch hospital pharmacies are realised in practice.

The next slide shows the hospital pharmacy I work in. The Central Hospital Pharmacy of The Hague of is the largest pharmacy of the Netherlands and one of the largest of Europe. It was founded 259 years ago. So it can be said we have a long and rich history. To give you an impression of its activities: we provide 28 health care institutions with pharmaceutical care; in the background you see one of the hospitals we take care of. There is a yearly drug turn over of 30 million euro. 220 employees work in the pharmacy, including 30 pharmacists and 100 technicians.

Content of my presentation: I will start with the scope of preparations: what are we actually talking about. Next, I will discuss with you product and process quality with a focus on GMP necessary for the hospital pharmacy.

Scope of preparations

The Netherlands have a long history of preparation of pharmaceuticals. Both stock production and dispensing were part of the tasks of the (hospital) pharmacy for decades. Until the beginning of the '90's, it was not uncommon to produce 30% of the total drug turn over in a Dutch hospital pharmacy. This production was mainly driven by economic reasons. Today, the perspective has changed; production in the pharmacy is no longer considered to be profitable. Availability in patient care is now the main reason for production, of course with a focus on quality. When a product is needed in patient care and it is not commercially available or not available in the required dosage form, it can and will be produced by a hospital pharmacy. The general volume of production, however, has changed dramatically.

In the next slide I will give you some facts and figures. The amount of preparations varies between hospital pharmacies. Some of the estimated data are presented in Slide 5.

As you can see, with a population of approximately 16 million people, a total of 8.9 million extemporaneous preparations are prescribed, divided over community and hospital pharmacies. These are mostly dermatological preparations.

The majority of stock production takes place in hospital pharmacies. I will show some examples in the next slide.

Ultimately, a large number of preparations is made for direct use in patient care. These are cytotoxic drugs, antibiotics etc. prepared for direct administration. You have to realise that only 1-2% is prepared in the pharmacy in a controlled area. The majority is prepared by

nurses on the ward in uncontrolled areas. So in my opinion a lot of quality improvement can be gained in this process!

Slide 6 shows some examples of products that are not available in the market. Some have never been available and some are withdrawn from the market for commercial reasons. Furthermore, there are preparations for clinical trial. As said before, the preparations for direct use in patient care and a specific category, the so-called “ready to use” preparations. This category needs some clarification.

A lot of products are being prepared on the ward. An example is shown in the next slide: noradrenalin. This product is available in ampoules with a concentration of 1 mg = 1 ml. However, it is used by the intensive care department in an infusion pump as a solution of 50 mg = 50 ml. This means that a nurse has to open 50 ampoules and put these in a syringe for a pump. This requires a lot of handling with a risk of contamination of the sterile product and potential picking errors. Quality can be improved by doing this process in a controlled area. The quality can be further improved and medication error risks can be reduced by preparation of a sterile solution of 50 mg in a bottle of 50 ml in the pharmacy based on a standardised product file. This product is “ready to use” by the nurse by simply putting the total amount in a syringe.

Product and process quality

The general requirements for product quality are described in de European Pharmacopoeia. Especially the general monographs are of interest, as they are applicable to all substances and preparations used and prepared in the pharmacy. These items were already addressed in a previous presentation this afternoon. Therefore, I will focus on good manufacturing practices.

These are complementary to the Pharmacopoeia requirements.

The GMP rules are written primarily for large-scale industrial drug production but they are also applicable to other areas of pharmaceutical preparation. GMP provides basic quality assuring guidelines for manufacturing drugs: clear goals are stated for all aspects of the organisation and its processes to assure the required quality. GMP has applicability in a broad sense; interpretation and deviation from the general rules are possible to a certain extent but only allowed if the stated requirement are not compromised. Specific fields of interest are outlined within annexes.

In practice the rules cannot be applied easily to the hospital pharmacy. The practice of the hospital pharmacy differs in several ways from industrial production, which is visualised in the next slide.

In hospital pharmacies we prepare a lot of different products in small batches. In industry only standardised processes are used. In the hospital pharmacy we also have non-standardised processes, for example the preparation of products for individual patients. To date, a specific annex for preparation in ‘Hospital pharmacies’ is necessary but absent.

Therefore, in The Netherlands a specific ‘Hospital pharmacy’ annex was written (next slide). This “GMP-hospital pharmacy” (or, in Dutch, the so called GMP-z) was written in close co-operation with the Dutch regulatory offices. The first edition was published in 1996.

The purpose of this document is to allow GMP to be realised on any type and level of manufacturing of drugs within the hospital pharmacy.

As visualised in the next slide, it can be seen as an annex to the European GMP; GMP hospital pharmacy does not replace the European GMP!

GMP-H (next slide) provides necessary supplemental information on specific topics that have not been described within the European GMP, such as small batches of products, drug manufacturing for individual patients. It takes into account the large variety and diversity of products. The specific circumstances regarding preparation of products with a short shelf life have been taken into consideration. Furthermore, it describes the handling of high-risk products.

For aseptic stock preparations the European GMP rules are applicable. However, in the daily practice of patient oriented care, we have to deal with aseptic preparations for individual patients. For this process, a broader interpretation of the GMP is necessary, since a strict interpretation would be impossible in daily practice.

A special annex, in the GMP-H describes aseptic preparation for individual patients. This annex 3 of the GMP-H was only recently (May 2006) updated.

Origin and rules of this annex

The guidelines upon which annex 3 is based are the draft version of the PIC/S Guide on “Good practices for preparation of medicinal products in pharmacies”, “The quality assurance of aseptic preparation services” issued by the NHS Quality Control Committee, the ASHP “Guidelines on quality assurance for pharmacy-prepared sterile products” and USP Chapter <797> “Pharmaceutical Compounding: Sterile Preparations”.

GMP-H can be compared to the PIC/S Draft Guide on “Good practices for preparation of medicinal products in pharmacies”. The added value of the GMP-H is the risk based approach and the proven applicability in hospital pharmacies by more than 10 years of experience.

When preparing sterile medication for patient care, the handling is mostly based on a closed process. Sterile components are used to prepare a product in a controlled area. In the annex on aseptic preparations account has been taken on the fact that there is a variety of environments in which products are prepared. A controlled area for high risk products in the pharmacy, a controlled area on the ward and for the majority of preparations uncontrolled areas on the wards. This differentiation in product protection has been taken into account when writing the GMP-H annexe 3.

Furthermore, this updated issue of the GMP-H annex 3 is based on monitoring and process validation results of several hospital pharmacies. The rules of this annex are based on the results of individual qualification programmes for personnel and the daily simulation of the preparation process with a broth fill.

The goals of GMP-H annex 3 are summarised in the next slide. The intention of the annex was to describe specific processes of aseptic preparation within hospital pharmacy. It is realised that there is a differentiation on basis of the complexity of the handling steps. We distinguish between a simple reconstitution of an antibiotic drug and a high risk complex preparation of an epidural solution. It is also realised, as said before, that there is a differentiation on basis of the magnitude of protection of the product during preparation. Furthermore, all necessary requirements for specific working situations and storage conditions are described. Application of all these aspects results in a maximum shelf life.

This is summarised in the next slide. Besides complexity and product protection requirements for training of personnel and validation and monitoring are given in this annex.

Consequences

It is generally agreed upon, amongst others by the Dutch inspectorate, that the GMP-H is the minimum standard for the production of pharmaceuticals in Dutch hospital pharmacies. GMP-H requires enormous investments in education of staff, quality systems and adequate facilities. Therefore, the Dutch hospital pharmacist has to make choices or has already made them: either investment in the production facilities or discontinuation of the stock production and sticking to individual dispensing only. Although choices have been (or will be) made, the availability of products for patient care is not compromised.

In The Netherlands, the delivery of products by one hospital pharmacy to another is allowed under the following conditions:

- There is a formal agreement between the “supplier” and the “client”
- Delivery is only allowed for not commercially available pharmaceuticals
- The supplier has to have a formal GMP-H status

To date, there already are a number of relatively large hospital pharmacies with several clients. Expectations are that in the near future stock production will take place in a few larger regional production centers only. All other hospital pharmacies will limit their production activities to dispensing for individual patients and will obtain the other necessary products from the GMP-H production centers.

Conclusions and take home message

Preparation in hospitals focuses on patient care and not on trading products; it is not driven by economic rules and the highest necessary quality should be realised.

There is no doubt that GMP describes the rules to obtain product quality.

However, GMP has not been written specifically for day-to-day hospital pharmacy practices.

The Dutch annex on GMP-Hospital pharmacy, the GMP-H, allows GMP to be realised on any type and level of preparation of drugs within hospital pharmacy

A specific chapter, GMP-H3, describes the hospital pharmacy specific situation of aseptic preparation which necessarily takes place on drugs that have to be prepared for use

It is recommended to adopt several parts of the GMP-H in the PIC/S draft guide e.g. the chapter “aseptic preparation”.

Acknowledgements

The content of this presentation was composed with the help of a number of colleagues. Not all are mentioned but special thanks to:

- The Royal Dutch Pharmaceutical Society (KNMP)
Y. Bouwman-Boer, PharmD
- The Dutch Hospital Pharmacists Association (NVZA)
President: R. van der Hoeven, PharmD
- The Committee on GMP-Hospital Pharmacy
Chairman: A. Vermes, PharmD, PhD
- The Committee on GMP-H3 – Aseptic preparation
M.A.L. Pluim, PharmD (chairman), F.A. Boom, PharmD

The full text of the English version of the GMP- hospital pharmacy can be down loaded from the website of The Dutch Hospital Pharmacists Association (WWW.NVZA.NL).

The view of hospital pharmacists

The need for new standards

Danish hospital pharmacies

Senior Scientist Prof. Dr Vagn Handlos, Capital Region Pharmacy (DK)

Prof. Dr Vagn Handlos' slides are available on page 40 of the Symposium,
Session 1: General Introduction
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

Danish Hospital Pharmacy (HP) production and preparation, legal background

The Ministry states the role of the Danish HP's in a special part of the law for pharmacies, generally setting frames for distribution and production. According to this HP's can apply for market authorisation on the same basics as industry for drugs mainly used in hospitals. Production of drugs described in the Pharmacopoeia Nordica 63 (no longer in action) are soled and produced from HP's based on a market authorisation given to a joined registration office owned by the Danish counties.

On behalf of the Danish HP's this office has by now market authorisation for 165 single drugs covering all dispensing forms from tablets to the standard assortment of Large Volume Parenterals. The HP's taking part of this "large scale production" are running and inspected according to the European rules for Good Manufacturing Practices (GMP) and should thereby be on the same quality level as products from the pharmaceutical industry. Beside this production Danish HP's has a relatively big preparation of drugs to single patients or groups of patients, drug which are either magisterially or extempore prepared. The frame for this preparation is given by the Danish Medicines Agency and put into action by the head of the agency through a special regulation called "Danske Lægemedel Standarder (DLS)" *Slide 5* published annually, with four supplements a year. Production facilities used for these preparations are of the same quality as for the above mentioned production and the inspection standard for the installations are also equivalent. But there are differences in QA and QC demands according to DLS.

It's important to mention that the rules for magisterially and extempore prepared drugs covers the whole range from a single tube of ointment which is not kept on stock to non sterile liniments on stock but also Total Parenteral Nutrition mixtures and reconstituted cytotoxics prepared by mixing a product with market authorisation with it's intended solvent. A procedure witch in the hospital clinic can take place solely under the responsibility of a MD in a non classified room!

Examples from the daily practices in a Danish Hospital Pharmacy

One of the goals for the pharmacy has for a long time been to deliver drugs to the wards in a ready to use form. This is to minimise dispensing errors and thereby increase the patient safety. In the presentation (*Slide 6*) the yearly turn over in numbers of produced Large Volume Preparations (LVP) and Small Volume Preparations are given together with other figures. *Slide 7* shows the expected numbers of extempore preparations for 2007.

Drugs for very rare disease are sometimes asked for by the hospital ward with a very short notice, a case showing the value of having hospital pharmacy personnel and expertise in the patient treatment team. An example showing this importance is given in *Slide 10*, where a patient with Wilson's disease needed a quick treatment with a copper complexing agent.

No drugs with market authorisation was available on the Danish market and there was not enough time to get it from the other end of the world. It was therefore decided to use the skills of the pharmacists in the clinic, production and the quality department to compose a safe and effective drug for the patient. A so-called Science Based Approach was used for tailoring capsules for this patient, as described in *Slide 10*. The patient was cured in a short time and the value of a producing HP was showed again.

Future

The cost of building facilities and maintaining a staff for production and quality control of magistral and extempore preparation following the Danish model is quit high and will in many cases be an obstacle to transfer preparation of drugs from the hospital wards to the qualified pharmacy. One obstacle to this process could be a more HP oriented GMP as proposed by PICS in the GMP for small scale production (preparation). Although the proposal released in 2005 is only a part of the way, it could be revised in a way that practice is more in focus without harming patient safety in European hospital.

Another solution to the problem could be robots transferring the content of a prescription for a magisterially drug directly to the finished product placed the ward and thereby overcoming the strict rules for pharmacies. An example of this equipment is shown in *Slide 11*.

The view of hospital pharmacists
View of French hospital pharmacies
Dr Patrick Rambourg
CHRU Montpellier Pharmacie St Eloi (F)

Dr Patrick Rambourg's slides are available on page 46 of the Symposium,
Session 1: General Introduction
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

As you see, the title of my presentation is "Quality standards for preparations in the hospital pharmacy: the view of French hospital pharmacists".

If the first question is: "do we want an optimum level of quality for the preparations made by hospital pharmacists?", of course the answer is "yes".

If the second question is: "do we want the same quality standards for the preparations made by hospital pharmacists and community pharmacists?", the answer is also "yes" !

Now, I would like to explain the reasons of our determination.

First, our law (the French code of public health) specifies that the preparation of drugs must be carried out in conformity with good practices and that these good practices envisage in particular the methods of follow-up making it possible to ensure the traceability of the drugs.

At the beginning of the millennium (two thousands one), the good practices for hospital pharmacy were published and we have now to work according to their principles and general rules. The chapters of the general recommendations are the same as in many countries: quality management and documentation, personnel, premises and equipment.

The first edition of these general recommendations was followed by specific recommendations relating to the sterilisation of medical devices that is under the responsibility of hospital pharmacists in France. These good practices for sterilisation contain different parts: Principles, responsibilities, personnel, premises, equipment, documents, disinfection, packaging, sterilisation, validation and control, labelling, transport, management of non-conformities, subcontracting...

During the year 2002, the French agency for health products started a working group with the objective to write good practices for preparations in the hospitals. Five years after, I'm now confident in the publication of these good practices. They will be published in a few months after the public survey which is taking place at this moment.

We must point out that these good practices are really different of good manufacturing practices for the industry.

In France, the law clearly defines several types of preparations. Hospital pharmacists can prepare, if they have the authorisation of health authorities, these different types of preparation for in- and out patients.

- Magistral preparations: they are prepared extemporaneously for a defined patient either in the pharmacy which dispense the preparation, or, under some conditions defined by the regulation, in a pharmacy which a subcontractor. This subcontracting needs a written contract and a preliminary authorisation delivered by the regional health authorities.

- Hospital preparations: they are prepared in advance for one or more patients (because of lack of patent medicines available). These hospital preparations must be declared to the French agency for health products.
- Officinal preparations: they are present in the National Formulary, which is a part of the French Pharmacopoeia.
- Preparations for clinical trials: they can be provided to the people included in the medical research.

The good practices for preparation, currently, as I said, in public survey, point out the principles which apply to the preparations, in particular magistrales, officinal and hospital, carried out in the hospital pharmacy duly authorised for these preparations.

That includes non sterile preparations (capsules, solutions, creams,...), sterile preparations (injectable medicinal products, eye solutions...), dangerous preparations for the operator (like cytotoxics), These good practices for preparations also apply to the preparations for clinical trials and radiopharmaceuticals.

I'm now going to try to summarise our key ideas, the general point of view of French hospital pharmacists:

- The good practices for preparations must be applied without differences between the different types of preparations and without differences between hospital pharmacy and community pharmacy
- Before any new preparation, the pharmacist must study the feasibility of this preparation
 - What is the therapeutic interest?
 - What is the medical risk for the patient?
 - What is the good use of the preparation in term of therapeutic objective, therapeutic adjustment, better acceptability, reinforced observance, risk reduction, traceability of the administration?
 - And last but not least, are we able to produce and control this preparation (personnel, premises, equipment)?
 - The pharmacist has the decision-making power on the preparation according to these definite criteria of feasibility. It is possible to propose to the medical doctor, according to the indications of the preparation, the modifications for an optimisation of the formula. In all circumstances, the pharmacist fully engages his responsibility in the realisation and the delivery of the preparation.
- No preparation has to be made in the care units. Only the reconstitution of patent medicines, according to official recommendations of health authorities, is allowed in the care units
- The subcontracting must be possible if the preparation require equipments and/or a particular technique for the operations of preparation and control.
- The authorisation must be given by the Health authorities only to some pharmacies for the sterile preparations and/or dangerous preparations for the operators after inspection by the regional health authorities
- We have also to point out the importance of
 - the staff education
 - the use of raw materials complying to the specifications of the pharmacopoeia
 - the control of raw materials and finished preparations
 - the qualification and the maintenance of the premises (controlled areas) and equipment

- We must increase the accessibility to some raw materials (in particular for preparation for pediatric use) from pharmaceutical industries, specially those which market patent medicines
- We have to set up the pharmacovigilance system for preparation and follow up the adverse effects
- One of our objectives is to modernise the National French Formulary with the integration of the hospital preparations most frequently made and/or presenting a risk for the health of the operator(s) and requiring particular procedures
- We have also to try to harmonise at an European level the definitions of medicinal products prepared in the pharmacies and the quality standards for preparation of these products.

Thank you for your attention

SESSION 2

The German system of standard licenses and standard registrations (Standardzulassung)

Dr Thomas Zapf, BfArM (D), Prof. Dr Stefan Mühlebach, Swissmedic (CH)

Slides are available on page 2 of the Symposium,

Session 2: Licensing

http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

By the German Drug Law, the Federal Ministry of Health has been empowered to decree standard licenses and standard registrations for well established drugs such as generic drugs, formulae magistralis et officinalis or medicines frequently produced in hospital pharmacies. Article 36 requires that all products which are covered by such an ordinance fulfil the same requirements as medicines licensed according to the regular marketing authorization procedures. Therefore, the procedure is called standard marketing authorization. In the case of homoeopathic products the procedure is called standard registration (Standard-Registrierung).

The standard marketing authorization is based on a dossier which is submitted to the licensing authority. This dossier is elaborated by a specific unit of the Federal Institute for Drugs and Medical Devices (BfArM). It is examined by the authority by the same principles as any regular dossier. If accepted the licensing department grants a license. The holder of the license is the BfArM. Complete licenses, supplemented by General notes are published.

The elaboration of a standard license can be initiated by any interested party by submitting a proposal examined by a committee, which elaborates a proposal for the Federal Ministry of Health. Upon a positive decision the project is added to the agenda of the relevant unit at the BfArM. The pharmaceutical and analytical development, the selection of the primary packaging material, and the testing of the long-term stability of the finished product; if necessary bio-equivalence and safety studies are done. The practical work is done by BfArM or external experts on behalf of the BfArM. All results are compiled in the CTD format dossier and submitted.

Based on the accepted “licensing dossier” a monograph is developed for publication as part of the ordinance of the Federal Ministry of Health and checked by the Committee. It contains the list of the ingredients, manufacturing procedures, analytical methods, primary packaging materials, shelf life, the labelling, package leaflet, and the information for experts. The published monograph serves as a basis for the production and marketing of the product; all detail published therein are mandatory.

Any manufacturer who wishes to use a monograph for production and marketing of the product has to inform the relevant authority. Should the manufacturer intend to use primary packaging material that differs from the listed material, the manufacturer has to proof the stability and safety to the satisfaction of the relevant authority.

To summarize: The standard licensing procedure is a different, but not a reduced of regular authorization procedure. It was established to overcome efficiently the problem of backlogs due to a change in the Drug Act. It used for well established drugs with documented efficacy and safety only. Normal surveillance and control product variability applies. It has a low cost in drug development and marketing authorisation and shows high transparency.

Standard licences and Formulae magistralis - The European perspective

Prof. Dr Dietrich Schnädelbach

Director, BfArM (D)

Prof. Dr Dietrich Schnädelbach's slides are available on page 8 of the Symposium,
Session 2: Licensing
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

Medicines need to be safe and effective. Therefore, they are developed according to the state of the art and are carefully tested in clinical trials. Finally, they are licensed according to current regulations. Once medicines are licensed they are produced from starting materials of appropriate quality according to GMP. Inspection ensures proper performance of manufactures and distributors of medicines. Thus, throughout Europe licensed medicines are of high quality and safe.

In order to cure rare diseases or to meet special requirements the use of unlicensed medicines is indispensable. Therefore, medicines are produced by pharmacists extemporaneously. Between the extemporaneous production of medicines by pharmacists and licensed medicines produced by the industry we have a variety of unlicensed medicines everywhere in Europe. In many European countries unlicensed medicines are produced according to magisterial formulas. Compared to licensed products medicines produced according to magisterial formulas are less regulated. However, the quality of the starting materials is regulated by pharmacopoeia monographs and composition and testing is regulated by magisterial formulas. If magisterial formulas are used like monographs of pharmacopoeias the end of the shelf life is reached once the preparation does no longer comply with the monograph. Therefore, studies on the shelf life of magisterial formulations are possible provided the magisterial formulas define the kind of containers which are to be used. It goes without saying that the test methods would need to be capable to detect any decomposition of the preparation. Unlicensed medicines may be produced at a small scale, more or less, by pharmacists, in hospitals, by wholesalers or others according to magisterial formulas. In fact the size of batches may vary considerably and the production may be used locally, or may be distributed. In addition on the European market we have medicines which still await any kind of regulation such as the medicines used for Traditional Chinese Medicine (TCM). The existence of less regulated or even unregulated medicines might be deplored as regulatory gap. On the other hand it can be seen as a European regulatory challenge.

If we reorganise the regulations for small scale production of medicines the first aim would be to harmonise the existing magisterial formulas. The harmonisation of magisterial formulas could be done within the existing Convention on the Elaboration of a European Pharmacopoeia since the convention covers the elaboration of monographs on preparations. The benefit of this exercise would be that we harmonise the composition and quality of European magisterial formulas. This would ensure that European citizens can receive the same product everywhere in Europe. A second aim would be to bring magisterial formulas as close to the quality standards of licensed medicines as this is achievable. The first step for the harmonisation of European magisterial formulas would be to make an inventory of the existing monographs. Then it would be necessary to do a priority rating in order to decide on the work programme. However, at the same time it may be necessary to agree on the

conditions under which European magisterial formulas would be elaborated. For instance, to avoid interference with licensing procedures we could agree to elaborate European magisterial formulas only if no licensed products of that particular composition or strength exist. Another matter to consider would be the role of the labelling section of such monographs. Monographs of the European Pharmacopoeia include a section “Labelling” which, however, is not mandatory since any decision on the labelling of a finished product is part of the licensing procedure. Probably we would prefer to add to European magisterial formulas a mandatory labelling section. Therefore, we should consider this matter. A solution could be that the European magisterial formulas are published in a separate volume of the European Pharmacopoeia, where the labelling section could be mandatory.

Matters such as indications are regulated by licensing authorities. Therefore, it is questionable whether such items can be part of the labelling. Obviously the role and content of labelling of European magisterial formulas would need to be discussed with European licensing authorities in order to reach an agreement.

Magisterial formulas cannot provide the whole range of regulations obtained by licensing procedures. However, they could be seen as a first step on the way to licensed products. In particular if a European magisterial formula was widely used all over Europe or if it was produced at a larger scale it would make sense to develop a licensed product. This could be done by interested manufacturers who wish to apply for a license. On the other hand manufacturers may find that the expected revenues do not balance the costs for the development of a licensing dossier and the licensing procedure. In this case it could be considered to elaborate a European standard license which could be used by manufacturers at low costs or for free. This would raise products to the level of licensed products and would enable manufacturers to sell them like any other licensed medicine. On the other hand would such a system enable Member States to initiate the licensing of important medicines which otherwise would not be licensed since for economic reasons manufacturers are not prepared to elaborate a licensing dossier.

The European Directorate for the Quality of Medicines & HealthCare could organise a European standard licensing programme. They could initiate the elaboration of licensing dossiers which would be elaborated according to the same principles and standards like any other licensing dossiers. Like monographs of the Pharmacopoeia the dossiers would need to be elaborated at the national level. Therefore, it would be up to the national authorities to organise the practical work. Probably it would be useful to examine the dossiers before submission. This could be done by special groups of experts organised by the European Directorate for the Quality of Medicines & HealthCare. Following the approval by the experts the files could be examined by licensing authorities like other dossiers. After approval by the licensing authorities the European standard licenses could be published and then be used by interested manufacturers. The system could be developed using the Danish and German experience with standard licenses and taking into account the comments of interested parties. The benefit of such a procedure for licensing authorities would be that they do not need to deal with major numbers of licensing dossiers where they cannot expect reasonable fees. Instead, they would be involved in a European procedure where they share the workload with other European licensing authorities. In total we would create a system where all European efforts are combined and any duplication of work would be avoided. All participants would get the maximum output at minimal costs. The whole exercise could at least partially be financed by contributions of those using a standard license.

The European Pharmacopoeia and some national pharmacopoeias have started the elaboration of monographs on herbs used for TCM. It is encouraging that new monographs on this topic are harmonised immediately at the European level. This creates a unified European market and increases the chance to succeed with European quality standards for TCM herbs. At the same time this exercise helps to avoid duplication of work and thus helps to make the best use of the very limited resources of national authorities. TCM uses many preparations including mixtures of herbs. Once a substantial number of starting materials for TCM is regulated by monographs of the European Pharmacopoeia it would be a logical step to elaborate magisterial formulas for preparations. This could prevent European states from the elaboration of regulations which later on would need to be harmonised. Instead we would start a system which is harmonised right from the beginning. It goes without saying that this would strengthen the European position in the field of TCM. It would also provide the basis for a Chinese-European co-operation on the quality and safety of TCM.

There may be areas in traditional European medicine where magisterial formulas or European standard licenses could be useful. Magisterial formulas could provide a first step of regulation for hitherto unregulated medicines. Standard licenses or standard registrations could facilitate the regulation of medicines where it is necessary to reduce the effort both for manufacturers and licensing authorities.

Many European countries seem to be interested to close the regulatory gap between extemporaneous production of medicines and the production of licensed medicines. Therefore, the European Directorate for the Quality of Medicines & HealthCare should enquire which member states would be interested in European magisterial formulas and/or in European standard licenses. Depending on the outcome of this enquiry the further steps should be undertaken. Probably it would be necessary to start two initiatives simultaneously. Firstly, the elaboration of European magisterial formulas could be initiated immediately. Secondly, the legal department of the Council of Europe could be consulted to decide which steps would be necessary to enable the elaboration of European standard licenses. It would be advisable to involve the European Union right from the beginning of this discussion.

A European regulation on small scale production would not necessarily have to deal with GMP. However, it could be considered to adapt the existing GMP guidelines in order to simplify their application to small scale production including extemporaneous production. This could be done on the European level using the experience of countries which already use such adapted GMP guidelines. It goes without saying that GMP for small scale production should not mean a kind of “GMP light”. The matter should be discussed as part of the proposed process which hopefully would provide a European answer to the challenge created by small scale production of unlicensed medicines. If a GMP guideline which is adapted to small scale production would be seen as useful its elaboration could be a part of the regulations on small scale production elaborated under the roof of the European Directorate for the Quality of Medicines & HealthCare. In this case it would be necessary to provide a legal basis.

Licensing of German standard preparations

Dr Susanne Keitel

BfArM (D)

Dr Susanne Keitel's slides are available on page 19 of the Symposium,
Session 2: Licensing
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

For a number of medicinal products, licensing of standard preparations may serve as an alternative to individual licenses, such as badly needed medicinal products with a small market share, e.g. certain antidotes or veterinary medicinal products. Standard preparations could also be of great interest for medicinal products to be manufactured on a larger scale in hospital pharmacies or on a small scale in pharmacies, in order to relieve these institutions from the burden to compile and submit individual applications for marketing authorisation (with regard to expenditures and time) and to avoid a high amount of corresponding similar - if not identical – marketing authorisation applications for the national competent authorities.

However, before entering any discussion on this topic, recital 2 of Directive 2001/83/EC, as amended, should be acknowledged: namely the fact that the essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health. As a consequence, before any kind of standard preparation can be defined for a medicinal product, it has to be demonstrated that all requirements related to quality, safety and efficacy are met. In this context, it may be necessary to limit standard preparations to certain methods, fields or ranges of application. For example, normally, the elaboration of a standard license monograph should be limited to APIs/medicinal products that do not need bioavailability/bioequivalence or local tolerance studies.

It is an important political demand that account is taken of the legitimate interests of the consumers of the medicinal product, the health professions and the pharmaceutical industry. The definition of the “scope” of standard preparations is within the obligation of legislature and/or competent authorities. Any kind of standard licensing system must ensure that medicinal products are only exempted from the obligation to obtain an individual marketing authorisation in so far as no direct or indirect danger to human or animal health is to be feared, since it is evident that the requirements with regard to the necessary quality, efficacy and safety have been met.

This presentation aims at providing examples of general principles to be considered from a regulatory point of view when setting up a standard licensing system. These principles are clearly intended to stimulate the discussion and to serve as “food for thought”, they do neither claim to represent the optimal solution nor do they attempt to be exhaustive.

To begin with, standard preparations described in any type of monograph or compendium should have a defined composition, i.e. they should not be based on models such as existing dosage-form specific monographs in some pharmacopoeias which just define nature and quantity of the active ingredient. The manufacturing process should be adequately defined and specifications set, of course including adequate acceptance criteria and test methods. In addition, the labelling, package leaflet and expert information need to be part of the monograph.

Given the legally binding nature of requirements of the European Pharmacopoeia for all EU Member States, all ingredients used in a standard preparation have to fully comply with pharmacopoeial requirements. This is of special relevance for the active substance, where the user of such a standard license should be obliged to demonstrate suitability of the monograph to adequately control the substance from a given source in the same way as for a “normal” marketing authorisation application – even if the data do not necessarily need to be submitted to a regulatory authority, but may be kept on site. Substances of animal origin have to fulfil the requirements of the general monograph “Products with a risk of transmitting agents of animal spongiform encephalopathies” as well as the current guidelines of the EU and the competent authorities. If excipients are used in a standard preparation that are not covered by a monograph of the Ph. Eur. or a pharmacopoeia of an EU Member State, the use of this excipient should be well established in pharmaceutical science practice and its quality should be specified in accordance with the monographs of the pharmacopoeia.

In order to make a system of standard preparations successful, there is a clear need to offer sufficient flexibility for the user opposed to too prescriptive requirements. As regards the composition it may be advisable, for example for immediate release tablets, to allow the amount of excipients listed in the monograph to be modified quantitatively up to a maximum of e.g. 10% of tablet weight while keeping both total amount of excipients and tablet weight unchanged, as long as the user demonstrates that the final product meets all specifications listed in the respective monograph. As regards the manufacturing process, there may be the need for the flexibility for the user of a monograph to either modify the defined manufacturing process or use an alternative one, provided it is demonstrated that they yield the same quality. For parenteral products, for example, the conditions for sterilisation listed in the monograph can be changed, provided that the efficacy of the modified method to attain sterility has been demonstrated and the selection of the sterilisation method is in accordance with the decision trees of the annex to the Note for Guidance on Development Pharmaceuticals.

In line with the general philosophy of the pharmacopoeia, changes to any in-process controls or analytical tests should be possible, again provided their equivalence has been demonstrated. Test methods for any additional stability testing performed by the user have to be stability indicating and adequate validation of the methods has to be documented. In those situations where no compendial reference standard is used, the suitability of a substance for the respective use has to be demonstrated.

It should also be possible to substitute container/closure systems described in the monograph with regard to geometry or composition. However, in these cases the user of the standard preparation monograph should clearly be responsible for the conduct of relevant stability studies and the assignment of a shelf-life which should be adequate for the requirements of distribution.

Of course this flexibility relies heavily on a responsible conduct of the user. It can only be exercised in the context of an adequate GMP surrounding, taking into consideration the need for quality risk management and the existence of an appropriate quality system. Thus, GMP inspections should play a vital role in putting a system of standard preparations in place.

As regards the issue of efficacy and safety, it is evident that the monographs should provide binding wording for the labelling of the respective products. Thus, users should be allowed

to renounce claiming an indication at their own discretion, but should not be allowed to add anything other than additional contra-indications, side-effects or interactions to the labelling. Renouncing the claim for an indication or mode of application, however, should not impact the requirements to list contraindications, side effects or interactions described in the respective monograph – unless they are specifically related to the renounced mode of application or indication in an unequivocal way. One benefit a system of standard preparations could offer to their users would be the introduction of a free choice of brand name in line with normal naming rules applied by the authorities without simultaneous indication of the name of the monograph.

Normally, one of the limitations to the use of standard preparations would be the use of an API/medicinal product needing bioavailability/bioequivalence or local tolerance studies. However, for example in the case of solid oral dosage forms, application of the biopharmaceutical classification system (BCS) may allow waiving the need to perform bio studies.

Last but not least, as a regulatory authority issuing any kind of monograph for standard preparations should meet the same requirements an applicant for an individual marketing authorisation will need to fulfil, results of all development activities should not only be documented in the laboratories, but should be compiled in a state-of-the-art dossier, applying EU standards (e.g. pharmacopoeial monographs, guidelines etc.), i.e. in the format of the Common Technical Document. The evaluation of the dossier should be performed by experienced assessors who have not been involved in the elaboration of the monograph.

Summary

Pharmacopoeial and regulatory standards applied to the manufacture of products covered by standard licences have to be state-of-the-art; authorities elaborating standard licences should compile CTD-format quality dossiers for the monographs. These dossiers should be assessed by appropriately qualified assessors who have not been involved in the development. Notification of the use of a monograph to the competent authority should be a “must”. Monograph- and GMP-compliant manufacture is within the responsibility of the user, same as the dossier- and GMP-compliant manufacture for any other medicinal product. Thus, establishment of quality systems by manufacturers and inspections play a vital role in quality assurance of medicinal products manufactured under a standard license.

It can be summarised that standard preparations can be regarded as a flexible and useful alternative to individual applications for a number of medicinal products, provided their range will be clearly and carefully defined and an adequate GMP and quality system will guarantee the surveillance of their application by stakeholders.

Viewpoint from an inspector

Ms Gudrun Eichler

Staatl. Gewerbeaufsichtsamt Hannover (D)

Ms Gudrun Eichler's slides are available on page 32 of the Symposium,
Session 2: Licensing
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

My task is to tell you something about special requirements in the regulations for “Standard Marketing Authorisations”. In part 1: “Labelling, leaflets and expert – information” and in part 2: “Critical issues for the inspection of such plants”.

Part 1: Labelling, leaflets and expert - information

As we heard already today the Standard Marketing Authorisations are regulated in the Guidelines 2001 slash 83 slash E and 2004 slash 27 slash EG concerning human medicinal products and the Guidelines 2001 slash 82 slash EG and 2004 slash 28 slash EG concerning animal medicinal products (*Slide 2*)

There are two different types of monographs (*Slide 3*):

- Those where the manufacturer has to follow all items strictly and
- Those where is prescribed only minimal or special wording.

In this case the manufacturer has to check whether the following sections of the German Drug Law:

- § 10: Labelling
- § 11: Leaflet
- § 11a: Expert information

apply to his product, and he has to fulfil their requirements.

General requirements are: *...the text quoting...* The purpose is consumer protection (*Slide 4*).

First: *Text quoting and then following comment (Slide 5):*

- PE can be: a marketer, a manufacturer or an importer, that means: the person or the firm, who / which is responsible to place a product in the market.
- The name is given by the monograph; if there is an imagination name, the name of the monograph has to follow immediately
- is prescribed in the monograph
- Batch-number constructed by the PE or, if manufacturing in batches is not possible, the date of manufacturing
- Pharmaceutical form, named in the monograph

In *Slide 6*

- The correct measures can be found in the Pharmacopoeias
- Application is also prescribed in the monograph
- the INNs or other generally known scientific names are to be used
- Expiry date: given in month and year

For example (*Slide 7*): “storage temperature” or “to keep out of the reach of children”
In the cases of veterinarian medicinal products additional items are required
There are other details required of special medicaments, as herbal products, nuclear medicaments etc.

“Standard Marketing Authorisations and section 11 of the German Drug Law” Concerning leaflets (*Slide 8*).

In *Slide 9*

- The title „Package Leaflet“ is obligatory
- the text has to be written and in an easily understandable German
- The information has to be in accordance with the concerning items in the expert-information;
- Here are also special regulations in the monographs possible
- If not: the rules of § 11 do apply

In particular the rules for identification or application (*Slide 10*)

Special important items as contra-indications, interactions or warnings

Special instructions concerning how to use the medicament:

Dosage, application form or how often or how long to use

In *Slide 11*

- In the leaflet has to appear the complete composition: Active substances and the other chemicals, their quantities etc.
- If the product is identically on the Market of other member states, there must be a list of all approved names of this medicament
- If an item didn't apply, it must be said! For example: no contraindications
- Known
- The date of last revision of the leaflet is important, if, for example, there took place a graduated plan
- Of course there is additional information necessary for veterinary drugs

For human and animal medicaments is valid: additional information is allowed (*Slide 12*)

- if it is necessary for a safe use of the drug
- if it doesn't contradict the official text and
- if it is recognisable separated from prescribed data.

Here also the title is prescribed (*Slide 14*). Every finished medicinal product can only be marketed with an expert – information. But: marketing without „EI“ is permitted, if none is available

In *Slide 15*

- If there is an “Expert information” it is to say: The text of the “EI” is provided by the BfArM.
 - I think it is clear why: they authorised the prescription, the composition and the tests.
 - the items follow a given order
 - especially the clinical, pharmacological and pharmaceutical data.
- They are required very detailed.

Animal drugs require more clinical details, e.g. concerning arrears and corresponding tests, warnings etc. (*Slide 16*).

If there are changes in the therapy scheme, the PE has the obligation to inform the experts. The BfArM can determine the form, the size and the extent of those information (*Slide 17*).

Second Part: Critical issues for the inspection of such plants

I never conducted an inspection at a manufacturer, who produced drugs based on Standard Marketing Authorisation (SMA).

But I have some ideas, what I would have to look for.

In *Slide 19*

- SMA-manufacturers are subject to the AMWHV, the EU Guidelines, the special annexes and the pharmacopoeias
- AMWHV sounds complicated, but it only is the abbreviation in German of “Operating Regulations for manufacturing Finished Medicinal Products and Active Substances”
- Of course all regulations of GMP, monographs etc. are to be followed
- And of course, all has to be documented.

There are different kinds of monographs for SMA (*Slide 20*):

- In the case of problematic substances or manufacturing processes the Monographs are very detailed and give no space for deviations
- the responsible persons have to follow strictly the given items

For less difficult products or processes you find only some basic regulations (*Slide 21*).

Here the Ph. Eur. or manufacturer has to take care himself: that means, he has to look whether the Drug Law, or the GMP Guide or any other regulation is concerned.

For example: he is responsible to use excipients or other auxiliaries in the right quality or quantity.

These monographs can cause more difficulties to the responsible persons than the detailed ones.

During an inspection I would compare the requirements of the monograph with the working formulas, with the testing procedures, and – very important - with the releasing procedures.

Also I would examine the defaults for purchase and the test results (*Slide 22*).

In *Slide 23*

- I would examine the specification, it's execution and the results of In-process- controls (IPCs).
- I would ask for explanation of the motives of that IPCs, and the risk analysis
- I would compare the required labelling with the reality.
- Special attention I would put on the deviations and how they will be handled.

Because of GMP (*Slide 24*) I would examine the :

- Quality Assurance System
- different risk assessments
- qualification of the equipment, room situations if applicable
- validation of the processes
- personnel's quality
- hygiene, cleaning and their suitability

Briefly said: all GMP relevant requirements are the same as those for Ph. Eur. or Manufacturers of Single Authorisations. I know from my colleagues that many responsible persons think that they have no personal responsibility if they work with SMAs. That is a fatal error.

I hope I could give you the most important information about the Standard Marketing Authorisations and the obligations of the Ph. Eur. in Germany.

Thank you - Danke - and Merci beaucoup

SESSION 3:

National Experiences of Formularies

The British experience

Dr Gerard Lee

Secretary and Scientific Director, British Pharmacopoeia Commission
Medicines & Healthcare products Regulatory Agency (MHRA) (UK)

Dr Gerard Lee's slides are available on page 2 of the Symposium,
Session 3: National Experiences of Formularies
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

Introduction

Article 5 of Directive 2001/83/EC, as amended, gives the authority to Member States (MS), in accordance with legislation in force and to fulfil special needs, to exclude from the provisions of the Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specification of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility. Products supplied in accordance with this exemption will be unauthorised or unlicensed products.

UK medicines legislation, The Medicines Act 1968, as amended, further allows pharmacists to prepare or dispense a product which does not have a marketing authorisation in response to a prescription from an authorised healthcare professional or for supply to a patient following a consultation. Such products would usually be prepared extemporaneously but could be prepared as a stock in anticipation of demand.

In the UK it is also possible to apply to the MHRA for a Manufacturing (Specials) Licence (ML). This licence exempts the holder from the requirements for a marketing authorisation for products manufactured under the licence provided the following conditions are met:

- the product is supplied to meet the special needs of a patient;
- the product is supplied to a healthcare professional or to a pharmacist for supply to a patient;
- the products that are manufactured under the licence may not be advertised;
- the manufacturing facilities comply with the requirements of Good Manufacturing Practice (GMP);
- the manufacturing process ensures the product meets the specification of the prescriber.

Holders of the ML (Specials) Licences are inspected by MHRA GMP inspectors against the EU guidelines for GMP and are expected to operate to standards equivalent to that of a full Manufacturing Authorisation issued in accordance with Article 40 of Directive 2001/83/EC. ML (Specials) sites are approved for general categories of formulations. Batches of unlicensed products will be manufactured by holders of these licences but there is an assurance that manufacturing has been undertaken in accordance with current GMP

requirements although requirements for efficacy and safety have not been assessed. ML (Specials) licence holders may not manufacture or supply an unlicensed product for which a pharmaceutically equivalent licensed product is available except to meet the special clinical needs of a patient.

In all these circumstances unlicensed (unauthorised) medicines which have not been assessed for safety, quality and efficacy by the Regulatory Authority will have been supplied. Consequently the British Pharmacopoeia (BP) has been seeking ways of creating standards for these products and enforcing these standards in the UK.

Pharmacopoeial Standards

Pharmacopoeias create publicly available standards for medicinal products. The monographs of the European Pharmacopoeia (Ph Eur) are brought into force through Directive 2001/83/EC. The monographs of the BP are legally enforced by the Medicines Act 1968. It is a legal requirement in the UK that, where a Pharmacopoeia monograph exists, medicinal products sold or supplied in the UK must comply with that monograph.

In addition to monographs for pharmaceutical substances, the BP contains monographs for finished dosage forms. It would be possible therefore to create enforceable standards for finished product formulations of unlicensed medicinal products by preparing and publishing monographs for these products in the BP. A general chapter on unlicensed medicines was published in the BP 2007. In the BP 2008, this general chapter has been extended and both a general monograph for unlicensed medicines and individual monographs for products have been introduced.

Standards of Unlicensed Medicines in the BP 2008

General Chapter, Unlicensed Medicines

The general chapter gives guidance to prescribers, manufacturers, and suppliers of unlicensed medicines on the legal and ethical considerations of such medicines. It also provides guidance on the standards for the preparation and manufacture of unlicensed medicines.

The background to the use of unlicensed medicines in the UK is explained together with the commonest reasons for requiring to produce them. These are:

- requirements for liquid formulations in the paediatric and geriatric populations;
- discontinued supply of licensed products;
- specialist products used in hospitals;
- novel therapies in hospitals and clinics
- low demand critical care products

The legal basis for the sale and supply of unlicensed medicines is described; these are the Directive 2001/83/EC, the Medicines Act 1968, and the ML (Specials) Licence. The conditions under which these exemptions apply are explained together with the restrictions that apply.

Guidance on ethical considerations is provided which includes the role, responsibilities and liabilities of the prescriber, the manufacturer, and the supplier. Reference is made to guidance on these issues from a number of regulatory and professional bodies in the UK. The importance of communications between healthcare professionals and patients or carers is also emphasised.

Standards for the preparation and manufacture of unlicensed medicines are also given. These are very general requirements but provide references to further information and guidelines.

General Monograph

The general monograph provides mandatory quality requirements that are generally applicable to all unlicensed medicines.

It defines an unlicensed medicine as one ... “which is prepared, at the request of an authorised healthcare professional, to address patient medical requirements that are unmet by current licensed medicines

There are sections on the scope of the monograph, production requirements, requirements for medicinal substances and excipients, and then general requirements for different formulations.

Importantly the general chapter includes requirements for the labelling of unlicensed medicines. The labelling requirements of Directive 2001/83/EC apply only to licensed products. By including the labelling requirements in the general chapter, they become a mandatory requirement for unlicensed medicines in the UK. These requirements are based on the Directive requirements but have been amended to take account of the differences of unlicensed medicines.

In the general section on oral suspensions, performance tests for dissolution and homogeneity of suspension are included.

Individual Monographs

Ten new monographs for unlicensed medicines are included in the BP 2008. These are:

- caffeine citrate oral solution;
- caffeine citrate injection
- dantrolene oral suspension
- menthol in aqueous cream
- mercaptopurine oral solution
- paediatric phenobarbitone oral solution
- sodium bicarbonate oral solution
- sodium chloride oral solution
- sodium fluoride oral solution
- potassium chloride oral solution

Each monograph includes the statement “There are currently no licensed formulations in the United Kingdom.” The general notices also include an explanation of the relevance of this statement and the fact that they are quality standards for products that have not been assessed for safety, quality and efficacy by the Regulatory Authority.

Future Work Programme of the BP

The British Pharmacopoeia Commission has created an Expert Advisory Group (EAG) to elaborate monographs for unlicensed medicines. It will develop 10 or more monographs each year. The EAG has members from hospital production and quality control laboratories and from the pharmaceutical industry who will participate in this work programme. Information is available to the EAG from National Health Service (NHS) Committees and working group to help prioritise the EAG work programme. Work is commencing on a priority list of 25 monographs.

It is planned to introduce product formulations into the general chapter when appropriate. These will be non-mandatory but will be supported by mandatory standards in the monographs. Discussions are on-going with clinicians and clinical pharmacists to rationalise the range of products manufactured by NHS hospitals and thus limit the number of monographs that will be required.

Summary

- BP monographs create enforceable standards for unlicensed medicines in the UK.
- The BP 2008 includes a general chapter, a general monograph and individual monographs for unlicensed (unauthorised) medicines.
- An annual programme of work is in place to develop monographs for unlicensed medicines in the BP.
- A formulary, for guidance only, will be introduced, as part of the general chapter on unlicensed medicines.

National Experiences of Formularies

The Italian experience

Prof. Maurizio Cignitti
Istituto Superiore di Sanità (I)

Prof. Maurizio Cignitti's slides are available on page 8 of the Symposium,
Session 3: National Experiences of Formularies
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

The first edition of the Italian Pharmacopoeia has been published in the year 1892. Its content was, in part, quite a number of galenical preparations taken from the numerous pre-existing Codex and in particular from the "Ricettario Fiorentino" (since 1492); the scientific progress influenced the evolution of the texts published in the successive editions: new analytical methods have been introduced in all monographs of active substances and formulated preparations in order to better guarantee their quality and safety.

In the year 1972 the Italian Pharmacopoeia has been divided in three parts:

- General prescription and general methods,
- Monographs
- Galenic Formulary, i.e. formulated preparations

Successively (1988) the monographs on formulated preparations (more than 300), presented in a format including items not directly related to quality (therapeutical category, posology, stability, etc.) were collected in two separate volumes, i.e. the National Formulary, and assembled in three groups

- Generics
- Large volume solutions
- Traditional magistral *formulae*

All the texts but those relative to magistral formulae were fully recognised by the national licensing authorities for the marketing authorisation procedure of generics.

Hospital and community pharmacies had to refer to the same texts in relation to their preparatory activity of officinal formulae.

The Formulary included also a general non-compulsory guideline for the extemporaneous preparations by pharmacies.

Since in the European Union, monograph on formulated preparations when present in the national Pharmacopoeia or Formulary (legally binding) of one Member State are quality standards officially recognised by all EU Member States, the following issue has been discussed during the annual meetings of the National Pharmacopoeia Authorities (2000-2002):

“a given formulated preparation described in a monograph of a national Pharmacopoeia or Formulary (legally binding) has to have its quality specifications harmonised with those of the same formulated preparation whose monograph is present in another national Pharmacopoeia/Formulary of a EU Member State”.

A positive outcome emerged from the discussion and an exercise between UK, I and Greece was done with the monograph on Paracetamol Tablets.

In the mean time the Italian Pharmacopoeia Commission, in order to start at national level a general harmonisation process, revised the format of all the National Formulary monographs deleting those sections not related to the “quality” and introducing the use of standard terms. The new texts have been published (2002) directly in the 11th ed. of the Italian Pharmacopoeia in a separate section (“Formulated Preparation Monographs”). Such process is going on particularly in relation to monographs for “generics”.

In view of the fact that the preparatory activity made by pharmacists has to be done within a Quality Assurance System the Italian Pharmacopoeia Authority has prepared compulsory “Guides” for the preparation of medicinal and radiopharmaceutical products.

It has to be noted that in the EU Member States the responsibility of such “rules” is not always under the “umbrella” of National Pharmacopoeia Authorities (NPA); indeed Licensing Authorities and Inspectorates are more involved than NPA.

In this contest the Italian Pharmacopoeia Commission adopted the following texts:

- “Good Practices for the preparation of medicinal products in pharmacies” Compulsory since 2003.
Quality controls of a finished magistral formula are less stringent than those required for a finished officinal formula. Sterile products are to be prepared following adequate procedure.
- “Good Practices for the preparation of radiopharmaceutical products for Nuclear Medicine”. Published since 2005, is going to be non-mandatory until 2008.

In relation to specifications for starting materials used for the extemporaneous preparations by pharmacies and radiopharmacies, the quoted “guides” underline:

- specifications of starting materials described in the Ph. Eur. or in a Pharmacopoeia of a EU Member State are to be those required by the relative monographs;
- specifications of starting materials not described in a Pharmacopoeia are those reported by the producers and are to be in line with the general monograph “Substances for pharmaceutical use”.

A unified European approach is positively needed.

National Experiences of Formularies

The French experience

Prof. Jean-Claude Chaumeil

Recherche et Développement Galénique, Université Paris Descartes.

Agence Générale des Equipements et Produits de Santé (F)

Prof. Jean-Claude Chaumeil's slides are available on page 13 of the Symposium,
Session 3: National Experiences of Formularies
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

The French National Formulary was firstly published in 1974, and additional monographs were entered in 1977.

The needs of such a Formulary were, for one part, to officialise several traditional preparations published before in previous editions of French Pharmacopoeias, for example cachets, potions, syrups, suppositories, enema, ointments, and for the other part to enter some recent formulae of dosage form, like tablets and unit injectable solutions and infusions.

So, the National Formulary contained either preparations suited to be prepared in the community and hospital pharmacies, the traditional ones, or in the industrial factories, the traditional and recent ones.

The purpose of these registrations was in this last case, to permit pharmaceutical companies, especially the smaller ones, to obtain marketing authorisations with a possible exemption from any clinical study. The registration in the National Formulary brought indeed a guarantee that the clinical activity and harmlessness of such drugs were demonstrated before. Consequently the manufacturer had only to present to the marketing authorisation committee a technical development dossier.

This possibility was cancelled recently, following a regulation European rule.

All the preparations registered in the National Formulary were classified as "officinal preparations".

Some of them were registered in the special list of "officinal divided products". These preparations were determined as stable enough to be manufactured in advance. They can be prepared by a pharmaceutical company and delivered to community and hospital pharmacists, under batch presentations. Then the community and hospital pharmacists have only to package them in unit dosage forms before delivery to patients. This list will be updated before long.

The French National Formulary is also important outside the French territory: it is well known and largely used in French-speaking countries, for example north and central Africa ones.

The current updating works began in 2002.

Before examining the formulae we studied the situation of raw materials used in preparations able to present some toxic potential risks, either to remove them, for example, ones from animal origin (peptone), or to limit their use (ex. camphor). Some non or badly defined substances were eliminated too (ex. white wine!).

Concerning dosage forms, the obsolete ones, like cachets, and the difficult to prepare in community pharmacists ones, like injectable solutions and infusions, were removed.

The general principles adopted for the redaction of the new edition of the French National Formulary were firstly to remove all the patent medicine formulae, corresponding to drugs marketed in France and in Europe. But if there would be, for a preparation, any difference in its composition, like the use of a different excipient from the patented drug, it would remain possible to register it.

Secondly, only preparations containing raw materials registered in the French and European Pharmacopoeias can be entered into the Formulary.

Concerning the therapeutic interests, if there would be any doubt about one of them, an opinion of the marketing authorisation committee must be requested.

There were some problems of connection with the Pharmacopoeia: some officinal preparations were previously registered in the 10th edition of the French Pharmacopoeia, and others in the National Formulary.

The separation between the 10th edition of the French Pharmacopoeia and the National Formulary was undertaken following the uses of these products: in the French Pharmacopoeia those without any therapeutic use must remain, like alcohol for technical uses, solution of saccharose or concentrated hypochlorite solution and in the Formulary the direct therapeutic use products will be registered, like alcohol for medical uses, simple syrup (saccharose syrup) or diluted sodium hypochlorite solution.

In order to be entered in the French National Formulary, new dosage forms with original formulae must show two characters: they have to demonstrate a therapeutic interest and they could be manufactured in community and hospital pharmacies.

The demands are currently mainly from hospital origin.

The hospital preparations are indeed submitted to a telereporting by French Medical Agency (AFSSAPs). The regular definition of a hospital preparation indicate that “it has to be prepared following the recommendations of the Pharmacopoeia, carried out only if it does not exist any patented drug, intended for in- or outpatients, and prescribed by one or several doctors”.

An official inventory of hospital preparations was begun since 2004. Every hospital pharmacy must do a telenotification for any new preparation to AFFSAPs, at least during the month following the first manufacturing..

The content of a monograph (*Slide 14, an example of a monograph*) must be redacted according to the following plan: firstly the reference to the classification of dosage forms of the European Pharmacopoeia, then the qualitative and quantitative formula with the function of all the components and the pharmaceutical references, then the manufacturing procedure, referring to officinal and hospital good manufacturing practices, indicating the materials to be used, and the possible cautions to be taken.

The control part must indicate the characters of the preparation and identification reactions. The technique of assay and dosage of main components have to be determined in order to can be done in a community or hospital pharmacy, without using, if possible, a so advanced method than it could be carry out only in highly specialised control laboratories.

The conditions of storage and the type of packaging materials must be specified.

The clinical use is referred to the Anatomical Therapeutic Classification (ATC).

The redaction committee had to answer to several questions:

- Excipient(s) choice(s): could they be freely chosen following the experience of the manufacturer and the previous scientific works? In the previous edition these choices were free, for example, for tablet composition. Could they be imposed?

According to the rules applied in dossiers of marketed drugs, all the excipients are imposed and their amounts to be used are specified.

- Time of use: the use-by date could be determined for every dosage form following the raw materials and drug stability. Or it could be possible to prescribe a same stability time for every preparation, for example one or two months for all dermatological preparations.

When the manufacturer is an industrial one, in the case of “officinal divided products”, he has to determine a stability time under his own liability.

- Feasibility of control techniques: as indicated previously, controls must to be workable using the manufacturer’s technical means. The community pharmacists are not, in most cases, equipped with advanced control devices.

On the contrary, several hospital pharmacies are well equipped with modern control devices and are able to carry out difficult control methods. Industrial manufacturers have also important means of control.

It could be always possible to subcontract the most difficult controls to a specialised control laboratory, but in common practice, it could be no so easy to do, especially for small batches needed by community pharmacists. So the control methods have to be as simple as possible.

A registration demand form is proposed to the practitioners who would want ask National Formulary committee for enter a new dosage form formula in the French national Formulary.

The following information must to be given:

- Name of the preparation, following the Pharmacopoeia’s recommendations,
- Current context: magistral (extemporaneous) or hospital preparation?
- Preparing frequency: only preparations frequently manufactured could be retained,
- The description of clinical use: it has to be demonstrated by clinical observations, if possible in different establishments
 - The using conditions, posology (dosage, time of administration), type of patients, for example: pediatric, adults, elderly people,
 - The eventual contrary indications,
- Detailed composition in the same form as the National Formulary preparation ones;
- Analytical controls, and stability time: only the most stable preparations could be retained.
- Bibliographic references: the medical interest of the preparation has to be confirmed by the scientific literature.

Actually 23 formulae are registered definitely in the new edition of the French National Formulary: mainly dermatologic dosage forms (ointments, creams, solutions, ...) and oral dosage forms (tablet, capsules). They were all accepted by the French Pharmacopoeia’s committee.

31 formulae are studying: dermatologic, oral and rectal dosage forms.

The telereporting allowed to record 20 main preparations prepared in several hospitals: oral dosage forms (capsules, syrups) and dermatologic solutions. Their examination will constitute the future works of our National Formulary committee.

National Experiences of Formularies
The Belgium experience in relation with the Therapeutic Magisterial
Formulary

Mrs Paule Jacqmain
Advisor general, Head of Department
“Production & Distribution”
Agence Fédérale des Médicaments et des Produits de Santé (B)

Mrs Paule Jacqmain’s slides are available on page 23 of the Symposium,
Session 3: National Experiences of Formularies
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

History

In January 1997, the Ministry of Public Health decides to suppress the reimbursement of a lot raw materials. This situation leads to a big dissatisfaction of the retail pharmacists because the magisterial preparations will not more be prescribed.

In March 1997, the reimbursement of the majority of the raw materials is again allowed but with 2 conditions

- the quality of the magisterial preparations must be guaranteed on basis of a validated Therapeutic Formulary
- and the pharmacists must follow a guide of good pharmaceutical practices.

Mid 1997, a Royal Decree is published in relation with the quality of raw materials. We judged that first it was necessary to use raw materials of quality to allow the improvement of the magisterial preparations.

An informel working group on the Therapeutic Magisterial Formulary is put in place. His chairman is Prof. Delattre and the Vice-Chairmain is Prof. Remon. All two are specialist in pharmaceutical technology. The other members are coming from

- The 2 most important Professional Associations of pharmacists: Association Pharmaceutique Belge and Ophaco,
- The Commission of Belgian Pharmacopoeia,
- The Commission of Registration of Medicinal Products,
- The Pharmaceutical Inspection,
- The Commission of Reimbursement of Medicinal Products,
- The Mutual Insurance Companies,
- The Association of general practitioners

Mid 1998

The conclusions of the working group are submitted to the Ministry of Public Health. The conclusions are the following:

- We select the products to be retained in the formulary with the help of the doctors
- We discuss the pharmacotherapeutic aspects with doctors and persons specialists in the pharmacology
- We take account of the social aspect

- We will introduce in the Formulary only validated preparations in relation with the aspect of pharmacology
- We will not introduce in the Formulary preparations for which the registration has been radiated for reasons of public health.
- In the case of the preparation corresponds with a registreted medicinal product, the preparation will be introduced in the formulary if the patient and Communauty win financially.

On the 11.11.98, Mr Colla, Ministry of Public Health at that time organised a seminar. The aim of this seminar was to discuss the different problems met by the pharmacists, for example: definition of a medicinal product and the problematic of the grey zone . Mr Delattre gives a report of the conclusions of the informal working group. The Ministry supports totally this initiative and to start with the dermatological preparations.

How is elaborated this Formulary?

In order to render the formulary *an official standard work*, the informel working group that was initially put in charge of his elaboration has been incorporated as *an official subcommittee into the Belgian Pharmacopoeia Commission*.

The members of this subcommittee are representatives of the two Belgian professional associations of pharmacists, professor of pharmaceutical technology of all Universities of Belgium, doctors, representatives of National Health services (INAMI – Mutual Insurance Companies) and of the Federal Agency for Medicines and Health Products. We have also a representative of a packager of raw materials.

The secretary of this subcommittee is assumed by the FAMHP.

This Formulary *has been approved by Royal Decree of 25.03.2003 and is obligatory present in all pharmacies*.

The decision is taken to validate all therapeutic, economical, analytical and pharmaceutical aspects of each preparation.

Therapeutic and economical validation means: an evaluation of the efficiency and cost price of the preparation by comparison with the corresponding registered medicinal product.

For each retained preparation, an appropriate formulation is developed in the Belgian universities (sharing of the work in function of the specialisation).

In case of preparations for which stability problems are expected, a stability study is performed by agreed laboratories at room temperature and at 4°C with a validated assay-method. A storage time of 2 months is generally adopted for all preparations except in case of proved stability problems. Why 2 months for the magisterial preparation? To avoid auto-medication, (dangerous for the Public Health).

The situation can be different for the officinal preparations for which it would be necessary to have supplementary stability studies.

Some formulations may show difficulties to be prepared in pharmacy. In order to verify the feasibility of the preparation of those formulations in pharmacy, a blind performance study is organised among several pharmacists, usually 10 pharmacists per preparation.

These pharmacists are selected by the professional Organisations. The raw materials and the packaging materials are furnished to the pharmacists. The control of the preparation is

performed by agreed laboratories. In some cases, a check of the microbiological purity should be necessary.

In some cases, the formulation has been adapted.

For each formulation, *an assay method* is developed. As far as possible, these assays are based on the assays indicated in the active substance monographs of the European Pharmacopoeia or failing that in another official pharmacopoeia. Then, they are approved by the Belgian Pharmacopoeia Commission. Those methods are held by the Agency and on request put at the disposal of the inspectors. Indeed these inspectors can take samples of these preparations during their inspections and then send the samples to laboratories.

Except for a few preparations, the *acceptance criteria* stated for the content of active substance are a minimum of 90% and a maximum of 110% of the prescribed amount.

Content of the TMF- pharmacists.

We have general principles of the magisterial preparations: with analytical norms, rules for the reimbursement and rules of labelling.

The rules of labelling are the following:

- name and address of the pharmacy
- number attributed to the preparation
- family name and surname of the patient
- family name and surname of the doctor
- qualitative and quantitative composition in active pharmaceutical ingredients
- posology
- if appropriate : “External use”

These indications are obligatory.

The pharmacist can also indicate.

- The shelf life
- The pharmaceutical form

We have also described *documents for the weighing*.

Why is it necessary to record this operation? To have a good traceability, it is necessary to indicate:

- The number attributed to each raw material
- The date of preparation
- The shelf life
- The signature of the person who realises the preparation and the signature of the pharmacist

These documents must be archived.

The first Part of the formulary includes *only dermatological preparations*.

Each presentation includes usage, adverse events, composition, method of preparation, storage conditions, shelf life, the way of administration and possible recommendations.

Publication of the TMF

2 versions : one for the doctors ; one for the pharmacists.

The TMF for the doctors is more axed on the therapeutic indications; for the pharmacists, the pharmaceutical technology is more important.

For the moments, the subcommittee is revising the first part and at the same time, elaborates the second Part with non dermatological preparations related to the cardio-vascular, respiratory, gastro-intestinal, hormonal and nervous systems.

The editing of the new Formulary should be finished in 2008 (?). While the first part was published as a ring-binder system for the pharmacist and in a pocket-form for the doctor, it's now questioned whether it should not be preferable to present it on a CD-Rom which allows rapid or regular revision when needed or in view of the evolution in scientific knowledge.

How to improve the quality of the magisterial preparations?

- By *editing the TMF* = compilation of magisterial preparations issued by the Belgian Pharmacopoeia Commission, adopted by the Ministry of Public Health with the purpose of promoting the quality and the prescription of magisterial preparations in pharmacy, in providing to pharmacists and doctors a compendium of standardised formulas.
- By *using raw materials authorised following the RD of 19.12.97*.
- By *editing a guide of Good Pharmaceutical practices*.
- By *editing a updated list of equipment obligatory in the pharmacies*

RD of 19.12.1997: Raw materials used by the pharmacists

The pharmacist must check if the raw material is *authorised*. The raw material can be authorised if he is described in the European Pharmacopoeia or in an official pharmacopoeia or in another monograph submitted to the Belgian Pharmacopoeia Commission with samples and adopted by the Ministry.

The manufacturer (packager) and distributor must be authorised in the case of authorised raw materials. To be authorised, he must follow the GMP and GDP rules.

However, the pharmacist can use raw materials not authorised only for magisterial preparations. In this case, the product must be accompanied by a certificate of analysis produced by a agreed laboratory. This certificate describes all the tests (identity – assay – purity) necessary to check the quality of the raw material

This RD is under revision, in particular

- to force the pharmacist to use authorised raw materials if they are available. So only authorised raw materials will continue to be reimbursed.
- to describe what to do with the “orphan” raw materials, with the aroma, flavours,...
- to oblige all the manufacturers and the distributors of raw materials to be authorised.

Guide of Good Pharmaceutical Practices

A *working group* issued from the *Belgian Pharmacopoeia* Commission is put in place with the participation of professors of pharmaceutical technology, representatives of Professional Associations of Pharmacists, Federal Agency of Medicines and Health Products.

The content of this guide will be the principles and directives of good pharmaceutical practices.

The *Requirements* of the good pharmaceutical practices are:

- the first concern of the pharmacist is the health and the quality of life of the patient and the wellness of the population in general.
- The pharmaceutical activity is the delivery of medicinal products and other health products with an appropriate information.
- The pharmacist must follow the legal and deontologic rules

For these requirements, the pharmacists *need to*

- Have programs of training
- Receive an objective updated information in relation with the medicinal products
- Do an auto-evaluation of their competencies
- Have good relations between the pharmacists, but also with doctors
- Have a contribution in the prescription to promotion an optimal and rational use of the medicinal products

Principles and general rules are described for personnel, premises, equipment, documentation, reception, storage of products, raw materials, officinal and magisterial preparations, pharmaceutical care, guards, complaints, recalls, auto-evaluation, treatment of medicinal products not used by the patient.

This guide must be completed by a manual of quality, SOP, work instructions.

This guide should be official. We are waiting for the RD.

Conclusions

The Formulary is a living document. Additions, modifications, suppressions should always be necessary to take account of the progress in the therapeutic field.

Each preparation described in the formulary is a preparation for which

- the therapeutic efficacy is proved,
- the formulation and the method of preparation have been validated
- if necessary, the stability has been proved
- the performance in retail pharmacist has been checked
- the raw materials are available and are authorised following the RD of 19.12.97.

With the Formulary, a good quality of the raw materials, an adapted list of equipment and good pharmaceutical practices. I think that we have improved the quality of the home-made preparations.

SESSION 4

The specific case of radiopharmaceuticals manufactured extemporaneously in hospital radiopharmacies

General introduction

Prof. Alfons Verbruggen

University Hospital Gasthuisberg and Laboratory of Radiopharmacy,
University of Leuven, Belgium (B)

Prof. Alfons Verbruggen's slides are available on page 2 of the Symposium,
Session 4: Radiopharmaceuticals
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

Radiopharmaceuticals (RPs) are medicinal products containing a radionuclide. They are mainly used for diagnosis and to a much lesser extent for internal radiotherapy. Most of these radioactive drugs are injections for intravenous administration. Only a limited number of these radiopharmaceuticals are manufactured by specialised companies under GMP conditions and delivered in ready-to-use form to the nuclear medicine or radiotherapy departments in hospitals. Because of the short physical half-life of some radionuclides (ranging from 13 s (^{81m}Kr) to a few hours (^{99m}Tc , $T^{1/2} = 6$ h)) or for reasons of limited stability and shelf-life (e.g. ^{111}In -octreotide) the majority of RPs has to be prepared shortly before use in a nuclear medicine department. Such preparations can be made using licensed labelling kits – containing the required non-radioactive reagents in sterile and apyrogenic form – and licensed precursor radionuclides or eluate of a licensed generator. In other cases the radioactive pharmaceutical ingredient is synthesised on site in (mostly) several steps starting from raw materials and (in house) cyclotron produced radionuclides, as it is the case for most RP's for positron emission tomography (PET). Radiolabelling of autologous isolated blood cells of a patient with a licensed radionuclide is still another possibility.

The preparation of radiopharmaceuticals in hospitals or specialised PET centres is largely different from a magistral or officinal preparation of drugs in a hospital pharmacy and constitutes a number of problems and unsolved issues for a variety of reasons:

- because of the need to manipulate radioactivity, special measures of radioprotection have to be taken, such as specific education requirements for the manipulators and working in controlled areas. As a result, radiopharmaceuticals are normally not prepared in the hospital pharmacy but in a laboratory of a nuclear medicine department (a so-called radiopharmacy, but often not designed as a pharmacy) or even in nuclear medicine departments outside a hospital. In many cases no pharmacist is involved in these preparations.
- the active pharmaceutical ingredient, i.e. the radioactive drug, is synthesised on site. Preparing a RP is not just mixing or reconstitution of pharmaceutical starting materials, but involves an extemporaneous rapid and highly efficient synthesis of a new (radio)chemical species starting from radioactive and non-radioactive precursors. This implies the need for reliable quality controls, which also have to be applied in a very short time, given the short half-life and shelf-life.
- the radioactive compound in a RP is present in nanomolar to micromolar quantities. This may constitute a challenge for applying an appropriate analytical technique. For

example, nuclear magnetic resonance spectrometry is not an option for identification of the active ingredient.

- especially in the field of PET-radiopharmaceuticals, new developments are frequent and rapid, and have resulted in several preparations with a clearly established medical usefulness. Because of the small market and in some cases the very short half-life (e.g. RP labeled with carbon-11, $T^{1/2} = 20$ min) radiopharmaceutical companies are not interested in applying for a marketing authorisation for these products. Usually, it also takes quite some years before a pharmacopoeial monograph on these preparations is available. As a consequence, several radiopharmaceuticals are being prepared and clinically used for which no clear requirements have been established with respect to purity, composition, pharmaceutical properties, Often, the non-radioactive precursors for such RPs are just reagents without approval as a pharmaceutical starting material.
- because of limited stability and the short physical half-life, thermal sterilisation of radioactive preparations for injection is rarely possible and reliable aseptic procedures have to be designed and applied. Up to now, however, there are no uniform guidelines throughout Europe for aseptic preparation of different classes of RPs. The situation varies from 'almost no rules' to evident overregulation in different countries.

The Radiopharmacy Committee of the European Association of Nuclear Medicine (EANM) has taken initiatives for drafting guidelines for appropriate 'radiopharmaceutical' handling procedures for different classes of RPs. However, apart from the difficulty to implement such guidelines in the respective countries, a number of open issues remains to be solved:

- with respect to ^{99m}Tc -generators, which yield the eluate used for preparation of several ^{99m}Tc -labelled radiopharmaceuticals:
 - has the generator to be stored and eluted in a class 100 laminar air flow cabinet?
 - if so, has this LAF cabinet to be installed in a class B or C or D environment?
 - ^{99m}Tc -generators are licensed products, manufactured under GMP conditions by specialised companies, but are transported to the nuclear medicine department (inside and outside hospitals) and are there operated during 1-2 weeks by personnel of various qualifications (technician, nurse, radiopharmacist, radiochemist, physician). So, once the generator has been delivered and is in use, the manufacturing company cannot guarantee anymore the quality of the eluate. Which quality controls have to be applied on the eluates of such generators and with which frequency? Who has the responsibility for the quality of the eluates?
- with respect to ^{99m}Tc -radiopharmaceuticals for injection, prepared using licensed labeling kits and the eluate of a ^{99m}Tc -generator:
 - must they be prepared in a class 100 LAF-cabinet or an isolator? The preparation comprises transfer of sterile generator eluate to a sterile vial or labelling kit and can thus be considered as a 'closed procedure'.
 - if the preparation must be done in a LAF cabinet, in which environment has this to be installed (class B/C/D)?
 - should the radiochemical purity be checked on each preparation, or at random on some preparations, or on each first vial of a new batch, ...?
 - some nuclear medicine departments are not in a hospital, so who is responsible for the quality of the final product? Is the presence or supervision of a certified (radio)pharmacist or qualified person required?
- with respect to PET-radiopharmaceuticals, prepared on site using a cyclotron produced radionuclide and chemical starting materials:

- which starting material can be used and which analyses have to be performed on these non-radioactive precursors? For several PET-RPs, no GMP produced starting materials are available, nor pharmacopoeial monographs for these starting materials.
 - which quality controls have to be applied on PET-radiopharmaceuticals for which no pharmacopoeial monograph exists?
 - if a monograph exists, is a full analysis according to the monograph required prior to release for use or is parametric release also possible?
 - under which conditions can PET-RP's be prepared for other hospitals?
 - can such PET-RP's be considered magistral or officinal preparations?
 - must PET-RPs be prepared under the responsibility of a licensed (radio)pharmacist or qualified person?
- other general issues
 - are there special requirements with respect to the radiolabelling of patients' autologous blood cells?
 - how to harmonise the different legislation regarding in-house preparation of radiopharmaceuticals in different European countries?
 - could centralised radiopharmacies be a solution for a number of the open issues?
 - which role can the European Pharmacopoeia (Commission) play to solve (some of) the mentioned problems?

**Current practices for preparation of radiopharmaceuticals in hospitals
and PET centres: experience and considerations from the field
Radiopharmacy practice in the UK**

Prof. Stephen Mather

Imperial Cancer Research Fund Department Nuclear Medicine, St
Bartholomew's Hospital, London (UK)

Prof. Stephen Mather's slides are available on page 12 of the Symposium,
Session 4: Radiopharmaceuticals
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

Abstract

Radiopharmacy practice in the UK is heavily regulated and must comply with regulations arising from both Pharmaceutical and Radiological legislation. The primary source of Pharmaceutical oversight is the UK Medicines and Healthcare Products Regulatory Agency (MHRA) which provides a system of licensing of approved radiopharmacies. Award of a "Specials Manufacturing" licence allows a Radiopharmacy to prepare a range of radiopharmaceuticals for use either within a single hospital or to other outlying hospitals. Licensed Radiopharmacies must comply with the Good Manufacturing Practice guidelines described in the Rules and Guidance for Pharmaceutical Manufacturers and Distributors.

This presentation provides some background information on the nature of Radiopharmacy Practice in the UK and describe the influence of the regulatory environment thereon.

**Current practices for preparation of radiopharmaceuticals in hospitals
and PET centres: experience and considerations from the field
Spain**

Dr Ivan Penuelas

Unidad de Radiofarmacia, Clinica Universitaria de Navarra, Pamplona (E)

Dr Ivan Penuelas' slides are available on page 22 of the Symposium,
Session 4: Radiopharmaceuticals
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

Radiopharmacy Practice in Spain

Spanish National Legislation

The legislation related with the preparation of radiopharmaceuticals (RP) in Hospitals and PET centers is quite ambiguous in Spain.

There is an old regulation from 1993 (RD 479/1993) where there is an Annex called "*Rules for correct extemporaneous preparation and use of radiopharmaceuticals*". Such text established general principles for Good Radiopharmaceutical Practices, including premises and equipment, work procedures, quality control and documentation.

However, such regulation was never adequately implemented, probably due to the lack of proper inspections by the authorities and the excessive general terms of this legislation.

Nowadays, it is evident that that regulatory effort was a good starting point but that is completely out-dated.

In this sense, professionals involved in radiopharmacy in Spain have long been trying to obtain a clear regulation for:

- Radiopharmacy Units (including premises, equipment, personnel, hierarchical dependence, etc.)
- Extemporaneous preparation of radiopharmaceuticals (including blood-labeled RP)
- Compounding of positron emission tomography (PET) RP
- Clinical trials with unlicensed RP

Taking into account the above-mentioned limitations of the legislation, the Group of Radiopharmaceuticals of the Royal Spanish Pharmacopoeia has been creating several Guidelines on Radiopharmaceutical Procedures. However, such guidelines do not have any legal binding force, as they are just recommendations. These guidelines have nonetheless been very useful for professionals in the field during these years.

In the new Spanish law on Medicinal Products from July 2006 (Law 29/2006), there is for the first time an official recognition of a "Radiopharmacy Unit", and it is said that the responsible person of the Radiopharmacy Unit must be a Specialist in Radiopharmacy. In addition, several specific statements for PET RP are laid down, although they will have no practical effect until additional technical legislation develops this general rule.

Qualified Person

Radiopharmacy is recognised in Spain as an Official Postgraduate Speciality. To have access to the 3-year training period, mainly Pharmacists and Chemists (but also Biochemists and Biologists) must pass a national exam. Only 8 Radiopharmacy Units are authorised to teach Radiopharmacy in Spain, but so far more than 50 specialists in Radiopharmacy (mainly Pharmacists and few Chemists) have obtained their titles after passing the residency education period. Roughly 60 other persons that had long been working in Radiopharmacy were granted the title of Specialist in Radiopharmacy by an exceptional once-ever accreditation system after evaluation of their merits by a specially designed commission.

Nuclear Medicine Physicians were involved in preparation of radiopharmaceuticals till the early 90's in Spain, but once the Speciality of Radiopharmacy has properly been developed and consolidated, they are not involved any more. However, there have been very many problems between Nuclear Medicine Physicians and Radiopharmacists until a very short time ago. Things seem to have been re-conducted to the desired and logical cooperation between these two groups of professionals that must work very closely, especially in the hospital environment.

Radiopharmacy Models

Two different models of radiopharmacy coexist in Spain: commercial centralised radiopharmacies and hospital radiopharmacies.

Centralised Radiopharmacies

Centralised Radiopharmacies provide unit dose to nearby hospitals and to stand-alone nuclear medicine centers.

These centralised radiopharmacies belong in many cases to big radiopharmaceutical companies, and are authorised in Spain either as radiopharmaceutical laboratories or as radiopharmacy units, depending on the autonomous regions of Spain.

Their main workload is to prepare unit-dose RP from multi-dose vials, although they can also supply ready-to-use RP (RP precursors). Logistic problems impede blood-cell labeling in centralised radiopharmacy units and in many cases, some hospital receiving unit-dose from centralised radiopharmacies receive from them the reactive equipment and a vial with $^{99m}\text{TcO}_4^-$ to label the cells inside the hospital.

The main interest of centralised radiopharmacies is commercial, and no research and development programs are usually carried out in them, although seldom collaborations with research centers might exist.

Hospital Radiopharmacies

Hospital Radiopharmacies are located in most big hospitals in Spain and are involved in extemporaneous preparation of kit-based RP, blood-cell labeling with RP and (exceptionally) compounding of PET RP exclusively for in-house use.

Most Hospital Radiopharmacies are constituted as Radiopharmacy Units, although the majority of them do not have an official recognition as such. There are many differences among the Hospital Radiopharmacies in different places, mainly related to the premises and equipment of the unit. The Head of the Unit is usually a Specialist in Radiopharmacy, although the hierarchical dependence of the unit also varies from site to site. In most cases the Radiopharmacy Unit depends of the Department Nuclear Medicine, in few cases it

depends of the Hospital Pharmacy and in very rare places the unit is independent. In all cases it has some kind of relationship with Hospital Pharmacy for legal reasons related to the supply of medicines to the hospital.

Preparation of Radiopharmaceuticals

When considering the preparation of RP in Hospital Radiopharmacies, and according to the Spanish National Legislation, different requisites must be accomplished depending on the type of RP prepared.

Elution of generators and extemporaneous preparation of RP

The procedures involving elution of generators and preparation of RP from authorised kits must be done “*in an installation that can assure hygienic conditions and avoid the risk of microbial contamination*”. There is no specific description of air classes, and only a reference to “*type C cabin*” (*sic*) is stated. Preparation of dose units of ready-to-use RP must be done in “*adequate hygienic cabins*”.

The usual every day practice is that these procedures are carried out in a class A LFC placed in a room without filtered air. In some cases (this is being more common nowadays) this room is also equipped with filtered air.

On the other hand, it is said that the eluate of the generators should be checked according to the QC established in the Ph. Eur. (this means the user should be obliged to check the eluate for radionuclidic and radiochemical purity). The usual procedure in hospital Radiopharmacies involves the elution efficiency, ⁹⁹Mo-breakthrough and Aluminium tests, although these QC procedures are very variable from one site to another.

Regarding the QC of the prepared RP (radiochemical purity by TLC), this is usually done in most Radiopharmacies, although with a very variable frequency. In some places it is done only once in every batch of the kit, and in other places it is done on every single preparation.

Labeling of blood cells with RP

Labeling of blood cells with RP must be done “*in a LFC in a room equipped with positive pressure and adequate filters*”. In this case, more stringent requisites are established by Spanish legislation. The usual every day practice is that these procedures are carried out always in class A LFC. In many cases, such cabins are placed in a room without filtered air, although facilities with appropriate HEPA filters and air quality monitoring is becoming more and more frequent.

PET radiopharmaceuticals

Specific characteristics of PET RP

Positron emission tomography radiopharmaceuticals are medicinal products labeled with ultra-short lived positron emitting radionuclides. The most commonly used radionuclides are fluorine-18 (109 min half-life) and carbon-11 (20 min), but others such as nitrogen-13 (10 min) or oxygen-15 (2 min). The reduced physical half-life of the radionuclides implies an extremely short effective half life of the radiopharmaceutical.

PET radiopharmaceuticals only have diagnostic uses due to the type of emission of the radionuclides. As other RP, this compounds are used only once (or a few times at most) in a patients' lifetime. The reduced half-life of the radionuclide permits the production of these radionuclides with extremely high specific activities, permitting in most cases the synthesis

of radiopharmaceuticals with very high specific activities that must be compounded just before being administered to the patient. In some cases, some the radiopharmaceutical has to be released for use before some of the quality controls are finished. This means that validation of procedures and the implementation of an appropriate quality assurance system is of utmost importance.

Preparation of PET RP

Only one PET RP has marketing authorisation (MA) in Spain: ^{18}F -fluorodeoxyglucose (FDG). Several PET Radiopharmaceutical laboratories are authorised to commercialise such RP under a MA. In this case, as for any other industrially produced RP, Directive 2001/83 applies, and full GMP compliance is compulsory. Marketing of FDG implies important logistic challenges, but an every-day growing market for FDG has made this a very profitable business.

On the other hand, there is a very wide variety of PET RP (most of them labelled with carbon-11 or with fluorine-18) that have no commercial interest at all. In most cases because it is almost impossible to commercialise a medicinal product with a physical half-life of 20 min –and consequently pharmaceutical companies would not be interested in such RPs. However, these PET RP are of capital importance for the diagnosis of multiple pathologies with the highest incidence in the western world (cancer, cardiovascular diseases and neurodegenerative disorders).

In hospital PET Radiopharmacies, PET RP are compounded following the principles of officinal compounding, and consequently prepared only for the patients served by the Radiopharmacy in question. In this case, Directive 2001/83 does not apply according to the exception established in article 3 of such directive. Principles of Good Radiopharmacy Practice are applied for compounding a variety of RP.

Spanish National Legislation establishes that Officinal Formulas must be described in the National Formulary, follow the rules established in the Royal Spanish Pharmacopoeia and be compounded in Pharmacies or Hospital Pharmacies by a Pharmacist. Regarding Magistral Formulas, they must be prepared from substances with actions and indications legally recognised in Spain, be prepared following “*Good Pharmacy Practices for Compounding and QC of Magistral & Officinal Medicinal Products*” (RD 175/2001) and be compounded by a Pharmacist.

However, substantial problems arise for the every day clinical use of unlicensed PET RP, because none of them are in the National Formulary and there are not official indications for any PET RP (except for ^{18}F FDG, the only one with MA). What options are there left in this situation?

Clinical trials with unlicensed RP

According to Spanish legislation, designation as Investigational Medicinal Product (IMP) is required for all MPs without MA or for MP with MA that are going to be used in a clinical trial in non-officially approved indications.

The real problem is that to obtain designation of IMP, a Radiopharmacy Hospital should be a Pharmaceutical Laboratory, and that is not realistic at all.

The possibility to consider in some cases RP as NIMP (Non-Investigational Medicinal Products, as defined in “*Guidance on IMPs and other MPs used in clinical trials*”. EUDRALEX Vol 10 - Clinical Trials; Chapter V) when RP are used to assess end points in a clinical trial is quite interesting, although the legal requirements for designation of a IMP and a NIMP are virtually identical.

It is also interesting to consider here several documents such as *the Position paper on non-clinical safety studies to support clinical trials with a single micro-dose* (CPMP/SWP/2599/02Rev1), the *Concept paper on the development of a CHMP Guideline on the non-clinical requirements to support early phase I clinical trials with pharmaceutical compounds* (CHMP/SWP/91850/2006), the *Guideline on requirements for first-in-man clinical trials for potential high-risk medicinal products* (CHMP/SWP/28367/2007)

Summary

Main Problems

In summary, we could say that the main problems in Spain is that the specific legislation for RP is quite ambiguous and out-dated, with unclear requisites for personnel, premises, equipment and documentation. Furthermore, the rules are interpreted in different ways in different territories, no clear requisites for inspection are established and inspections are not as common as they should be. In addition the Spanish National Formulary from 2005 is adapted to s. XIX Pharmacy, not to the current state of the art knowledge of Pharmacy in general and Radiopharmacy in particular.

There is quite a limited knowledge of authorities on Radiopharmacy as this is quite a small speciality as compared to other pharmaceutical or medical ones.

The use of unlicensed PET RP needs urgent legal clarification, as this is the part of Radiopharmacy that is growing faster not only in Spain, but also in many European countries. Clinical trials with unlicensed RP (mainly PET) are also a problem for institutions willing to have high-level research in the field.

Positive developments and proposal of solutions

In the last years, Spanish authorities have started to consider radiopharmacists' claims and several fruitful meetings took place since 2003. As a result, we have seen some legislative developments in 2006, although there is already much to be done.

The solutions for many of the problems we currently have would come if a specific legislation for RP were established. Requisites of facilities, equipment, documentation, personnel and procedures should be clearly stated, as well as the inspection stipulations. Such regulation should also consider specific rules for PET RP.

The participation of experts in Radiopharmacy in the drafting of such rules should be an unavoidable requisite, along with working groups with other interested parties (such as Nuclear Medicine Physicians, the industry and the patients).

The implementation in our national legislation of rules based on *European Association of Nuclear Medicine (EANM) Guidelines of Good Radiopharmaceutical Practice* would be very positive, as such Guidelines have the support of thousands of professionals all across Europe.

In addition, a transversal deep analysis of the general legislation of MP should be carried out taking into account the peculiarities of RP, with the will to introduce appropriate changes whenever necessary. In some cases, specific exceptions should be considered.

Nonetheless, some of these changes would mean changes in the European Legislation. We should not be afraid of that. It might take time, but the effort would for sure be worth. Our main interest is not other than to provide our patients with RP of the highest quality and efficacy for a better global healthcare.

Guidelines for Good Radiopharmaceutical Practice (from the Radiopharmacy Committee, European Association of Nuclear Medicine)

Dr Clemens Decristofo

Radiopharmacy Committee, European Association of Nuclear Medicine
Clinical Department of Nuclear Medicine (A)

Dr Clemens Decristofo slides are available on page 31 of the Symposium,
Session 4: Radiopharmaceuticals
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

The European Association of Nuclear Medicine (EANM) is the umbrella organisation of Nuclear Medicine in Europe and represents the sector towards the European Institutions. It was founded in 1985 as a professional non profit medical association, serving as a communication platform for clinical and research excellence in Nuclear Medicine. There are two membership branches of the society: one being 34 national societies (member states of the Council of Europe), the other being individual members (3.474 members), comprising physicians, radiologists, chemists, radiopharmacists, physicists and technologists. Among 11 committees representing the most important sub-specialties of Nuclear Medicine the Radiopharmacy Committee deals with issues concerning Radiopharmaceuticals and Radiopharmacy practice both concerning scientific as well as regulatory aspects.

The strength of Nuclear Medicine lies in its unique ability to image molecular processes with high sensitivity (Molecular Imaging) relying on radiopharmaceuticals that are highly specific for certain targets such as enzymes, receptors or transporters. Whereas Single Photon emitting (SPECT) radiopharmaceuticals have been used for several decades and are firmly established in the routine diagnostic work-flow, the recent years have seen the increasing clinical application of very short lived radiopharmaceuticals for Positron Emission Tomography (PET). The progress of this technology is highly dependent on the availability of a great variation of radiopharmaceuticals in the hospital setting.

Radiopharmaceuticals are usually sterile formulations involving radionuclides with a very short physical half-life. They are therefore mostly prepared in hospital radiopharmacies or laboratories, and supplied locally for individual use or a small numbers of patients on a daily basis. Pharmaceutical regulations for these small scale extemporaneous preparations show a great variety in Europe, some countries apply full GMP regulations whereas in others no specific regulations are enforced. The Radiopharmacy Committee of EANM has therefore recently drafted specific guidelines for a good radiopharmaceutical practice (Guidelines at www.eanm.org).

The guideline is divided in two parts. The first one gives a framework for kit-based preparations and mainly covers the practice of the preparation of Technetium-99m radiopharmaceuticals from generators and labelling kits (SPECT), that is performed in practically every Nuclear Medicine institution. It addresses on the one hand practical issues of this pharmaceutical practice, including definitions of qualifications of facilities, clothing, training and quality control (frequency of testing, method validation) and many more. On the other hand this part aims at introducing specific GMP related aspects such as complaint, self inspection or operator qualification.

The second part covers the small scale preparation of other radiopharmaceuticals, mainly for PET. PET radiopharmaceuticals are prepared using readily produced radionuclides applying more or less complex chemical synthesis strategies including semi- or fully automated synthesis approaches. These are very often performed in small units in hospitals or research organisations. Therefore this part includes important aspects of a small scale production such as facilities, control of starting materials, production control and stability testing taking into account limitations in space and personnel resources. It also defines details of GMP related aspects such as qualification of personnel, cleaning validation, OOS, complaint handling etc.

This EANM guideline is intended as a basis for uniform regulations for small scale, non commercial preparation of radiopharmaceuticals in hospitals and research institutions.

Another important aspect in this highly specialised field of radiopharmacy is the need for training of responsible persons. Therefore the EANM has initiated a specific educational program and a certificate for the qualification in the small scale production of radiopharmaceuticals. This program is on the one hand based on a defined syllabus with three blocks of training courses currently being offered in four different European countries. On the other hand candidates require the proof of 2 years of practical experience covering all aspects of radiopharmacy practice including radiopharmaceutical chemistry, pharmacy and regulatory topics. These courses have been run for several years with great success and the certificate is intended to form a uniform European qualification of responsible persons for the small scale preparation of radiopharmaceuticals in hospitals and research institutions. The Certificate has been recognised by some authorities in European countries.

All these initiatives hopefully will help to achieve a more unified and standardised practice of extemporaneous preparation of radiopharmaceuticals in Europe. They aim to increase quality and raise standards in the field thereby avoiding overregulation that may detain patients from the highly sensitive and effective molecular imaging procedures in Nuclear Medicine

**EU Guidelines to Good Manufacturing Practice
Annex 3: Manufacture of Radiopharmaceuticals**

Dr Elisabeth Norbygaard
Medicines Inspector, Danish Medicines Agency (DK)

Dr Elisabeth Norbygaard's slides are available on page 39 of the Symposium,
Session 4: Radiopharmaceuticals
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

The backgrounds for my speak will be the revision of the annex 3 of the EU GMP guide and the comments received.

I would like to give a short presentation on the legal regulations for medicinal products and then give some examples on the comments we have received during the hearing period. The annex 3 has been drafted together with the inspectors group in EMEA.

At the same time another group is working on a revision on the note for guidance on radiopharmaceuticals. This guidance focus particularly on quality aspects of the application file for marketing authorisation for all radiopharmaceuticals including PET products

The commission directive from 2003 mention that all medicinal products for human use are to be manufactured in accordance with the principles of Good Manufacturing Practice. So this means that also radiopharmaceuticals should be manufactured according to GMP.

In the foreword to the GMP guideline is mentioned that the principles of GMP also is relevant for all large scale pharmaceutical manufacturing processes, such as that undertaken in hospitals, and for the preparation of products for use in clinical trials

In the directive 2004 no 27 is mentioned that a Member State may exclude medicinal products, formulated in accordance with the specifications of an authorised health care professional, and for use by an individual patient under his responsibility.

This sentence gives the member States the possibility to define if radiopharmaceuticals manufactured in hospital pharmacies or other institutions and without a marketing authorisation, should or should not be manufactured according to the EU GMP guide and annex 3.

That is why there is no harmonised approach to regulation of manufacture of radiopharmaceuticals in hospitals and other units in the EU.

The EU guideline for manufacturing - Part I and Part II with the annexes is the basis for inspections of GMP inspectors in the EU.

For some of the manufacturing processes different annexes will apply simultaneously.

Ex. for radiopharmaceuticals the annex 1 for sterile products and annex 2 for biological products annex 8 for sampling and so on.

The intension of a revision of annex 3 for radiopharmaceuticals is to modify the basic requirement laid down in Part II (ICH Q7A GMP manufacturing of Active Pharmaceutical Ingredients) and to update the annex to current state of the art in all relevant aspects of GMP. I would like to stress that the annex 3 is not a stand-alone annex so it should be read together with the rest of the general guidelines.

The next slides will show some of the headlines in the annex and some of the comments received during the hearing.

An effective quality assurance system for radiopharmaceuticals is of outmost importance. Because of the complexity of the production of radiopharmaceuticals (generators) special attentions should be paid to methods for obtaining and maintaining sterility during manufacture.

For radiopharmaceuticals containing radionuclides of short physical half-life, which can be released before results on finished product testing are available special attention should be devoted to in- process controls for critical parameters of the production process and the manufacturing process should be validated (QW).

I do not think that any one disagree in this point of view during the hearing.

In the annex 3 a qualified person is mentioned.

Batch release and certification of a batch by a QP is mentioned in annex 16 in the EU guide. This annex does also cover radiopharmaceuticals and it mentions that each batch of a finished product must be certified by a QP before being released for sale or supply or for export.

In some hospitals units, there are major concerns on the term Qualified Person because most employees in charge do not have the formal qualification of a QP.

A revision of the annex do actually not change the situation as it is to day, even if the new annex will mention the QP, because the requirement for certification before release of a radiopharmaceutical should be done according to annex 16.

To introduce an authorised person to certify final products for all radiopharmaceuticals is not within the scope of this revision.

The premises for production of sterile products should comply with the annex 1 in EU GMP.

The draft annex allows the use of class C environment for closed automated systems – in the hot cell and in the room. But it also mentions that there should be appropriate level of cleanliness for the type of operation performed, which means that class A is required during dispensing the filtered solutions.

This specification is not totally in line with the annex 1 for aseptic production (A/B) so may be we will have to specify the maximal dispensing time and small contra large volume solutions.

In the current annex 3 total containment work stations could be in a class D environment. But it actually means that every time the containment has been opened a fumigation of the containment should take place to reduce microbiological contamination

We have received several comments on the requirement for integrity testing pre and post filtration.

All comments have recommended only post filtration testing when small batches have to be prepared. Some declare that most filters used in PET productions are blocked or destroyed when pre- filter testing is applied. Others suggest that certified sterile filters should be used and tested for integrity before release of the product (QW)

The wording – if possible – is obviously not acceptable in the draft and should be changed.

The annex 3 mentions that some radiopharmaceuticals may have to be distributed and used even though all chemical and microbiology tests have not been completed.

The time required for quality testing of radiopharmaceuticals with short half-life, can exceed the half-life of the product.

The suggestion is to make distribution acceptable for radiopharmaceuticals before QC test have been finalised.

Others suggestion is that quality control testing of one or more trial batches should be performed before manufacturing of batches for patient use. And it should be stated in a procedure which tests are normally undertaken before the release of the product for use and which are undertaken after release. The latter should be justified (QW)

This headline deals with the test for sterility and proposes that the QP could provide a risk assessment, as part of the process validation, to use products before the test results are available

The sterility test result is in most cases not available before use of the product, neither are the results of the pyrogen test or residual solvent content or other test. So I agree that we must revise this chapter to cover not only sterility testing but also other tests and not only for short lived but also longer lived radiopharmaceuticals.

In the annex 3 we mention short-lived or long lived radiopharmaceuticals several times in the annex.

Comments form the hearing suggests that we should define short or long lived in the annex and determine requirement for air classification, production parameters, release- and QC test accordance with the half-life.

The problem is that the suggestion differs quite a lot:

- Short < 120 min
- 15 days as separation between short and long
- Ultra short-lived 20 min (C-11) short-lived 110 min (F-18), long-lived 8 days (I-131) or 6 h (Tc-99m)

I hope that we will be able to use these suggestions to revise the annex and to apply GMP standards and define short, perhaps also ultra short and long lived radiopharmaceuticals.

During the hearing some new subjects have been suggested.

The annex 19 in the EU GMP guide on reference samples do actually not mention radiopharmaceuticals, so it will be appropriate to create a section in annex 3 specific for radiopharmaceuticals.

Also parametric release has been mentioned several times in the comments.

In annex 17 in the EU GMP guide is mentioned that a comprehensive set of in- process tests and controls may provide greater assurance of the finished product meeting specifications than finished product testing.

For product with a marketing authorisation parametric release can only be approved for products terminally sterilised in their final container.

As far as I know authorities have only approved parametric release for a few radiopharmaceuticals.

Suggestions to write a section on Investigational Medicinal Products for use in clinical trial should be considered. EU GMP annex 13 actually already deals with IMP, but we will look into the situation for radiopharmaceuticals and find out if there is any deviation from the general requirements that should be considered

Finally I would hope that we would be able to agree on a revised annex 3. During the next 2 month my co-rapporteur from Sweden and myself will look into all the comments and make a new draft for the EMEA meeting in the inspectors group in September.

POSTERS SESSIONS

Slides are available under SymposiumPosterSession
http://www.edqm.eu/site/Proceedings_of_International_Conferences-83.html

POSTER NO. 1

Dr Corinne CIVADE

French Health Products Safety Agency (AFSSAPS)

635 Rue de la Garenne

34740 VENDARGUES, France

Tel: +33(0)467913941, Fax: +33(0)467913983, corinne.civade@afssaps.sante.fr

POSTER DETAILS

Poster Title :	<i>Analysis of pharmaceutical preparations made up in pharmacy by near infra red spectroscopy.</i>
First Author	Hervé REBIERE
	AFSSAPS – DLC – PCM2 635, RUE DE LA GARENNE – 34740 VENDARGUES – France herve.rebiere@afssaps.sante.fr
Initials, last name and institution of all other authors:	H. REBIERE ¹ , P. CHAMINADE ² , M. MATOGA ² , C. CIVADE ¹ , P-A. BONNET ¹ , M-H. TISSIER ¹ 1 : AFSSAPS, DLC, Vendargues – France 2 : Faculté de Pharmacie, Chatenay-Malabry – France

When a specific drug or dosage form (e.g. paediatric form), is not commercially available, physician can prescribe the delivery of a preparation for which he indicates the exact composition and formula. The pharmacist is in charge of manufacturing this prescription, which will be delivered by name for the duration of the treatment. The “magistral preparation” is defined in the French public health code (L5121-1 article) like "any drug extemporaneously made up in pharmacy according to prescribed medication for a particular patient ". These preparations, according to the L5311-1 article, are in the sphere of activities of the French Health Product Safety Agency (AFSSAPS) concerning evaluation, regulation and control.

For magistral preparations which concern only one person (compared to a drug with Market Authorisation), AFSSAPS encounters difficulties to exert its mission of market control. According to specific inspections in relation with accidents, the quality control of the raw materials and finished product are not often carried out, and good manufacturing practices are not always applied. Moreover, magistral preparations are sometimes made in series.

Several pharmacovigilance declarations, going until the death of a patient, have been reported to AFSSAPS these last two years. Samples from six different origins and affairs have been received for analyses in AFSSAPS laboratories. Due to the weak quantity of sample, control strategies had to be adapted, and the use of non destructive methods was chosen for an adequate problem targeting. Then, in a second step, classical analytical controls have been done.

NIRS (Near Infra Red Spectroscopy) meets the previous strategy, and is more and more used in control laboratories. The NIR spectroscopy can be defined as the study of absorption of the light's radiation by organic material in the 800 and 2500 nm region. Near infrared radiation penetrates through the capsule shield and allow a non-destructive spectral measurement of the pharmaceutical formulation. The whole capsules of magistral

preparation, powder capsule and raw materials alone and in a mixture were analysed by NIRS in diffuse reflexion mode.

Study of these medicines by NIRS gave us several information of interest. The spectral signature of the analysed product has been obtained in a simple, fast and non destructive way. Measurement and interpretation of spectra allow to appreciate qualitative intra and inter-batches homogeneity, and to evaluate the qualitative and quantitative composition. Nevertheless, some NIRS limits have been highlighted such as excipient and capsule shell interferences, or limit of detection of API in low dosage forms.

POSTER NO. 2

Dr Corinne CIVADE

French Health Products Safety Agency (AFSSAPS)

635 Rue de la Garenne

34740 VENDARGUES France

Tel: +33(0)467913941, Fax: +33(0)467913983, corinne.civade@afssaps.sante.fr

POSTER DETAILS

Poster Title:	<i>CONTROL METHODS OF PREPARATIONS IN HOSPITAL: investigation in hospital pharmacies and project to development of reference frames.</i>
First Author	Bérangère Parry
	DLC – AFSSAPS 635, rue de la garenne - 34740 Vendargues (corinne.civade@afssaps.sante.fr)
Initials, last name and institution of all other authors:	B. Parry, J.C. Tenon, C. Civade, P.A. Bonnet, M.H. Tissier AFSSAPS, DLC, Vendargues - France

When pharmaceuticals are not available or adapted, Hospital Pharmacies make up preparations, which, in France, have to be declared to the French Agency of Medical Safety of the Health Products (AFSSAPS). To respect good manufacturing practices and to assure the quality of their preparations, pharmacies have to keep equipment necessary to ensure adapted controls on the raw materials and finished product. Likewise, the agency has a role of control on the level of preparations in a public health context. But actually, there is a lack of reference frames about formulas to be used or the types of control to be carried out.

An investigation was necessary in hospital pharmacies in order to draw up the inventory of the control methods applied in current practice to the twenty most made up Hospital Preparations (this was the result of declaration to AFSSAPS).

Consequently, a questionnaire about these 20 Hospital Preparations was sent by mail to all the 133 pharmacies which declared them to AFSSAPS. The questions were particularly about the description of the analysis methods applied and corresponding references or bibliography used specially for the identification of the active ingredient (after conditioning) and its dosage.

The analysis of the 48 answers obtained showed that the active ingredient in the Hospital Preparations was measured in 36% of cases. The practices were very different between all the pharmacies, some controlled just the raw material and others used for the control of the preparations different tests like mass uniformity and content uniformity with HPLC. This investigation made it possible to refer the whole of identification and assay methods used by pharmacies in order to control their preparations. Some of them have used “in house” methods which have been validated by them because of a lack of reference frame. This information about the control methods is very precious and could be a starting point in order to compose a common referential.

Concerning the expiration dates, they were very variable and quite often arbitrary. Stability tests were not often done. They were generally fixed according to the expiry date of the active.

The results of the investigation confirmed the importance of developing reference frames about formulas and identification and assay methods for Hospital Preparations in order to harmonise practices and to optimise quality. These reference frames could be used to control preparations in case of pharmacovigilance or to assure quality issues. These methods, composed in collaboration with pharmacies, would be proposed for validation and inclusion in the National Formulary (French Pharmacopoeia).

POSTER NO. 3

Prof Stefan Mühlebach

Swissmedic

Hallerstrasse 7

3000 Bern 9, Switzerland

Fax: +0041 31 324 0200, stefan.muehlebach@swissmedic.ch

POSTER DETAILS

Poster Title:	<i>Chromatographic methods suitable for a Podophyllotoxin monograph</i>
First Author	Sarah Cron
	Universität Basel Moosstrasse 15, CH 4562 Biberist E-mail: sarah.cron@stud.unibas.ch Tel. 032 672 35 22 Natel 079 293 62 73
Initials, last name and institution of all other authors:	C. Kirchhofer, A. Häberli, J. Riedl, S. Mühlebach (all Swissmedic)

Introduction and Aim

Podophyllin, a plant extract from *Podophyllum* sp., was used for a longtime to treat anogenital warts (*Condylomata accuminata*). The extract showed variable composition, low efficacy, and high toxicity; it is not longer considered suitable for patient's treatment. Most Pharmacopoeias have deleted the monographs since. However, podophyllotoxin, the main component and active principle of podophyllin, is documented as alternative local treatment but not included in pharmacopoeias [1,2]. The Swiss pharmacopoeia authority is currently elaborating the respective national monograph. Based on literature, a suitable TLC method for identification and a HPLC for assay and related substances were elaborated and tested for specificity, sensitivity, reproducibility, and robustness.

Material and Methods

Podophyllotoxin analytical grade (> 95%) purchased from Sigma-Aldrich and Arcos and samples of podophyllotoxin from two European manufacturers of authorised topical preparations were used. Picropodophyllotoxin, an isomer and one of the main impurities, was synthesised from podophyllotoxin (EtOH abs, NaAc 1M, heated at reflux for 16 hrs) and characterised by ¹H-NMR. To demonstrate a suitable separation by TLC, etoposid from Bristol Myers Squibb was used. TLC: test solutions (0.5 mg/ml in acidified MeOH) were applied on silica gel plates using a Camag band applicator (10 µl); the mobile phase consisted of MeOH mixed with different apolar solvents; spraying with MeOH- sulfuric acid (9+1) and heating at 140°C (15 min.) was used for detection. HPLC: 10 µl were injected on different 250 mm C₁₈-columns using different MeOH-water or acetonitrile-water mixtures (isocratic and non-isocratic mobile phases; 1 ml/min). Detection was at 240 nm.

Results

TLC: silica gel plates and MeOH-Toluol (1:5) as eluent showed an RF of podophyllotoxin of about 0.3 with clear separation from etoposid. HPLC: With an ODS Hypersil column, an isocratic MeOH-water mixture (45:55) and a column temperature of 40°C, podophyllotoxin showed a retention time of about 13 min with a good separation of impurities tested.

Discussion

The TLC method from the BP monograph “Podophyllum Resin” [3] was optimised by the use of toluol instead of chloroform achieving even sharper spots. The method proved to be suitable as identity test.

A HPLC method published by Lim *et al.* [4] was improved: the acidified test solution showed better stability. The wavelength at 240 nm was more suitable than 280 nm to detect related substances. Compared to a draft from an EDQM group of experts using two different HPLC methods, this single modified method was appropriate to test related substances. It was found to be selective, precise, sensitive, and robust.

References

- [1] Von Krogh G., Longstaff E. Podophyllin office therapy against condyloma should be abandoned. *Sex. Transm. Inf.* 2001;**77**:409-412.
- [2] N. N. *Swissmedic J.* 2005;**4**(10):759: Unterschiedliche Qualitäten von Podophyllin - Vorsicht bei pharmazeutischer Verwendung (http://www.swissmedic.ch/files/pdf/10_2005.pdf)
- [3] British Pharmacopoeia. London: The Stationary Office
- [4] Lim C. K. Analysis of aryltetrahydronaphtalene lignans and their glucoside conjugates in podophyllin resin by high-performance liquid chromatography. *J. Chromatogr. A.* 1996;**722**:276-71.

POSTER NO. 4

Ms Maria Gard
Apoteket AB
Quality Management
Stockholm
Sweden

Pharmaceutical compounding in Sweden

Background

Apoteket AB produces individualised drugs in different scales at 4 production plants and 33 hospital pharmacies in Sweden. The pharmaceuticals are prescribed by doctors but not provided by pharmaceutical companies.

Method

The medicines are produced in order to fulfil the special need for each patient, i.e. pharmaceuticals without preservatives or raw materials that cause allergic reactions, with a special strength or in a special mixture of different active ingredients. The batch sizes differ from production for the treatment of one patient to the treatment of many patients. For the smallest batch sizes several controls are made before, during and at the end of production by a pharmacist but usually no laboratory controls are performed. At a certain batch size depending on the type of the dosage form, laboratory tests are made before release. At batch sizes of more than about 600 packages pro year the products are manufactured in small scale industrial production according to the Eudralex with release by Qualified Person.

The quality control also comprehend monitoring of process, operators, equipment as well as environmental monitoring.

Results

By applying the European principles and guidelines according to Eudralex or the Swedish legislation for extemporaneous products (SLS) Apoteket is able to produce unlicensed medicines in different scales at a cost effective and secure way mostly at very short time of delivery.

POSTER NO. 5

Dr Mona Tawab

Central Laboratory of German Pharmacists

Carl-Mannich-Str. 20

D-65760 Eschborn, Germany

Tel: 0049 6196 937 955, Fax: 0049 6196 937 810, m.tawab@zentrallabor.com

POSTER DETAILS

Poster Title:	<i>Quality assurance of extemporaneous preparations in Germany in the frame of round robin tests</i>
First Author	Mona Tawab
	Central Laboratory of German Pharmacists
Initials, last name and institution of all other authors:	H. Latsch, A. Kaunzinger, M. Schubert-Zsilavec, Central Laboratory of German Pharmacists, Eschborn, Germany

Introduction:

In spite of the wide offer of industrially manufactured products, extemporaneous dispensing in pharmacy is still contributing to a large extent to bridge therapeutic gaps and is therefore considered to be an indispensable part of therapy.

In order to ensure the quality of about 25 million preparations dispensed annually in German pharmacies, corresponding to 1100 preparations per pharmacy per year, an efficient quality management system has been set up starting from the logistics ending up with a comprehensive quality assurance.

So extemporaneous preparations in Germany are only dispensed by well trained persons working according to well-elaborated guidelines covering all relevant topics like principles and plausibility of prescription, standard preparation procedures of prescription drugs, hygiene guidance and quality control measures.

Role of the ZL in assuring the quality of extemporaneous preparations:

Above all pharmacies are given the chance to assess the current quality status of their dispensed formulations in the frame of periodic round robin tests offered by the Central Laboratory of German Pharmacists (ZL). „ZL“ is the Central Laboratory of German Pharmacists founded over 35 years ago by the Pharmaceutical Associations to control drug quality and promote pharmaceutical research in different fields.

Every year German pharmacists are called on to participate in one of the three round robin tests. Usually high value is set on choosing formulations of practical importance and galenical challenge. As can be seen in Fig. 1 the participants have been increasing permanently.

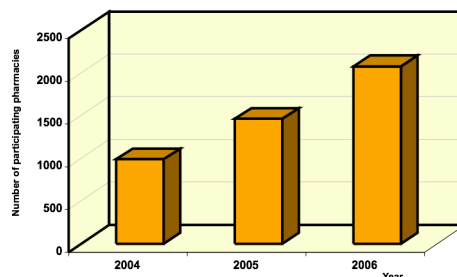


Fig. 1: Total number of participating pharmacies in the last three years

The goal of round robin tests

The main goal of round robin tests is to assure quality and to sensitize pharmacies for problematic formulations. By delivering insight into common dispensing challenges round robin tests have greatly contributed to the optimization of preparation procedures in daily practice. In addition to quality certification in the frame of established quality management systems, the quality proof of dispensed formulations contributes a lot to highlight the pharmacists' know-how towards physicians and health insurances.

Procedure

Following the announcement of the round robin tests in the pharmaceutical press and circulation letters of the German pharmaceutical associations, pharmacies register themselves on-line or per fax. Participating pharmacies are divided into groups, each being assigned a certain day of preparation. The dispensed formulations should be delivered promptly to the ZL, where they are analysed focusing on the following parameters:

- identity and content of the active ingredient
- homogeneity of the formulation
- microbiological quality
- consistency
- individual parameters like uniformity of mass / pH / density etc.
- packaging material
- declaration

Whereas only successful pharmacies get a quality certification, every pharmacy receives a certificate of participation and eight education points. All examinations in the ZL are carried out under GMP conditions.

Achievements of the round robin tests so far:

Round robin tests in Germany have shown that German pharmacies are able to dispense high quality extemporaneous preparations and that galenical challenges are handled excellently.

Based on the thorough evaluation of the preparation protocols, every participating pharmacy has to fill out, valuable recommendations are made regarding the proper use of balances, application of automatic preparation systems and pharmaceutical calculations carried out.

Conclusion:

On the background of the tremendous success and enormous contribution of round robin tests to assuring and optimising the quality of extemporaneous preparations in Germany, pharmaceutical political institutions recommend participation at least once per year.

Furthermore it is intended to change German pharmaceutical work rules in line with that recommendation, underlining the indispensable role of extemporaneous preparations in bridging therapeutic gaps.

POSTER NO. 6

Dr Andreas Kiefer

Central Chamber of Pharmacists (Bundesapothekerkammer)

Rheinland-Pfalz

Am Gautor 15

D-55131 Mainz, Germany

Tel: + 49 613 1270120, Fax: + 49 613 12701222, a.kiefer@sophien.apo.de

POSTER DETAILS

Poster Title:	<i>Guidelines and standards for the quality management system in community pharmacies: the German experience</i>
Initials, last name and institution of the author:	A. Kiefer, Bundesapothekerkammer, Berlin

Concepts for quality management (QM) in community pharmacies have been developed by the 17 German Pharmacy Chambers in the 1990ies, and QM is now being established in the 21.500 pharmacies on a voluntary basis. The concepts include a certification process, and certain standards adopted according to individual needs. A unique pattern is given by the ABDA – Bundesvereinigung Deutscher Apothekerverbände in 2006 with the “Mustersatzung für das Qualitätsmanagement der deutschen Apotheken”.

Specific guidelines (“Leitlinien zur Qualitätssicherung”) have first been published in 2000 by the “Bundesapothekerkammer” (BAK). By now, 23 guidelines are implemented and ready for download on the ABDA-homepage, covering a wide range of topics, from information management and counselling to dispensing, physiological tests, and hygiene management. Eight of them refer to the preparation and testing of starting material (active ingredients, excipients, containers, water) and compounded drug products. The most important one is the guideline “Herstellung und Prüfung der nicht sterilen Rezeptur- und Defekturzneimittel”, its 2nd revision dating from 2006, which covers the majority of the pharmacy made medicines out of extemporaneous and small-scale preparation.

The guidelines chiefly do not define pharmaceutical quality on their own but rather give a summary of cited directives and regulative documents, thus representing the current status of good pharmacy practice. Among these standards are the European and the German Pharmacopoeia, the “Deutsche Arzneimittel-Codex” (DAC) as a German extra pharmacopoeia, the DAC-associated formulary [“Neues Rezeptur-Formularium” (NRF)], recommendations of the pharmacist laboratory [“Zentrallaboratorium Deutscher Apotheker” (ZL)], the pharmacy supervising personnel [“Arbeitsgemeinschaft der Pharmazieräte Deutschlands” (AGP)], scientific associations, and the “Arzneimittelkommission der Deutschen Apotheker”, an ABDA-institution for drug safety and risk management. Almost permanent contact to these institutions leads to periodical revisions, and none of the guideline texts dates before 2004.

POSTER NO. 7

Mrs Yvonne Bouwman

Laboratory Dutch Pharmacists of the Royal Society of Dutch Pharmacists

Alexanderstraat 11

Den Haag, 2514 JL, The Netherlands

Tel: +33170 3737210, Fax,+33170 427 4801, y.bouwman@winap.nl

POSTER DETAILS

Poster Title:	<i>Formularies: the Dutch experience</i>
Initials, last name and institution of the author:	Y. Bouwman, Laboratory Dutch Pharmacists of the Royal Society of Dutch Pharmacists

Formularium der Nederlandse Apothekers

The Formularium der Nederlandse Apothekers (FNA) was first published in 1967 and is frequently (at least yearly) updated. It contains 200 formulations. Each formulation has to be accepted country-wide as therapeutically necessary, it is pharmaceutically well-designed, its stability has been proved and an instruction for analysis is provided. A formulation is only included if it is not available as an industrially produced medicine, in The Netherlands or in any other European country from which it eventually can be obtained by ‘import’.

The support of preparation in pharmacies consists except for the Formulary of three other items:

- about 150 SOP’s for (parts of) general preparation operations
- about 400 batch preparation records; which can be used with a dedicated software program to adapt them to the actual batch size and other local circumstances
- a textbook ‘Recepteerkunde’ (‘Compounding’ or ‘Small scale preparation’)

Level of standardisation

The total amount of preparation in public pharmacies in NL is 6,5 million per year which accounts for 5% of the delivered medicines. About 50% of the preparation in public pharmacies follows the FNA. In hospital pharmacies the percentage is not known but standardisation has evolved to a further extent.

Non-standard formulations and quality standards

The FNA is not immediately up to date with all formulations which become necessary for patients. We counted for instance in 1,5 year 25 industrial products which were therapeutically absolutely necessary, which suddenly got unavailable: for the time being too long for the patient, or forever. In such cases we try on our website Farmanco to provide pharmacists as quickly as possible with chemical, pharmaceutical and pharmacotherapy information and information about ‘import’. But for the actual preparation the pharmacists have to decide and act on their own as is the case with preparations which are only locally justified. After the patient’s need is justified, the availability predominates the quality of the product. Of course the patient has to get the best quality, but if there is no ‘best quality’ available, the next best may be sufficient. It has to be judged by pharmacist and physician, and probably even with a contribution of the patient himself. If GMP-like guidance is prohibiting the patient to get any ‘next best’ medicine, the patient doesn’t get the medicine at all, which cannot be considered as good care. Within the quality management legislation, further guaranteeing the minimal quality of the medicine is possible. In our view it is a

challenge to frame this situation in a guideline which values GMP principles as well as care responsibility.

European cooperation

For many years, the FNA and the German NRF are exchanging formulations as much as possible. Due to pharmacotherapy differences the number of identical formulations is still not more than about 10. But all the same the cooperation on procedures, guidelines and working methods is very fruitful and gradually develops into harmonisation.

POSTER NO. 8

Dr Holger Reimann
Govi-Verlag Pharmazeutischer Verlag
Pharmazeutisches Laboratorium des Neuen Rezeptur-Formulariums
Postbox 5360
D-65728 Eschborn, Germany
Tel: +49-6196 928 331, Fax: +49-6196 928 330, reimann@govi.de

POSTER DETAILS

Poster Title:	<i>Formularies: the German experience</i>
Initials, last name and institution of the author:	H. Reimann, Govi-Verlag Pharmazeutischer Verlag

Neues Rezeptur-Formularium

The „Neue Rezeptur-Formularium“ (NRF) was first published in 1983 by the pharmacists association, ABDA – Bundesvereinigung Deutscher Apothekerverbände, in the tradition of former German formularies, e. g. the Reichsformeln (RF; 1940) or the Deutsche Rezeptformeln (DRF; 1950). But most of the 300 RF and DRF formulas had become obsolete, and only a few formulas could be adopted for the NRF. The NRF is part of the „Deutsche Arzneimittel-Codex“, a German extra pharmacopoeia published by ABDA and complementary to the official pharmacopoeia. DAC and NRF are present in each of the 21.500 German pharmacies. Updates of DAC and NRF are issued annually. By now the NRF includes 239 formulas, about half of them being assigned to cutaneous use. After the German reunification many formulas out of the official GDR-formulary („Standardrezepturen 1990“) were reevaluated and transformed to NRF-monographs. Formulas are generally adopted after discussion in the “Arzneimittelkommission der Deutschen Apotheker”, an ABDA-institution for drug safety and risk management. Most of the monographs are unique, having no corresponding industrially prepared medicinal product marketed in Germany. If there are similar drug products in the market the NRF-formulas often differ in a particular way, e. g. in the preservative, a certain (pediatric) dose or concentration.

The need for a preparation is not only regarded in terms of quantity, but also on the background of particular needs of certain patients. NRF-monographs usually base originally on real prescriptions, but are re-designed and standardised chiefly for extemporaneous preparation. In this way they differ from monographs of the official German “Standardzulassungen“ and other formularies, e. g. the hospital pharmacists “Formularium hospitale“. The monographs are clearly structured, and they include detailed information on starting material quality, instructions for compounding, and apparatus, inprocess testing and stability data. Testing procedures and specifications are for NRF-internal use only.

Additional information

The general chapters of the NRF give additional information about specific dosage forms, instructions for the use of and the supply with starting material and general compounding instructions. Information is given for the use of appropriate scales and principles of stability data to be assigned to applicable preparations before and in use, to ointment bases and stock preparations als bulk. A NRF in short form is issued for the information of medical doctors. Because of the low level of standardisation of about 5–20% (most of the prescriptions are not referring to NRF) working party in the NRF laboratory provides a data base with about

550 documents on formulas and pharmaceutical topics in the internet and a helpdesk giving Information.

Cooperation

Working on the NRF is done in permanent cooperation with many pharmaceutical institutions in Germany and with the laboratory of the Dutch pharmacists (LNA), editing the Dutch formulary (FNA).

POSTER NO. 9

Dr Wolfgang Kircher

Arbeitsgemeinschaft der Pharmazieräte Deutschlands

Hauptstr.24

D – 82380 PEISSENBERG, Germany

Tel: +49-8803 860 Fax: +49-8803 3307, info@sankt-barbara-apotheke.de

POSTER DETAILS

Poster Title:	<i>Supervision of extemporaneous and small-scale preparations in German community pharmacies</i>
Initials, last name and institution of all other authors:	Ch. Bauer, H. Buttle, S. Demelius, IL-U.Plener, all authors: Arbeitsgemeinschaft der Pharmazieräte Deutschlands

The regulation concerning the extemporaneous and small-scale preparations are standardised throughout the Federal Republic with the exception of a few regional variants. There is an intensive communication between the different pharmaceutical authorities (for example regional health authorities, BAK, ABDA, ZL, NRF) in order to achieve a high standard of pharmaceutical quality. These quality standards are further developed and brought up to date on a regular basis. The Arbeitsgemeinschaft der Deutschen Pharmazieräte (that is the association of German state board inspectors) passes resolutions on quality standards of extemporaneous and small-scale preparations at frequent intervals.

POSTER NO. 10

Mr Dirk W. Groot

RIVM-KCF

PO Box 1

NL-3720 Bilthoven, The Netherlands

Tel: +31 30 274 4224, Fax: +31 30 274 4462, kik.groot@rivm.nl

POSTER DETAILS

Poster Title:	<i>Quality aspects of a medicines dispensing system</i>
Initials, last name and institution of all other authors:	E.K. de Rooij, D. de Kaste, RIVM, the Netherlands

Recent developments show the need for simplification of the medication process, especially for multi-using patient groups. Arguments given are:

- difficulties by pressing the tablets/capsules out of the blister;
- difficulties by taking the correct medicines at the correct dosing time;
- mistakes made by the nursing staff.

As the tablets/capsules are repacked (from blister to canister), stored in a computer driven dispensing machine, where they are “free-falling” collected in multi-dosing sachets (medication rolls), cross contamination between patients and shortening of the expiry date were expected.

Results of a survey will be presented where samples from these medication rolls were controlled on their aspects of 1: labelling; 2: content; 3: level of contamination.

POSTER NO. 11

Dr Sebastian Herbig

ADKA Ausschuss für Arzneimittelherstellung und Analytik

University clinic Essen

Pharmacy service- Hufelandstrasse 55

D-45122 Essen, Germany

Tel: +49 201 7231 933, Fax: +49 201 723 1937, sebastian.herbig@uk-essen.de

POSTER DETAILS

Poster Title:	<i>Standards for compounding in German hospital pharmacies</i>
Initials, last name and institution of all other authors:	H. Schneemann, University clinic Essen, -Pharmacy service-

Hospital pharmacies in Germany are strongly involved in the preparation of drug formulations and the development of quality assuring systems.

The “Formularium hospitale” is the most important collection of formulas meeting the special needs of hospital pharmacies. These drug products and its formulas are developed in highly specialised institutions and are approved by the working group of the ADKA (Federal association of German hospital pharmacists) called “Ausschuss für Arzneimittelherstellung und Analytik”. The working group is also responsible for continuous education and support of the maintenance of good pharmaceutical practice in compounding. Communication platforms are the internet and the monthly issued publishing organ “Krankenhauspharmazie”. The latest guideline for good pharmaceutical practice in hospital pharmacies is published in *Krankenhauspharmazie* 29 (9) 2005: 348-362.

BIOGRAPHICAL NOTES

Dr Agnès Artiges graduated in pharmacy from the University of Bordeaux (France) and has a PhD in the same subject, as well as a degree and a PhD in law, the latter from the University of Paris, France. In her postgraduate law degree she specialised in European Institutions.

She was Assistant and Assistant Instructor in the Toxicology Laboratory of the Faculty of Pharmacy of Bordeaux before joining the French Ministry of Health in 1971. During her career with the Ministry, she held the posts of Head of the French Pharmacopoeia, Head of the Registration Authority for Medicinal Products for Human Use and Head of the Sub-directorate of Scientific and Technical Affairs.

In addition, she was Chairman of the European Pharmacopoeia Commission from November 1989 to November 1992 and a member of the former Quality Working Party of the Committee for Proprietary Medicinal Products (CPMP) of the EC and was Chairman of this Working Party from December 1991 to March 1993.

Dr A. Artiges left the French Ministry of Health in April 1993 to take up the post of Director of the European Directorate for the Quality of Medicines (European Pharmacopoeia and European Network of Official Medicines Control Laboratories/OMCL) - Council of Europe.

Prof. Jean Claude Chaumeil obtained his degree in pharmacy in 1965, and his PhD in 1974 in Agence Generale des Equipements et Produits de Santé (AGEPS) of Assistance Publique- Hôpitaux de Paris). He worked first in Lebanon, then in Faculté de Pharmacie in Paris on drugs for orphan diseases. For his research works he obtained, with others pharmacists of AGEPS, the Galien's price in 2002.

He is currently responsible of the pharmaceutical research department in Faculté de Pharmacie, Université Paris Descartes, and AGEPS in Paris.

Mr. Maurizio Cignitti graduated in chemistry from Rome University "La Sapienza" (1955). He did a post-doc in theoretical chemistry at the University of California, Davis Campus (1962-63) and at the Illinois Institute of Technology, Chicago (1963-64). During his career at the Istituto Superiore di Sanità in Rome (1957-97) he has been head of the Pharmaceutical Chemistry Department (1990-97) and teacher of General Chemistry at the University of Rome, Medical School (1968-84).

After retiring (1997) he continue to devote his efforts to the Secretariat of the Italian Pharmacopoeia. He his currently member of the European Pharmacopoeia Commission since 1994 and vice-chair of the Italian Pharmacopoeia Commission since 1990.

Dr Clemens Decristoforo. obtained his degree in pharmacy from the Lepold Franzens University, Innsbruck, Austria in 1991. He started his career as radiopharmacist at the Department of Nuclear Medicine in Innsbruck and obtained his PhD in 1997. From 1997-1998 he worked as a Post-Doc Marie Curie Fellow at the Nuclear Medicine Research Laboratory, St.Bartholomews Hospital, London, UK. In 2001 he became Associate Professor in Radiopharmacy at the Medical University Innsbruck. He is a member of Group 14 of the European Pharmacopoeia Commission and currently chairs the Radiopharmacy Committee of the European Association of Nuclear Medicine.

Ms Gudrun Eichler graduated in 1975 in pharmacy from the University of Bonn. She worked for 5 years in her own pharmacy in Dortmund. She was Pharmaceutical Officer with Borken and Coesfeld for 5 years. She has worked for 20 years as Pharmaceutical Director, with the Government of Lower Saxony, Hanover, and has been a GMP Inspector since 1987. He is a member of the German Expert Committees for Blood and Biotechnology, corresponding member of the German Expert Committee for Validation, and a member of the Quality Management Committee for Health of Lower Saxony.

Mr V'Iain Fenton-May. Qualification B.Pharm., F.R.Pharm.S.. Recently retired hospital pharmacist. Formally head of pharmaceutical quality for the Welsh hospitals and head of one of the largest hospital preparative services in the UK. Member of the British Pharmacopoeia Commission. UK delegate to the European Pharmacopoeia Commission

Prof. Dr Vagn N. Handlos. June 1969 Cand. Pharm. From the Royal Danish School of Pharmacy. November 1974. PhD in pharmacy. Theses: Radiation crosslinking of polyethylene. September 1986. Dr. pharm. Theses. Technical aspects of gas sterilisation of medical devices.

70-76 PhD student at the Royal Danish School of pharmacy (RDSP), 73-76 Assoc. professor at RDSP, 76-79 Senior research fellow at RDSP, 79-87 Assoc. professor at RDSP and research chemist at the Risoe National Laboratory, 87-96 Director of the Rigshospitalet Pharmacy, 96-2005 Director of the H:S Pharmacy

1990 - Assigned professor at Royal Danish School of Pharmacy

2005 Senior Scientist at the H:S Pharmacy

Others: 81-92 Chairman of the national Danish autoclave standardisation committee, 83-96 Member of the Ph. Eur. Expert group on plastic materials and containers, 85-88 Member of the Danish Technical Research Council, Chemistry commission, 89-92 Delegate to the EU Advisory Committee on Pharmaceutical Training, Bruxelles, 89-95 Chairman of the Danish Pharmaceutical Society, 92- Member of the Danish Pharmacopoeia Commission, 95-99 Chairman of the Assoc. of Danish hospital pharmacy directors.

2005- Director of Education, Science and Research. European Association of Hospital Pharmacists.

Present work. Research areas:

Liposome as drug carrier for new anticancer drugs based on gene therapy.

Cytotoxic drugs in the work place of Scandinavian hospital pharmacies.

Pulmonary drug delivery for IC-patients.

Ms Paule Jacquain obtained her degree in pharmacy in 1971 from University of Louvain (Belgium). She starts her career in 1971 as pharmacist in a retail pharmacy and joins the public services in 1978.

Her first task is the secretary of the Belgian Pharmacopoeia Commission. A few time after, she is nominated as delegate for Belgium near the European Pharmacopoeia Commission. From 1987 to 1996, she is chairwoman of the group 3 of this Commission. Together with the activities of the Pharmacopoeia, she acts as GMP inspector during more than 10 years.

Since 2004, she is Advisor general, Responsible of the Department "Production & Distribution" in the FAMHP (Federal Agency for Medicines and Health Products) and leads all the services of inspection, and different other units: Fraud, Rapid Alert, Pharmacopoeia Commission and Formulary.

She is also member of different national and international Commissions and Committees.

Dr Susanne Keitel is a licensed pharmacist and holds a PhD in pharmaceutical technology. Her working experience includes 10 years in pharmaceutical development in industry, including five years as head of the department “Pharmaceutical Development/Oral Dosage Forms” at Schering AG, Berlin. From October 1997 to June 2005, Dr S. Keitel held the position of Division Head Pharmaceutical Quality at the Federal Institute for Drugs and Medical Devices (BfArM), Germany. In addition, she served as Acting Head of the division European Procedures. As of July 1, 2005, Dr S. Keitel is now Head of EU and International Affairs at BfArM.

Since 2000, she is chair of the German Pharmacopoeia Commission and the German Homoeopathic Pharmacopoeia Commission. At an EU-level, she is vice-chair of the Joint CHMP/CVMP Quality Working Party and a member of the EMEA Paediatric Working Party, the Notice to Applicants Group and has been rapporteur for the ICH stability guidelines. At present, she is EU-topic leader of the ICH-Expert Working Group “Pharmaceutical Development” (ICH Q8).

Dr Paul P. H. Le Brun obtained his degree in pharmacy from the Groningen University in 1982. He started his career in the Dutch Laboratory of Pharmacists. From 1985 tot 1988 he trained and worked as a hospital pharmacist, joined Merck Sharp&Dohme from 1999 to 1992 as production pharmacist and was appointed as head of production of the Central Hospital Pharmacy of The Hague in 1992, where he is still working.

He obtained his PhD in 2001 on the improvement and development of antibiotic inhalation in CF patients, for which research he received the innovation award of the Royal Dutch Society of Pharmacists. He further specialised as clinical pharmacologist in 2002. To date he is a member of the board of the Dutch Society of Hospital Pharmacist.

Dr Gerard Lee B.Pharm, PhD, FRPharmS, MRSC, CChem is currently Group Manager for Laboratories and Pharmacopoeia at the Medicines and Healthcare products Regulatory Agency (MHRA) and is the Secretary and Scientific Director to the British Pharmacopoeia Commission. He previously held the post of Group Manager Laboratories and Licensing. He joined the MHRA in 1999 and prior to that held a number of senior quality control posts within the NHS; most recently Regional Quality Controller for Mersey Regional Health Authority (1985-96) and Director of Quality Control in the Liverpool Health Authority Pharmacy Practice Unit (1996-99).

Prof. Stephen Mather obtained his degree in pharmacy from University of Nottingham in the UK. He subsequently obtained an MSc in Biopharmacy and a PhD in Radiopharmacy from Kings College University of London. He was made a Fellow of the Royal Pharmaceutical Society in 1998. He is currently Professor of Radiopharmacy and Head of Cancer Imaging at the St Bartholomew's and Royal London Hospitals School of Medicine and Dentistry, University of London and Head of the Cancer Research UK Nuclear Medicine Research Laboratory at St Bartholomew's, Hospital

Dr J. Michael Morris graduated from the University of Manchester, UK, with a degree in Pharmacy and a PhD in Pharmaceutical Chemistry. Following some early work in R&D in industry, he moved to QC/QA in hospital based pharmaceutical manufacturing operations. In 1987 he joined the NDAB in Dublin, Ireland, as Senior Pharmacist and became Pharmaceutical Director of the newly formed Irish Medicines Board in 1996. As the IMB is the competent authority for animal and human medicines, Dr J. M. Morris was in charge of pharmaceutical assessment activities, until a reorganisation took place in 2003. Currently he is Senior Scientific Advisor and a member of the Management Committee to the IMB.

Dr M. Morris was a member of the Quality Working Party, EMEA until 2003, and a former member of the Biotechnology Working Party. Since 1996, he has been a representative for Ireland of the European Pharmacopoeia Commission and was elected to the post of President in March 2004. He has also been active in ICH during this period and is currently EU topic leader for its Q4B group (pharmacopoeial harmonisation).

Prof. Stefan Mühlebach, obtained his diploma in pharmacy from the University of Berne, Switzerland, in 1975. He obtained his PhD degree in Pharmacology and Toxicology in 1979 being a research assistant in the Department of Pharmacology.

He started his career in hospital pharmacy in 1980 at Biel, Switzerland. He was appointed chief pharmacist at the hospital pharmacy in Aarau, Switzerland 1987. He kept the part-time position in research and teaching at the Pharmacology Department at the University in Berne. He did his habilitation “*Venia docendi*” 1993 in Berne and in 2000 at the Medical Faculty of the University of Basle, Switzerland. In 2004 he was appointed professor of pharmacology and hospital pharmacy.

In 2005 he moved to the regulatory authority (Swissmedic) and became Head of the Pharmacopoeia in Switzerland. He was nominated president of the National Pharmacopoeia Commission and Head of the Swiss delegation of the European Pharmacopoeia Commission in 2006.

Dr Elisabeth Norbygaard obtained her degree in pharmacy from the University of Copenhagen, Faculty of Pharmaceutical Sciences. She developed her career as radiopharmacist at the Isotope - Pharmacy for more than 12 years. She is currently a Medicines Inspector at the Danish Medicines Agency and conducts GMP inspections nationally as well as internationally.

Dr Iván Peñuelas graduated in Biology in 1990 and in Pharmacy in 1993 and received his PhD from University of Navarra (Spain), after a stay at the National Institute of Mental Health in Bethesda, USA in 1993. He received his title of Pharmacist Specialist in Radiopharmacy in 1998. He was Research Associate at the department of Biochemistry and of Pharmacology between 1993 and 1995, when he joined the University Hospital of Navarra.

He is currently Radiopharmacist Consultant and Head of the Radiopharmacy Unit of the University Hospital of Navarra, and Associate Professor of Radiopharmacy at the Faculty of Pharmacy. He has developed his career mainly in PET Radiopharmacy, pioneering this field in Spain since 1996. Deeply involved in radiopharmacy-related legislation, he is Expert of Group 14 of the European Pharmacopoeia and Expert of the Group on Radiopharmaceuticals of the Royal Spanish Pharmacopoeia.

Former president of the National Commission of Radiopharmacy in Spain (2003-2006), he is currently member of such commission and also of the National Council of Specialities in Health Sciences of the Spanish Ministry of Health.

Dr Patrick Rambourg obtained his degree in pharmacy from Reims University (France) in 1977. He studied for his PhD at Paris University and obtained his PhD in 1981. During the period 1982-2000, he was chief pharmacist at the teaching hospital of Reims and associate professor at the Faculty of Pharmacy. Since 2000, he is chief pharmacist at the teaching hospital of Montpellier and now, through the new rules of hospital organisation, he is responsible of all the pharmaceutical activities in this hospital. He is at present the president of the French commission of Pharmacopoeia.

Dr Dietrich Schnädelbach obtained his degree in pharmacy from the university in Tübingen, Germany in 1968. He studied for PhD at the university in Tübingen and the Free University in Berlin, Germany. He obtained his Ph. D. in 1974. From 1969 to 1974 he was research assistant at the universities of Tübingen and Berlin. During the same period he provided tuition and practical instructions for pharmacy students dealing with the pharmacopoeia.

1974-1977 he was head of the quality control laboratory of the hospital pharmacy of the Rudolf-Virchow-Krankenhaus, Berlin.

Since 1978 he has been an employee of the Federal Institute for Drugs and Medical Devices. Since 1989 he has been head of the German pharmacopoeia unit and member of the European Pharmacopoeia Commission. Since 2005 he has been head of the pharmacopoeia and standard licensing unit.

From 1992 to 1995 he was vice president and from 1995 to 1998 President of the European Pharmacopoeia Commission. Since 1997 he has been a member of the International Laboratory Forum on Counterfeit Medicines, since 1998 vice president of the German Pharmacopoeia Commission and the Homoeopathic Pharmacopoeia Commission, since 2003 a member of the Council of Europe Ad hoc Group on Counterfeit Medicines, since 2006 a member of the HMA Working Group Enforcement Officers.

Biographical note

Prof. Alfons Verbruggen studied Pharmacy at the Katholieke Universiteit in Leuven (1967-1972) and obtained his Ph.D. degree in Pharmaceutical Sciences in 1975. He is head of the radiopharmacy of the University hospital of the University of Leuven since 1977. Lecturer in Radiopharmacy at the University of Leuven since 1977 and full professor in pharmaceutical and radiopharmaceutical chemistry since 1986. He is member of group 14 of the European Pharmacopoeia (radioactive compounds) since 1993 and chair of this group since 2001. Has been dean of the Faculty of pharmaceutical sciences in Leuven (1992-2001).

Dr Pieter Vree obtained his degree in pharmacy from Leyden University in The Netherlands. He specialised in Hospital Pharmacy and Nuclear Medicine at the Academic Hospital of Utrecht University. He practised as hospital pharmacist for almost 20 years. In 1990 he became Chief Pharmaceutical Inspector and Chair of the National Pharmacopoeia Authority in the Netherlands.

PARTICIPANTS LIST

Title	Name	Employer	Ctry
Mrs	ANDERSSON Inger	APL Apoteket AB	S
Mme	ANDLAUER Béatrice	EDQM	COE
Ms	ANTALFFY Maria	Institute of Isotopes Co	H
Mr	ARDIET François	Cooper	F
Ms	BALD Melanie	EDQM	COE
Mrs	BALSERIENE Rasa	Ministry of Health	ZLI
Ms	BARRE Emmanuelle	Hopital Saint Louis	F
Ms	BAUMGARTHEN Francine	EDQM	COE
Dr	BLANC Ariane	Hôpital Robert Debré	F
Dr.	BOEUF Didier	Pharmacie du Viaduc	F
Dr.	BONETTO Francesco	Ministry of Health - Directorate of Drugs and Medical Dev	I
Prof	BONNET Pierre Antoine	AFSSAPS	F
Mrs	BOUAKAZ Elli	DEQM	COE
Mrs	BOUWMAN Yvonne	Royal Society Dutch Pharm.	NL
Mrs	BRUNNER Catherine	ICHV	CH
Dr.	BRUNO Fabien	Pharmacie Delpech	F
Mr	CASTLE Peter	EDQM	COE
Mrs	CEDERLUND Helena	Apothek AB	S
Dr	CHARTON Emmanuelle	EDQM	COE
Prof. Dr.	CHAUMEIL Jean-Claude	Université Paris V	F
Mr	CHIGAYO Kayini	Medicines Control Authority	ZW
Prof	CIGNITTI Maurizio	Istituto Superiore di Sanità	I
Mrs	CINGRIA Laurence	Pharmacie Hug	CH
Ms	CIVADE Corinne	AFSSAPS	F
Ms	COHEN Virna	Afssaps	F
Dr.	D ARPINO Alessandro	SIFO	I
Dr.	DE BECO Virginie	Hopital Avicenne	F
Prof	DE JONG Hendrick Jan	Institut de Recherches Int. Servier	F
Dr	DE KASTE Dries	RIVM KCF	NL
Dr	DECRISTOFORO Clemens	Univ Klinik für Nuklearmedizin	A
Ms	DELMULLE Lies	Fagron N.V.	B
Mr	DESPINIS Stephane	AFSSAPS	F
Mr	DETOUR Julien	Department of Pharmacy	F
Mme	DICHOU Sofia	AFSSAPS	F
Dr	DORPEMA Jan Willem	HAL Allergy	NL
Dr.	DUATTI Adriano	University of Ferrara	I
Ms	EICHLER Gudrun	Gewerbeaufsichtsamt Hannover	D
Mrs	EK Marianne	Medical Products Agency	S
Mr	FENTON MAY V Iain	Moonfleet	GB
Dr.	FROEHLINGSDORF Bernd	Gagron	D
Mrs	GARD Maria	Apoteket AB	S
Ms	GARNIER-POIDEVIN Anne	EDQM	COE
Mr	GERMANAUD Jérôme	Fagron SAS	B
Ms	GILCHRIST Fiona	EDQM	EDQ
Dr	GIRON Maria Cecilia	University of Padova	I
Mr	GROOT D.W.	RIVM	NL
Dr.	HAEBERLI Adrian	Swissmedic	CH
Prof. Dr.	HANDLOS Vagn N	Rijshospitalet	DK
Mme	HANSEN Josée	IGZ Health Care Inspectorate	NL

Title	Name	Employer	Ctry
Dr	HARTMAN Neil	Barts and The London Hospital	GB
Mr	HEIMGARTNER Frederic	Hôpital Neuchâtelois-Pourtales	CH
Mrs	HENRIOT Anne Caroline	Lab. Phyto Prevent	F
Dr.	HERBIG Sebastian	University Clinic Essen	D
Mme	JACQMAIN Paule	Agence Féd. des Méd. Produits de Santé	B
Mrs	JACQUEL Brigitte	EDQM	COE
Dr	KEITEL Susanne	BfArM	D
Dr.	KIEFER Andreas	Central Chamber of Pharmacists	D
Mr	KINLOCH Simon	G.E. HealthCare	GB
Dr.	KIRCHER Wolfgang	APD	D
Ms	KIRCHHOFER Carla	Swissmedic	CH
Ms	KOSTOVA Ljuba	Bulgarian Drug Agency	BG
Prof. Dr.	KROENER Irene	University Mainz	D
Mrs	KULBERKIENE Jurate	Ministry of Health	ZLI
Ms	KULEYA Chipso	Medicines Control Authority	ZW
Ms	KURELAITYTE Milda	Ministry of Health	ZLI
Mrs	LARSEN LE TARNEC Caroline	EDQM	EDQ
Mme	LE An	AFSSAPS DLC	F
Dr.	LE BARS Didier	CERMEP	F
Dr.	LE BRUN Paul H	Central Hospital Pharmacy	NL
Dr	LEE Gerard	MHRA	GB
Dr	LEVEAU Pierre	EDQM	COE
Prof	LIPTAK Jozsef J	National Institute of Pharmacy	H
Prof. Dr.	MATHER Stephen J	Center for Cancer Imaging	GB
Dr	MAYRHOFER Andreas	AGES PharmMed	A
Mrs	MCCARTHY Claire	Irish Medicines Board	IRL
Mrs	MEDZIAUSAITE Irma	Ministry of Health	ZLI
Mrs	MERCIER Isabelle	EDQM	COE
Mrs	MEULENBELT Simone	Xendo Pharma Services	NL
Dr	MIKECZ Pál	University of Debrecen	H
Prof. Dr.	MILIC Jela	University of Belgrade	SRB
Dr	MINGHETTI Paola	University of Milan	I
Mrs	MOCKUTE Roma	State Medicines Control Agency	ZLI
Dr	MORRIS Michael	IMB	IRL
Prof. Dr.	MUHLEBACH Stefan	Swissmedic	CH
Dr	NABOULET Jean Philippe	Weleda	F
Mr	NEMETH Tamas	National Institute of Pharmacy	H
Prof	NICOLAS Alain	Faculté de Pharmacie	F
Ms	NORBYGAARD Elisabeth	DKMA	DK
Dr.	PENUELAS Ivan	Unidad de Radiofarmacia	E
Dr	PICKETT Roger D	GE Healthcare	GB
Dr.	RAMBOURG Patrick	CHRU Montpellier	F
Dr	REIMANN Holger	Govi-Verlag Pharmazeutischer Verlag GmbH	D
Dr	RIESE Stefan	GE Healthcare	D
Dr.	RIZZO PADOIN Nathalie	Hopital Lariboisiere	F
Mr	RUUT Juhan	State Agency of Medicines	ZES
Dr	SALVADORI Piero A	CNR Institute of Clinical Physiology	I
Dr.	SANTIMARIA Monica	Medipass Spa	I
Mrs	SAUSSOL Jeannine	AFSSAPS Unité CBR	F

Title	Name	Employer	Ctry
Dr	SCHNÄDELBACH D	BfArM	D
Dr	SEGUR FANTINO Nelly	Laboratoires Weleda	F
Dr.	SINIVUO Kaarina	National Agency for Medicines	FIN
Ms	SKUTNIK Janeen	Pfizer Eur. Service Center	B
Dr.	SMITH Robert	University of Cambridge	
Ms	STEFANINI ORESIC Laila	Agency Med. Products Medical Devices	CRO
Dr	STEINER Samuel	Health Department Canton of Bern	CH
Mrs	SUNELL HUET Jonna	EDQM	COE
Dr.	TAWAB Mona	Central Lab. German Pharmacists	D
Dr	TISSIER Marie H�el�ene	AFSSAPS DLC	F
Mrs	TOVMASYAN Eranui	Ukrainian Pharmacopoeia	ZUK
Prof	VERBRUGGEN Alfons	Laboratory of Pharmacy	B
Mrs	VILAIN Caroline	AFSSAPS	F
Mr	VIOT Gilles	Laboratoire cyclopharma	F
Dr	VREE Pieter H		NL
Dr	WESTERA Gerrit	University Hospital Zurich	CH
Dr	WIERER Michael	EDQM	COE
Dr.	WITT Walter	ISO-Arzneimittel GmbH Co. KG	D
Mr	ZUECK Gerhard	Faust Apotheke	D

